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The Role of Heart Rate as a Risk Marker for Predicting Adverse Outcomes

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Abstract

Background and Aim

Cardiovascular disease is one of the leading causes of death around the world. Resting heart rate has been shown to be a strong and independent risk marker for adverse cardiovascular events and mortality, and yet its role as a predictor of risk is somewhat overlooked in clinical practice. With the aim of highlighting its prognostic value, the role of resting heart rate as a risk marker for death and other adverse outcomes was further examined in a number of different patient populations.

Materials and Methods

A systematic review of studies that previously assessed the prognostic value of resting heart rate for mortality and other adverse cardiovascular outcomes was presented. New analyses of nine clinical trials were carried out. Both the original and extended Cox model that allows for analysis of time-dependent covariates were used to evaluate and compare the predictive value of baseline and time-updated heart rate measurements for adverse outcomes in the CAPRICORN, EUROPA, PROSPER, PERFORM, BEAUTIFUL and SHIFT populations. Pooled individual patient meta-analyses of the CAPRICORN, EPHESUS, OPTIMAAL and VALIANT trials, and the BEAUTIFUL and SHIFT trials, were also performed. The discrimination and calibration of the models applied were evaluated using Harrell's C-statistic and likelihood ratio tests, respectively. Finally, following on from the systematic review, meta-analyses of the relation between baseline and time-updated heart rate, and the risk of death from any cause and from cardiovascular causes, were conducted.

Results

Both elevated baseline and time-updated resting heart rates were found to be associated with an increase in the risk of mortality and other adverse cardiovascular events in all of the populations analysed. In some cases, elevated time-updated heart rate was associated with risk of events where baseline heart rate was not. Time-updated heart rate also contributed additional information about the risk of certain events despite knowledge of baseline heart rate or previous heart rate measurements. The addition of resting heart rate to the models where resting heart rate was found to be associated with risk of outcome improved both discrimination and calibration, and in general, the models including time-updated heart rate along with baseline or the previous heart rate measurement had the highest and similar C-statistics, and thus the greatest discriminative ability. The meta-analyses demonstrated that a 5bpm higher baseline heart rate was associated with a 7.9% and an 8.0% increase in the risk of all-cause and cardiovascular death, respectively (both $p<0.001$). Additionally, a 5bpm higher time-updated heart rate (adjusted for baseline heart rate in eight of the ten studies included in the analyses) was associated with a 12.8% ($p<0.001$) and a 10.9% ($p<0.001$) increase in the risk of all-cause and cardiovascular death, respectively.

Discussion

These findings may motivate health care professionals to routinely assess resting heart rate in order to identify individuals at a higher risk of adverse events. The fact that the addition of time-updated resting heart rate improved the discrimination and calibration of models for certain outcomes, even if only modestly, strengthens the case that it be added to traditional risk models. The findings, however, are of particular importance, and have greater implications for the clinical management of patients with pre-existing disease. An elevated, or increasing heart rate over time could be used as a tool, potentially alongside other established risk scores, to help doctors identify patient deterioration or those at higher risk, who might benefit from more intensive monitoring or treatment re-evaluation. Further exploration of the role of continuous recording of resting heart rate, say, when patients are at home, would be informative. In addition, investigation into the cost-effectiveness and optimal frequency of resting heart rate measurement is required. One of the most vital areas for future research is the definition of an objective cut-off value for the definition of a high resting heart rate.

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Author's Declaration

This thesis has been composed by myself and has not been submitted in any previous application for a degree. The work reported within was executed by myself, unless otherwise stated.

Publications

Original research publications authored by the candidate on work related to this thesis:

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Abbreviations

ACE	Angiotensin Converting Enzyme
ACS	Acute Coronary Syndrome
AF	Atrial Fibrillation
ANOVA	Analysis of Variance
ARB	Angiotensin-II Receptor Blocker
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
CHD	Coronary Heart Disease
CCB	Calcium Channel Blocker
CI	Confidence Interval
CV	Cardiovascular
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram/Electrocardiography
eGFR	estimated Glomerular Filtration Rate
EF	Ejection Fraction
HDL	High Density Lipoprotein
HF	Heart Failure
HR	Hazard Ratio
LDL	Low Density Lipoprotein
LV	Left-Ventricular

LVEF	Left-Ventricular Ejection Fraction
LVSD	Left-Ventricular Systolic Dysfunction
MI	Myocardial Infarction
NSTEMI	Non-ST-Elevation Myocardial Infarction
NYHA	New York Heart Association
PAD	Peripheral Artery Disease
PCI	Percutaneous Coronary Intervention
PTCA	Percutaneous Transluminal Coronary Angioplasty
OR	Odds Ratio
RR	Relative Risk
SBP	Systolic Blood Pressure
STEMI	ST-Elevation Myocardial Infarction
TIA	Transient Ischemic Attack
UK	United Kingdom
US	United States
WHO	World Health Organisation

Summary

It has been previously demonstrated that resting heart rate is a strong and independent risk marker for adverse cardiovascular events and mortality. However, the role of resting heart rate as a predictor of risk is perhaps undervalued in clinical practice. Compared to the number of studies that have investigated the risk associated with a single resting heart rate measurement using standard Cox proportional hazards regression, few have assessed the prognostic value of multiple heart rate measurements entered into the extended Cox model as a single time-dependent variable, and less have performed meta-analyses of the results from different studies. Furthermore, the majority of studies have been of subjects from the general population, often with no existing cardiovascular disease.

The aim of this thesis is to highlight the importance of heart rate as an indicator of risk, by further examining the role of resting heart rate as a risk marker for death and other adverse cardiovascular outcomes in a number of different patient populations. In particular, the risk associated with multiple resting heart rate measurements is assessed using the extended Cox model, and both standard and individual patient meta-analyses are performed.

Chapter 1 begins by presenting the relationship between heart rate and life span in mammals, as well as the current human and economic costs of cardiovascular disease. The concept of the cardiovascular disease continuum is introduced, and the prevalence of the risk factors known to initiate the series of events leading to end-stage heart failure is described. The association between heart rate and such risk factors is discussed, and other factors that can affect heart rate are briefly mentioned. An overview of the methods of measuring resting heart rate, along with recent recommendations for its measurement, and the methods used in the nine trials newly analysed in the thesis, is given. Finally, hazard ratios are briefly introduced, and it is explained that although hazard ratios are often reported as an increase or decrease in

risk in the field, and are reported as such throughout the thesis, strictly speaking, it is not the risk of death or an event, but the hazard of death or an event, that is increased or decreased. An alternative interpretation is then described to help highlight the distinction.

Chapter 2 presents a systematic review of studies that analysed resting heart rate as a risk marker for mortality and other adverse cardiovascular outcomes, distinguishing between studies that used a single heart rate measurement to predict risk from those that used multiple heart rate measurements.

New analyses of nine clinical trials are presented in Chapters 4 to 9, and information about these trials is given at the beginning of Chapter 3. Chapters 4 to 8 employ similar methods of analysis, and a description of these methods follows. Finally, the methods used in the meta-analyses presented in Chapter 9, including the random-effects restricted maximum likelihood method, is described.

Chapter 4, Section 4.1, investigates the association between baseline resting heart rate and adverse outcomes in patients after acute myocardial infarction with heart failure, left-ventricular systolic dysfunction, or both, by performing a pooled individual patient meta-analysis of the CAPRICORN, EPHESUS, OPTIMAAL and VALIANT trials, using the High Risk Myocardial Infarction Database. The predictive value of time-updated heart rate measurements in the CAPRICORN placebo population is then examined in Section 4.2. Chapters 5 to 7 further assess the predictive value of baseline and time-updated heart rate measurements for death and other adverse outcomes in the EUROPA, PROSPER, and PERFORM trial populations, respectively. Similar analyses of the BEAUTIFUL and SHIFT placebo populations are carried out in Chapter 8 Sections 8.1 and 8.2, respectively. Since both studies included patients who had left-ventricular systolic dysfunction, a pooled individual patient meta-analysis of the two placebo populations is subsequently presented in Chapter 8 Section 8.3.

Following on from the systematic review of Chapter 2, a meta-analysis of the published prospective evidence on the relationship between baseline heart rate and the risk of all-cause and cardiovascular death is presented in Chapter 9 Section 9.2. A similar meta-analysis of time-updated resting heart rate is presented in Section 9.3. The results from Chapters 4 to 8 are also included in the analyses.

Finally, Chapter 10 discusses the thesis as a whole.

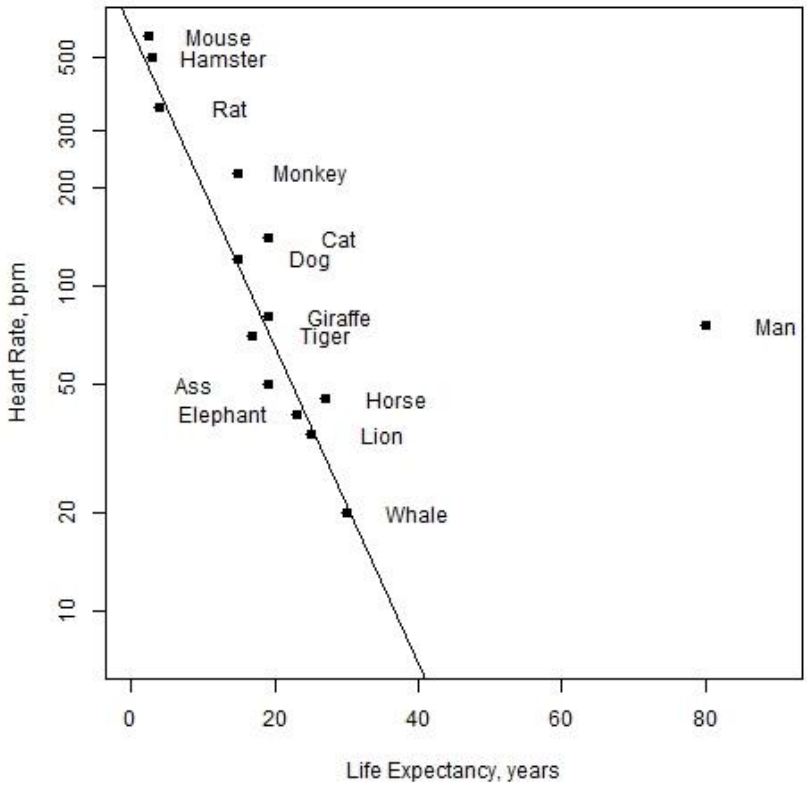
Chapter 1

Introduction

1.1 Resting Heart Rate and Life Expectancy among Mammals

Heart rate among mammals varies considerably between species. Small animals have high heart rates, while larger animals have much lower heart rates. The heart rate of a hamster, for example, is around 400bpm, while that of a horse is around 40bpm[1]. Smaller species of mammals also have shorter lives than larger species. Hamsters, for example, live for around 2-3 years, while horses live for around 25-30 years. It could be surmised that animals with a slow heart rate live longer than those with a fast heart rate, and this is indeed the case[2,3]. Levine 1997[2] demonstrated that heart rate is negatively correlated with life span in mammals, as shown by Figure 1-1.

Figure 1-1: The relationship between resting heart rate and life expectancy in mammals, adapted from Figure 1 in Levine 1997[2].



Note that the y-axis was plotted using the natural log values of the heart rates stated on the axis.

In fact, overlooking some variations, all mammals excluding humans appear to use the same number of heart beats during their lives: interestingly, regardless of species, the heart of a mammal beats approximately 1.1 billion times over their lifetime[2].

Figure 1-1 shows that humans are an exception to this rule. The average resting heart rate of a human lies between 60 and 100bpm, similar to that of other large mammals such as the polar bear or tiger[1]. However, unlike polar bears or tigers who live for around 20 years, humans often live long into their 70s and 80s. Indeed, the human heart beats approximately 3 billion times over a lifetime[4] – two billion more times than that of other mammals.

A plausible explanation of this difference between humans and other warm-blood animals is that humans are able to extend their lives through improvements in living standards and use of modern scientific methods. At the end of the 19th century the median age of British men and women was around 47: by the beginning of the 21st century it had increased to around 80[5]. During the 20th century, much of society benefited from access to more nutritious diets, cleaner drinking water, and vaccines that prevented potentially life-threatening parasitic and infectious diseases, such as measles, polio, smallpox and tuberculosis[6]. Techniques and treatments found to effectively intervene in the process of heart disease were also discovered. Increased knowledge about the effect of diet, smoking, and physical activity on the development of atherosclerosis likely contributed to the decrease in its prevalence observed over the late 20th century[7]. In addition, implementation of procedures such as defibrillation, percutaneous coronary intervention (PCI), and pacemaker implantation, along with access to a range of pharmacologic drugs such as thrombolytics and beta-blockers, means that individuals who develop heart disease are now able to live longer than they would have done in the past.

1.2 The Current Costs of Cardiovascular Disease and Death

Despite recent advancements in medicine, the human and economic costs of cardiovascular (CV) disease are still high across Britain, Europe and the United States (US).

In 2008, CV disease was the primary cause of death worldwide, accounting for 30% of all deaths. At that time, 17.3 million deaths per year were caused by CV disease. By 2030, this number is anticipated to have increased to over 23.6 million[8,9].

CV disease is the main cause of death in Europe and the US. In Europe, over four million deaths each year are due to CV disease[10]. In the US, 2,150 Americans die every day from some form of the disease, equating to one every 40 seconds[8]. In Europe, and the US, more lives are lost because of CV disease than all forms of cancer combined.

Conversely, in 2012, for the first time since the British Heart Foundation was created in 1961, cancer was responsible for more deaths than CV disease in the United Kingdom (UK). While 29% of British deaths were caused by cancer, 28% were still due to CV disease[11].

A significant number of premature deaths, defined as deaths before the age of 75 years old, are also due to CV disease. In Europe, 37% and 38% of premature deaths in men and women, respectively, are caused by CV disease[10]; In Britain, 26% and 18% of men and women, respectively, died prematurely because of CV disease in 2012[11].

The number of people living with some form of CV disease in these countries is also considerable. Over 2.3 million residents of the UK have coronary heart disease (CHD), more than half a million have heart failure (HF), 1.15 million have atrial fibrillation (AF), and more than 1.3 million have previously had a stroke[11]. Approximately 27% of Americans are living with some form of heart disease or the after-effects of a stroke[8].

Both the direct and indirect costs of CV disease are huge. In the US, an estimated $320.1 billion is spent each year[8]. More than £6.8 billion was spent on treatment within the National Health Service in England in 2012/13[11]. In addition, production losses associated with the disease, and informal care, cost the UK over £6 billion and around £3.8 billion in 2009, respectively[12]. It is estimated that CV disease costs the European Union economy almost €196 billion a year: 54% of which is direct health care costs, 24% of which is from losses in production, and 22% of which is related to informal care[10].

1.3 The Cardiovascular Disease Continuum

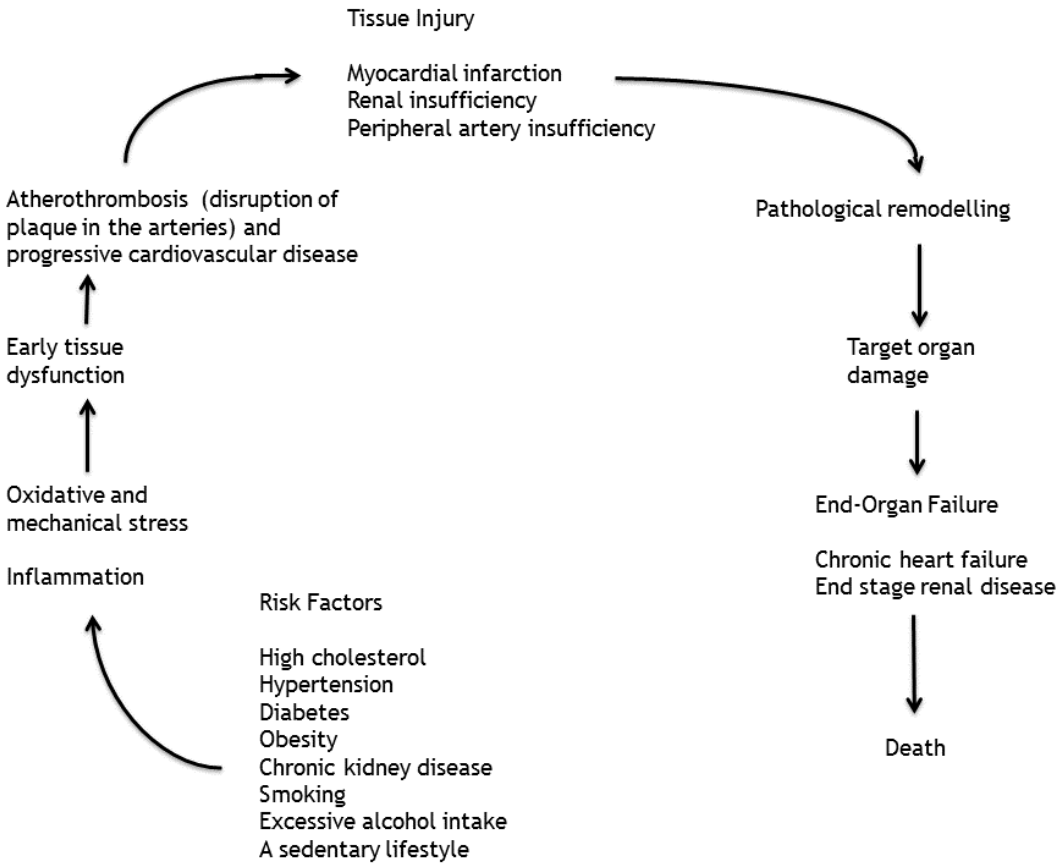
The progress made in CV research at the end of the 20th century highlighted the importance of identifying factors that possibly increased the risk of someone developing CV disease. Dzau et al. 1991[13] put forward the idea that CV disease was the outcome of a chain of events, set in motion by a variety of different risk factors, that could ultimately alter the heart and its structure.

The group of researchers proposed that disrupting this chain of events, perhaps at several different stages of the chain, could help to delay and even possibly prevent symptomatic heart disease from developing, thus prolonging life. At this point in time, however, there was a lack of pathological evidence and clinical trial data. They acknowledged that further research was required to vindicate their theory.

Over the next 15 years, new landmark clinical trial data and discoveries relating to the fundamental pathology of heart disease, along with the development of pioneering drugs, substantiated the notion that CV disease was the result of such a chain of events - named the CV disease continuum[14,15]. These advancements in the field also reinforced the concept that disrupting the chain at any or multiple points could impede the progression of heart disease. Moreover, they indicated that the continuum was set in motion earlier in life than initially thought, suggesting that CV disease is established over decades.

Taking this new evidence into account, Dzau et al. 2006 introduced an updated CV disease continuum[14,15]. While the initial idea concentrated on risk factors for CHD and its sequelae, the updated continuum incorporated additional conditions including peripheral artery disease (PAD), cerebrovascular disease, and renal disease, as shown by Figure 1-2[14,15]. Risk factors such as smoking, diabetes, elevated cholesterol, hypertension, alcohol consumption and obesity were now known to instigate the sequence of events leading to HF. Dzau et al. 2006 went on to propose that prevention or management of these factors through lifestyle adjustments, such as losing weight and stopping smoking, was a crucial component of preventative cardiology.

Figure 1-2: The updated cardiovascular disease continuum presented by Dzau et al. 2006, adapted from Figure 2 in Dzau et al. 2006[14].



1.4 The Prevalence of Risk Factors for Cardiovascular Disease

1.4.1 High Cholesterol

High cholesterol is the one of the leading physiological risk factors for CHD[16]. The World Health Report 2002 approximated that 60% and 40% of CHD and ischemic stroke in developed countries, respectively, was attributable in part to high cholesterol[10,17]. The World Health Organisation (WHO) Global Status Report on Noncommunicable Diseases 2010 reported that prevalence of raised cholesterol (≥5.0mmol/L or 190mg/L) was greatest in the European Region, at 54%, followed by the Region of Americas, at 48%[9]. Approximately 53.4% of Americans adults had high cholesterol in 2011 to 2012[8]. Increased physical activity and adjustments to diet – particularly reducing the consumption of saturated fats – can lower cholesterol.

1.4.2 Hypertension

High blood pressure, also known as hypertension, is directly linked to an increased risk of developing CV disease[16]. The World Health Report 2002 approximated that more than 50% of CHD and almost 75% of stroke in developed countries was due in part to the condition[10,17]. An estimated 972 million people worldwide had hypertension in 2000[18]. The National Health and Nutrition Examination Survey data from 2009 to 2012 found that approximately 32.6% of American adults had high blood pressure[8]. In England, the prevalence in 2012 was 31% and 27% among men and women, respectively[19]. Similar to high cholesterol, increased physical activity, weight loss, and an improvement in diet can effectively lower blood pressure[20].

1.4.3 Diabetes

Diabetes also increases the risk of CV disease. In addition, people with diabetes are about three times more likely to have a heart attack compared to those who do not[21]. Not only that, but the effects of other risk factors, such as high cholesterol and

hypertension, are amplified by the presence of the condition[10]. In 2010, the prevalence of diabetes across the globe was estimated to be 6.4%, equating to approximately 285 million individuals; it is projected to increase to 7.7%, equating to 439 million individuals, by 2030[8]. The National Health and Nutrition Survey further revealed that 21.1 million and 8.1 million American adults had diagnosed and undiagnosed diabetes, respectively[8]. Around 3.2 million people living in the UK have been diagnosed with the disease[11]. Being overweight is one of the primary causes of the onset of type 2 diabetes[22]. In a small study conducted by Newcastle University, 11 people with diabetes were limited to 600 calories each day for 8 weeks: after three months, 7 of the 11 people no longer had diabetes[23].

1.4.4 Obesity

Obesity, in particular abdominal obesity, majorly increases the risk of CV disease, including CHD, stroke, AF and congestive HF[24-27]. It is also one of the key risk factors for raised cholesterol, hypertension, and diabetes[10]. In 2008, approximately 1.46 billion adults were overweight or obese worldwide[8]. Recently gathered data from across the UK and US revealed that 24.8% of British adults were obese[11], and that 69% of American adults were obese or overweight[8]. WHO data from 2008 showed that national mean body mass index (BMI) levels for men and women across Europe varied between 24 and 28 km/m^2 – considerably higher than the ideal mean BMI of a population, 21km/m^2 [10].

1.4.5 Chronic Kidney Disease

People with chronic kidney disease and end-stage renal disease are at an extremely high risk of experiencing CV disease-related events[8]. End-stage renal disease is defined as the need to receive chronic renal replacement therapy, such as haemodialysis or kidney transplantation; chronic kidney disease is the last stage before end-stage renal disease. Whether chronic kidney disease is an independent risk factor for CV disease is still being disputed[8]. However, those with chronic kidney disease are more likely to die from a CV-related cause than to progress to end-stage renal disease[8]. Over 26 million

Americans have chronic kidney disease[28]; in 2008, 547,982 were found to have end-stage renal disease, 70% of whom were being treated with haemodialysis[8].

1.4.6 Cigarette Smoking

In spite of 50 years of strong evidence that smoking is a very harmful habit, it is still commonplace. It is also one of the leading modifiable risk factors for premature death and CV disease[16]. Among its many negative health-related effects, it raises blood pressure which in turn increases the risk of developing CHD[11]. The World Health Report 2002 estimated that more than 20% of CV disease in developed countries was attributable to smoking[17]. According to estimates from 2011, 20% and 18% of English men and women, respectively, were regular smokers[11]. Similarly, data from 2013 found that 20.4% and 15.5% of American men and women smoked[8].

1.4.7 Alcohol Consumption

High levels of alcohol consumption increase the risk of CV disease[10]. Excessive drinking increases blood pressure as well as the levels of fat in the blood, known as triglycerides, which leads to an increased risk of developing atherosclerosis[11,17]. In England, the percentage of men and women exceeding the recommended daily allowance of alcohol (up to four units for men and three for women[12]) on their heaviest day's drinking was 37% and 28%, respectively, in 2012[11,19]. Similarly , in Wales, 48% of men and 36% of women disclosed drinking more than the recommended amount in 2013[29].

1.4.8 Physical Inactivity

Another primary risk factor for CV disease is physical inactivity. A sedentary lifestyle can lead to obesity, hypertension, high cholesterol and diabetes[30]. Conversely, an active lifestyle corresponds with a decrease in the risk of CV-related death[31]. In England in 2012, 33% and 45% of men and women did not meet physical activity guidelines, respectively[19]. Across the European Union, 39% of adults reported that they never participated in exercise or sport[10]. Moreover, in 2013 it was discovered that

30.5% of American adults did not partake in any form of physical activity in their leisure time[8].

1.5 The Association between Heart Rate and Risk Factors for Cardiovascular Disease

As yet, resting heart rate has only been established as a true modifiable risk factor for adverse CV-related outcomes in patients with a resting heart rate of at least 70bpm, in sinus rhythm, with left-ventricular systolic dysfunction (LVSD) and chronic HF[32]. However, resting heart rate has been shown to be significantly associated with all of the risk factors discussed in Section 1.4, excluding cholesterol: it appears that there have not yet been any studies of the association between resting heart rate and cholesterol.

1.5.1 Heart Rate and the Development of Hypertension

Heart rate is a significant and independent predictor of the onset of hypertension[33-41]. Palatini et al. 2006 showed that both baseline and changes in clinic heart rate over the following 6 months independently predicted long-term hypertension (a systolic blood pressure (SBP) >140mmHg or a diastolic blood pressure (DBP) >90mmHg[10]) in young people[39]. Those who had a heart rate ≥85bpm throughout the study were found to be at twice the risk (95% confidence interval (CI) 1.4 to 2.9) of acquiring long-term hypertension requiring blood pressure medication compared to those with a heart rate <85bpm. Similarly, Inoue et al. 2007 revealed that normotensive middle-aged subjects with a heart rate ≥71bpm were 1.61 times more likely (95% CI 1.10 to 2.37) to become hypertensive compared to those with a heart rate <59bpm[40]. More recently, Wang et al. 2014 found that a 10bpm higher resting heart rate was significantly and independently associated with an 8% increase in the risk of new-onset hypertension in an Asian population[41].

1.5.2 Heart Rate and the Development of Diabetes

An elevated resting heart rate is also known to be associated with an increase in risk of diabetes[42-48]. Bemelmans et al. 2012, for example, demonstrated that an elevated resting heart rate was independently associated with an increase in risk of type 2 diabetes in patients with different forms of vascular disease (CHD, PAD, cerebrovascular disease and abdominal aortic aneurysm)[47]. Firstly, subjects with a heart rate ≥70bpm were discovered to be at a 65% higher risk (95% CI 15 to 136%) of developing diabetes compared to those with a heart rate <55bpm. Secondly, a 10bpm higher resting heart rate was borderline significantly associated with a 10% increase in risk (95% CI 0 to 21%). When subjects were stratified by age (<55, 55-63 and >63 years), the risk was found to be especially high in the 55-63 year-old group: a 10bpm higher resting heart rate was associated with a 22% (95% CI 4 to 43%) increase in risk. Grantham et al. 2013 also recently showed that participants in a large population-based cohort with a heart rate ≥80bpm were 1.89 times (95% CI 1.07 to 3.35) more likely to develop diabetes compared to those with a heart rate below 60bpm[48]. When the subjects were divided by sex and obesity, non-obese men with a raised heart rate were found to be an especially high 5.61 times more at risk (95% CI 1.75 to 17.98).

1.5.3 The Association between Heart Rate and Obesity

Furthermore, a high heart rate has been shown to be an independent predictor of being overweight and obese[43,49]. Shigetoh et al. 2009 showed that a high resting heart rate predicted future obesity in a general population of subjects independent of age, sex and initial BMI[43]. Those who had a baseline resting heart rate ≥80bpm were 2.34 times (95% CI 1.09 to 5.90, $p<0.05$) more likely to be obese 20 years later, compared to those who had a heart rate <60bpm. Palatini et al. 2011 demonstrated that both baseline resting heart rate, and change in resting heart rate over follow-up, independently predicted being overweight or obese approximately 7 years later[49]. In the population of young subjects screened for stage 1 hypertension, both heart rate measurements were

independent predictors of BMI at the end of follow-up (p = 0.007 for baseline and p = 0.036 for change). Additionally, after adjustment for a variety of other baseline risk factors including BMI, blood pressure, smoking, and alcohol consumption, a 10bpm higher baseline heart rate and change in heart were associated with a 30% (95% CI 10 to 50%, p = 0.0003) and 17% (95% CI 6 to 28%, p = 0.003) increase in the risk of being overweight or obese, respectively.

1.5.4 The Association between Heart Rate and Kidney Disease

Moreover, it has recently been shown that heart rate is a predictor of kidney disease[50,51]. Bohm et al. 2008 revealed that a higher heart rate was significantly associated with an increase in the risk of microalbuminuria - an indicator of impaired renal function[50]. In the population of high-risk patients with hypertension, subjects with a heart rate between 80 and 100bpm were found to be 1.47 times (95% CI 1.29 to 1.68, p<0.0001) more likely to have impaired renal function, compared to those who had a heart rate <60bpm. Subjects with a heart rate above 100bpm were found to be at an even higher risk of 1.56 times (95% CI 1.22 to 1.99, p = 0.0004). In a large general population of men and women, Inoue et al. 2009 showed that subjects with a baseline heart rate ≥72bpm were 1.29 (95% CI 1.06 to 1.57) times more at risk of developing chronic kidney disease after around 5 years compared to subjects with a heart rate <60bpm[51]. When the population was split by age (≤48 years and >48 years) an increase in heart rate category was associated with a 15% (95% CI 5 to 25%, p = 0.0016) increase in the risk of chronic kidney disease in the older subjects (using the fully adjusted model), but no significant association was observed in the younger subjects.

1.5.5 The Effect of Smoking on Heart Rate

Smoking is known to increase heart rate[52-54]. While the most noticeable effect occurs shortly after use, if smoking is a regular habit then the heart rate is continually increased[52]. A study of both young and middle-aged smokers by Hering et al. 2006 showed that cigarette smoking substantially increased the heart rate in both groups.

The increases in the younger group (22 ± 2bpm) were found to be significantly higher than those in the middle-aged group (13 ± 2bpm, $p<0.001$), suggesting that the effect is age-dependent. In response to this finding, Papathanasiou et al. 2013 focused on the effect in young people[54]. Resting heart rate was significantly lower among the young people who did not smoke compared to those who smoked 20 or more cigarettes a day, regardless of sex. The mean resting heart rate of the women who did not smoke was 70, while that of the women who did was 76.4 ($p<0.001$). Among the men, those who did not smoke had a mean resting heart rate of 66.3, while the heart rate of those who did was 72.8 ($p<0.001$).

1.5.6 The Effect of Alcohol Consumption on Heart Rate

A few studies have shown that alcohol consumption is positively associated with heart rate[55,56]. Ryan and Howes 2002 found that alcohol consumption was an independent predictor of 24-hour heart rate ($p = 0.008$)[55]. Ohira et al. 2009 further demonstrated that habitual alcohol intake was associated with increased 24-hour heart rate, as well as heart rate while awake and asleep[56]. The heavy drinkers had significantly higher mean 24-hour, awake and asleep heart rates than the non-drinkers, light drinkers and moderate drinkers. The mean 24-hour heart rate of the non-drinkers, for example, was 68.2bpm, while that of the heavy drinkers was 72.2bpm ($p<0.01$).

1.5.7 The Effects of Physical Activity on Heart Rate

Physical activity can decrease resting heart rate[57-59]. Wilmore et al. 2001 found that a 20-week endurance training program decreased resting heart rate by 4.6 to 2.7bpm in a group of healthy subjects who previously led sedentary lifestyles[57]. Huang et al. 2005 performed a meta-analysis of controlled aerobic training on resting heart rate among sedentary older adults and discovered that the overall mean reduction in heart rate was 6bpm, ranging from 2 to 12bpm[58]. The analysis also revealed that training of more than 30 weeks results in a larger statistically significant decrease. A study by Genovesi et al. 2007 compared the awake and asleep heart rates of trained athletic and sedentary

young males and females, and found that the athletic subjects had significantly lower heart rates than the sedentary ones, irrespective of sex[59]. The physically active group of males, for example, had a mean sleeping heart rate of 51bpm, while the sedentary groups' mean was 59bpm ($p<0.001$). Similarly, the physically active group of females had a mean sleeping heart rate of 61bpm, while the sedentary group had a mean of 69bpm ($p = 0.002$).

1.6 Additional Factors that Affect Heart Rate

Aside from smoking, alcohol consumption and physical activity, a number of other factors can influence resting heart rate. As well as being an independent predictor of hypertension, heart rate is positively correlated with blood pressure[60,61]. Furthermore, several studies have found that female gender is a determinant of elevated heart rate[62-64]. Various medical conditions, such as anxiety, pain, dehydration, and fever, can also cause the heart rate to increase[65]. In addition, CV diseases, such as CHD, myocardial infarction (MI) and HF can result in the heart beating faster than normal. If blood cannot travel as easily through the vessels because of plaque, for example, or if the heart muscle has been damaged and cannot pump as effectively as it once could, the heart attempts to maintain adequate cardiac output by increasing the heart rate[66,67].

1.7 Methods of Measuring Resting Heart Rate

Resting heart rate can be measured using the following methods: pulse palpation; auscultation (using a stethoscope to listen to the heart beat); using an ECG; or using an electronic heart rate monitor[68]. Pulse palpation is the simplest method of measuring resting heart rate. The pulse rate can be felt at any location on the body where an artery is near the surface: commonly the temporal, carotid, radial, and brachial arteries, located at the temple, the neck below the jaw, the wrist, and the inside of the forearm at the elbow, respectively[68,69]. Once the pulse rate is located, the number of beats can be counted over a certain length of time, such as 30 or 60 seconds, and then multiplied if necessary to estimate the number of beats per minute. This is the method

of heart rate measurement used by clinicians and other healthcare professional in daily practice, and can potentially be performed by anyone, in any setting. Auscultation is a similar method of measurement. It involves listening to and counting the number of heart beats over a certain length of time using a stethoscope, and then multiplying the number counted to estimate the number of beats per minute if required. An ECG, on the other hand, uses electrodes attached to the skin to record the electrical activity of the heart over a certain length of time. It is the method normally used in critical care medicine, such as when a patient is admitted to hospital in an emergency setting with suspected HF[68]. Finally, electronic heart rate monitors are generally made up of two parts: a transmitter that is placed over an artery, and a receiver such as a wrist watch that displays the heart rate, sometimes along with other information such as the average or maximum heart rate over some period of time[68]. These devices are not commonly used to measure resting heart rate; they are mainly used by athletes and other sportspeople to monitor their fitness and performance[68]. ECGs and electronic heart rate devices provide more precise measurements of heart rate compared to palpation and auscultation, and allow for the heart rate to be monitored over longer lengths of time.

There is uncertainty as to whether ECG should be preferred to pulse palpation since ECG is a more accurate method of measurement. It is used in the majority of clinical trials for this reason, whereas in epidemiological studies, around 50% of measurements are acquired using palpation, and 50% are acquired using ECG[68]. The use of ECG, however, is implicitly more expensive than pulse palpation. Furthermore, there is no evidence that the added precision of ECG renders more meaningful data, or is advantageous in clinical practice or research. In addition, the studies by Erikssen and Rodahl 1979[70], and Sbarouni et al. 2015[71], found a strong correlation between the two measurements in healthy men, and in patients with stable CHD, respectively, with correlation coefficients of more than 0.9 in both studies.

Moreover, ECG is executed in the lying (supine) position, whereas pulse palpation can be performed in the sitting position, along with blood pressure[72]. The panel of experts who recently took part in the second consensus conference endorsed by the European Society of Hypertension, deemed that the sitting position should be favoured since blood pressure is normally measured in such a position, and thus heart rate can be measured directly after each blood pressure measurement[72]. The panel therefore recommended that pulse palpation be used, with the pulse rate counted over 30 seconds, and stated that while ECG measurement is permitted, it is not recommended even for research[72]; in some cases, such as when a patient has AF, heart rate should be measured using auscultation, since some heart beats can be missed using palpation[68].

Since heart rate can be affected by various factors, as discussed in Section 1.6, including the position of the body, mental stimuli, and environmental factors, the panel made further recommendations for the measurement of resting heart rate, with the aim of minimising the effect of such confounding factors[72]. Firstly, individuals should refrain from exercising, smoking, and drinking alcohol or coffee in the hours before measurement. Secondly, they should be permitted to sit and relax as much as possible prior to measurement, for at least five minutes: a longer relaxation period may be required if the individual is anxious, for example. In addition, the individual should be instructed to avoid talking during measurement. The room, and the temperature of the room, should be comfortable, and any sources of noise should be eliminated where possible. Finally, the individual should be seated comfortably, with their legs uncrossed, and at least two heart rate measurements should be taken, the average of which should be calculated. If blood pressure is also being measured, heart rate should be measured after each blood pressure reading; these recommendations are very similar to those for measurement of blood pressure. The panel further advocated that all scientific studies focusing on heart rate supply the following information: the length of time of rest prior to measurement; the conditions of the environment where measurement was performed, such as the temperature; the method used for

measurement; the number of measurements taken; the duration of each measurement; the time interval between measurements; the position of the individual, such as whether they were sitting or lying down; and details about the observer, such as whether they were a doctor or a nurse, or whether an electronic heart rate monitor was used[72].

The majority of scientific publications, however, do not even state the method used for heart rate measurement, let alone any of the additional information listed above, even when heart rate is one of the main variables of interest[73]. In regards to the trials newly analysed in this thesis, information about the method of resting heart rate measurement was not available for five of the nine trials, in any of their related publications. In three of the trials, resting heart rate was measured using ECG, and in one, resting heart rate was measured using palpation, auscultation, or ECG, according to the investigator's decision (see Section 3.2 for details).

1.8 Interpretation of the Hazard Ratio

Section 1.5 discussed the associations between heart rate and risk factors for CV disease. In Section 1.5.2 for example, it was stated that subjects with a heart rate ≥70bpm were found to be at a 65% higher risk (95% CI 15 to 136%) of developing diabetes compared to those with a heart rate <55bpm in the study by Bemelmans et al. 2012[47]. This association between resting heart rate and risk, along with the others described in Section 1.5.2, was quantified using Cox proportional hazards analysis[74], which is introduced in detail in Chapter 3 Section 3.3.3. Cox proportional hazards analysis is used in situations where the total number of events that occur, as well as their timing, are of interest[75]. It allows the effect that a baseline measurement (such as resting heart rate) has on the risk of a future event (such as the development of diabetes or hypertension) to be estimated; this effect is expressed by the hazard ratio (HR).

The HR, sometimes called the relative hazard, describes the relative risk of experiencing an event, such as death or the development of diabetes, given that an individual has survived, or not yet experienced the event, up to a certain point in time[76]. In other words, it is the probability of experiencing an event in the next time interval, given that it has not already occurred, divided by the length of the next time interval[76,77]. Thus, the length of time that the individual is followed-up for is conceptually divided into intervals: these intervals are made very short, however, so that in effect the HR represents an instantaneous rate[77]. One of the main assumptions of Cox proportional hazards analysis is that the HR is approximately the same for each time interval, and so is essentially constant over the duration of follow-up (see Sections 3.3.3 and 3.2.6). The HR therefore represents the risk of experiencing an event over the follow-up period, at any point in time.

In Section 1.5, and throughout the following chapters, HRs were, and are, generally reported as an increase or decrease in risk of death or the event of interest. This is commonly how HRs are reported in the field. In the study by Bemelmans et al. 2012[47], for example, the HR for the development of diabetes associated with a heart rate ≥70bpm, compared to a heart rate <55bpm, was 1.65 (95% CI 1.15 to 2.36), which was reported in Section 1.5.2 as a 65% higher risk (95% CI 15 to 136%) of developing diabetes. In the original publication[47], it was stated that "subjects in the highest quartile of resting heart rate (Q4) had a 65% higher risk of incident type 2 diabetes mellitus compared with those in the reference Q1 (HR 1.65, 95% CI 1.15 to 2.36) based on the fully adjusted model." Similarly, the study by Palatini et al. 2011[49] found that the HR for becoming overweight or obese associated with a 10bpm higher baseline heart rate was 1.30 (95% CI 1.10 to 1.50), which was reported in Section 1.5.3 as a 30% (95% CI 10 to 50%, p = 0.003) increase in the risk of being overweight or obese. In the original publication[49], it was stated that "there was a 30% increase in the risk of Ov-Ob (overweight or obesity) for a 10bpm increment in baseline clinic heart rate (HR 1.30, confidence interval = 1.10-1.50)". The articles by Barraclough et al. 2011[78] and

Sedgwick et al. 2015[76], entitled "What a Clinician Ought to Know: Hazard Ratios" and "Interpreting Hazard Ratios", respectively, also recommend this interpretation of the HR. Barraclough et al. 2011, for example, advise that an HR of 0.75 for death, associated with taking a new medication compared to an old medication, be interpreted as a 25% lower risk of death, assuming proportionality of hazards[78]. Furthermore, Sedgwick et al. 2015, using as an example a trial which investigated the impact of isoniazid prophylaxis on mortality in children with HIV, and discovered that the HR for death associated with treatment compared to placebo was 0.46 (95% CI 0.22 to 0.95), advise that the HR be interpreted as a 54% lower risk of mortality[76].

Although this interpretation of the HR is frequently used, strictly speaking, it is not the risk of death or an event, but the *hazard* of death or an event, that is increased or decreased. Thus, going back to the study by Bemelmans et al. 2012[47], technically the HR for the development of diabetes of 1.65 means that subjects with a heart rate ≥70bpm had a 65% higher *hazard* of developing diabetes compared to subjects with a heart rate <55bpm, or, in other words, had a 65% higher risk of developing diabetes *specifically during follow-up*. HR results should only be applied to the subjects studied over the duration of follow-up: using them to make broad inferences should be done with caution, and is not generally recommended[78]. One reason for this is that proportionality of hazards may no longer hold outwith the follow-up period. As the standard interpretation is used throughout the thesis, this should be kept in mind.

An alternative interpretation, which may highlight the distinction, is described as follows[77]. In the context of the study by Bemelmans et al. 2012[47], the HR of 1.65 is equivalent to the odds that a subject with a heart rate ≥70bpm develops diabetes before a subject with a heart rate <55bpm.

The odds of developing diabetes, is equal to the probability of developing diabetes, divided by the probability of not developing diabetes, which can be calculated using the formula

$$Odds = \frac{p}{1-p} \tag{1-1}$$

where p is the probability of developing diabetes.

As the HR is equivalent to the odds, it follows that

$$HR = \frac{p}{1-p} \tag{1-2}$$

Rearranging Equation 1-2 so that p becomes the subject of the formula gives

$$p = \frac{HR}{1+HR} \tag{1-3}$$

Thus, a subject with a heart rate ≥70bpm who is at a 65% higher *hazard* of developing diabetes compared to a subject with a heart rate <55bpm, has a 62% *chance* of developing diabetes before a subject with a heart rate <55bpm.

1.9 Chapter Summary

This chapter began by presenting the negatively correlated relationship between heart rate and life expectancy among mammals. It was demonstrated that humans are the exception to this rule: the human species has a much longer lifespan than expected given their average heart rate, perhaps because human lives can be extended through improvements in living standards and the application of modern scientific techniques. A summary of the current human and economic costs of CV disease - one of the leading causes of death in the Western world – was then given, and the concept of the CV

disease continuum was introduced. The prevalence of the risk factors known to set the chain of events leading to end-stage HF in motion was described. Evidence on the association between resting heart rate and these risk factors was subsequently presented, and additional factors than can affect heart rate were briefly mentioned. An overview of the methods of measuring resting heart rate, along with recent recommendations for its measurement, and the methods used in the nine trials newly analysed in the thesis, was then given. Finally, a brief introduction to hazard ratios was provided, and it was explained that although hazard ratios are often reported as an increase or decrease in risk in the field, and were reported as such throughout the thesis, strictly speaking, it is not the risk of death or an event, but the hazard of death or an event, that is increased or decreased. An alternative interpretation was then described to help highlight the distinction.

A considerable number of observational studies and post-hoc clinical trial analyses have also examined the association between resting heart rate and adverse CV events and mortality: Chapter 2 presents a review of such studies.

Chapter 2

A Systematic Review of Heart Rate as a Prognostic Risk Marker for Mortality and Adverse Cardiovascular Outcomes

2.1 Introduction

As well as being independently associated with established risk factors for CV disease, as discussed in Chapter 1, over the past three decades extensive evidence from epidemiological studies and clinical trials designed for other purposes have demonstrated that heart rate is a strong and independent prognostic risk marker of adverse CV events and mortality. At the moment, however, the predictive value of resting heart rate is given less consideration in clinical practice than perhaps it should be, in view of the evidence and the fact that it is straightforward and inexpensive to measure.

There are a multitude of discursive (non-systematic) reviews available on the subject, most of which include discussion of the pathophysiological mechanisms linking heart rate and CV disease, and the experimental effects of heart rate reduction[79-93]. The majority of the reviews that discuss heart rate as a risk marker are limited to studies of the predictive value of resting heart rate measured at a single point in time at the beginning of follow-up. The recent review by Inoue et al. 2013[92] distinguished some studies that used multiple heart rate measurements updated after the beginning of the study period to assess the risk of adverse events.

This chapter provides a systematic review of observational studies and post-hoc clinical trial analyses that focused on the prognostic value of resting heart rate for mortality and adverse CV outcomes in a number of different populations, available at the end of April 2015, specifically distinguishing between studies that used a single heart rate measurement from those that used more than one heart rate measurement. The aim

was to provide a comprehensive guide of the predictive value of resting heart rate, thus highlighting its importance as an indicator of risk, as well as avenues for future research. Subsequently, in Chapter 9, meta-analyses of the risk of death from any cause and death from CV causes are presented, including the published prospective evidence identified in the review, as well as the results from Chapters 4 to 8 of this thesis.

2.2 Methods

2.2.1 Literature Search

The systematic review followed the PRISMA guidelines[94,95] as extensively as possible; the PRISMA 2009 checklist is given in Table A1-1 provided in Appendix 1. MEDLINE (1946-present) and Embase (1947-present) were searched for relevant studies. Ovid was used to search MEDLINE and Embase simultaneously.

The focus of the review was the prognostic value of resting heart rate for death and adverse CV outcomes. They key concepts were therefore "heart rate", "death", and "adverse CV outcomes". Thus, the first search term to be decided upon was "heart rate": "resting heart rate" was not used as it was thought to be too specific. Corresponding MeSH terms of "heart rate" are "pulse" and "pulse rate", and so they were included in the search term as well. As studies focusing on the prognostic value of heart rate were of interest, "prognos**" was chosen as a search term, along with its synonym "predict**". Note that adding ** to the end of a search term in Ovid retrieves unlimited suffix variations i.e. "predict**" searches for "prediction", "predictive", "predictor", and so on. "Outcome**" was additionally chosen to be included, along with "event**", as the two are often used synonymously. "Adverse" was also included, in addition to "death", its statistical synonym "mortality", and "survival", which is the corresponding MeSH term for "mortality".

Thus, the final search term used was ("heart rate" OR "pulse" OR "pulse rate") AND ("risk" OR "hazard" OR "prognos**" OR "predict**" OR "event**" OR "outcome**" OR "adverse" OR "death" OR "mortality" OR "survival"), and a Title search was specified. A Title as opposed to a Keyword or Topic search was used since only studies that specifically focused on the prognostic value of heart rate were of interest. The Ovid search also specified the following limits: English Language; Full Text; Human and Humans. The set of results was then automatically de-duplicated, and search terms were used to exclude irrelevant groups of studies; details of the search strategy are given in Table A1-2 provided in Appendix 1. Reference and citation lists of included studies were searched for additional relevant publications: Web of Science was used to search citations. The census date for the search was the end of April 2015.

2.2.2 Eligible Studies

Studies were accepted for inclusion in the systematic review if the full-text PDF version of the article was available online in English; conference abstracts and other forms of publications such as letters and reviews, were excluded, as were studies for which no PDF could be obtained. Eligibility assessment was performed independently in an unblinded standardised manner. No other investigators took part in the literature search, or eligibility assessment and selection of studies.

2.2.3 Eligible Heart Rate Measurements and Outcomes

Only studies which specifically focused on the association between the risk of at least death or an adverse CV outcome and resting heart rate (measured by pulse or electrocardiography (ECG)) were of interest. Studies which analysed admission, discharge, or in-hospital heart rate were also included, but studies focusing only on short-term heart rate variability, response, pattern, exercise heart rate, or heart rate measured by Holter over a period of say, 24 hours, were excluded. Studies of heart rate measured during an episode of angina or MI were excluded. Studies that assessed heart rate and the risk of conditions such as the development of hypertension or diabetes

were also excluded, as were studies which only analysed a non-CV endpoint such as cancer death, or the association between heart rate and physiological measurements.

2.2.4 Eligible Participants

The selection of studies was also restricted to adult populations that were generally healthy or had been drawn from the general population and those with diabetes, hypertension, CHD, HF, kidney disease/failure or any other form of vascular disease (including those who had previously experienced an acute coronary syndrome (ACS) event such as an MI, a stroke, or a coronary artery bypass graft (CABG)).

Studies which analysed some other specific groups of subjects were excluded, such as those with asymptomatic aortic stenosis, suspected myocarditis without known HF, AF (and none of the other included conditions listed above), multiple organ damage, or those who had undergone a transplant.

2.2.5 Further Exclusions

Further exclusions were made for: studies that looked at determinants of heart rate; studies that only used a log-rank test to evaluate the relationship between heart rate and outcomes as opposed to some form of regression analysis; and studies involving only babies or children.

2.2.6 Data Extraction and Organisation of Studies

Where possible, the following data were extracted from each publication: the first author's last name; the year of publication; the name of the study if it had one; details about the study population including age, sex, location, and any underlying diseases or conditions; the number of subjects included in the final analysis; the mean or median length of follow-up; the type of heart rate measurement used; the type of model used to analyse the association between heart rate and risk; and outcomes relevant to the

review (death or adverse CV-related outcomes) that were analysed. No other investigators assisted in the data extraction process.

Studies chosen for inclusion were grouped by whether they analysed the risk associated with a single heart measurement obtained at the beginning of the follow-up period, or with at least one or more heart rate measurements obtained after the beginning of the study. The first of these two types of studies are referred to as 'baseline heart rate' studies, and the latter as 'multiple heart rate measurement' studies.

The baseline heart rate studies found were further grouped according to the common condition of the participants. The multiple heart rate measurement studies, which were fewer in number, were classified into two groups: those which included a general population of subjects, or those which included subjects with a specific pre-existing disease or condition.

2.2.7 Assessment of Risk of Bias

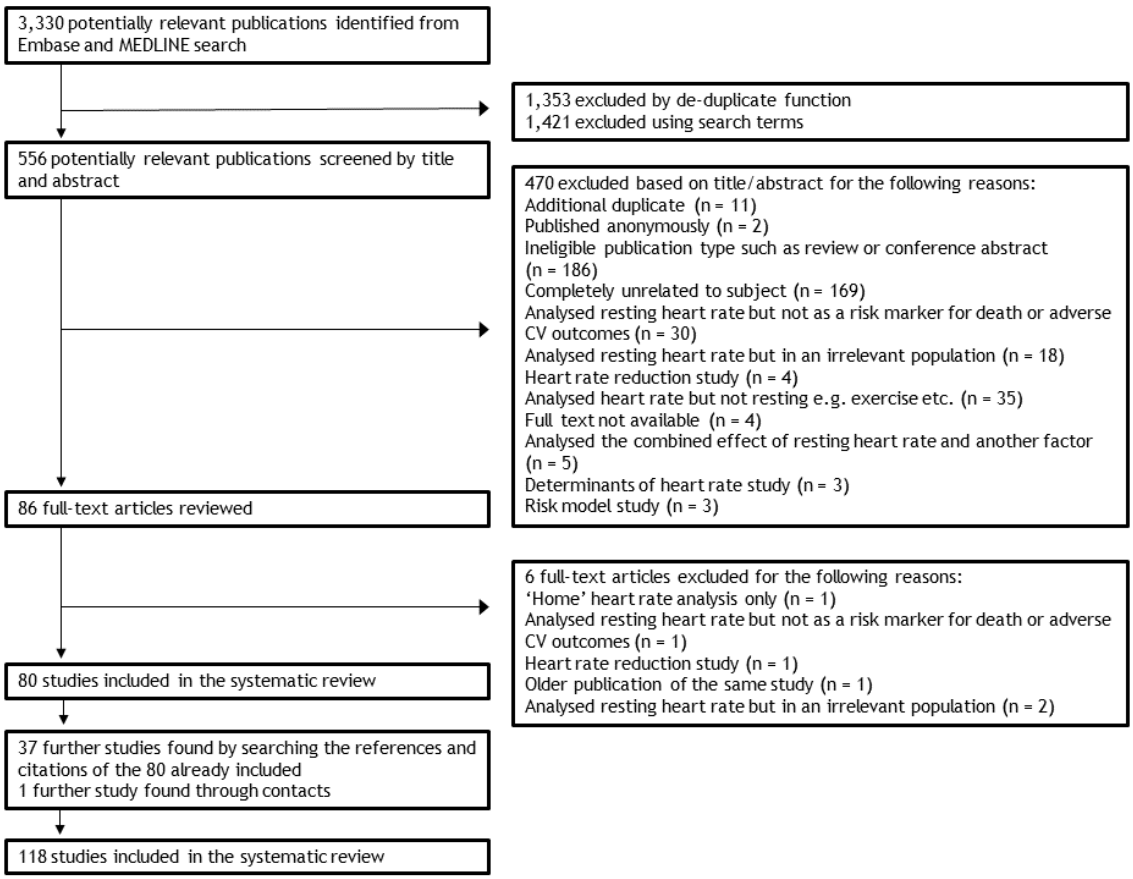
Study quality was appraised using the 9-star Newcastle-Ottawa Scale[96], which is widely used for assessing the quality of observational studies and post-hoc clinical trial analyses. It awards a maximum of nine stars to each study being assessed, with higher quality studies attaining a greater number of stars. Stars are awarded in relation to the following three categories: selection (4 stars); comparability (2 stars); and outcome (3 stars).

2.3 Results

As shown by Figure 2-1, the search of Ovid returned 3,330 studies. After exclusion of duplicates using the de-duplicate function in Ovid, and irrelevant groups of studies using search terms (see Table A1-2), 556 studies remained. The remaining studies were screened by title and abstract, and a further 470 were excluded for the reasons outlined in Figure 2-1. Thus, 86 full-text articles remained to be reviewed. Of the remaining 86

articles, 6 were excluded for the reasons outlined in Figure 2-1, which left 80 studies to be included. Searching the reference and citation lists of each of these remaining 80 studies identified a further 37 studies for inclusion, and 1 other publication was found through academic contacts. Thus, 118 studies were included in this systematic review, published as far back as 1980.

Figure 2-1: Flow chart of the selection process of the studies included in the systematic review.



2.3.1 Baseline Heart Rate Studies

A total of 98 of the 118 studies chosen for inclusion analysed the risk associated with a single heart rate measurement obtained at the beginning of follow-up. They were grouped into the following 11 categories and are discussed accordingly: (1) general populations of participants; (2) subjects with diabetes; (3) subjects with hypertension; (4) subjects with CHD; (5) post-MI/ACS subjects; (6) subjects with HF; (7) subjects with left-ventricular (LV) dysfunction; (8) CABG subjects; (9) subjects with mixed types of vascular disease; (10) post-stroke subjects; and (11) subjects with kidney disease. The

quality of each study, appraised using the Newcastle-Ottawa Scale[96], is given in Table A1-3 provided in Appendix 1. Study quality was high, ranging from 5 to 9 stars: 95 out of the 98 studies were awarded 7 stars or more.

2.3.1.1 General Populations

A total of 42 of the 98 single heart rate measurement studies found analysed baseline heart rate as a predictive risk marker for adverse events in subjects drawn from the general population, often with no evidence of existing CV disease or CHD. An overview of each of these studies is given in Table A1-4 provided in Appendix 1. The length of follow-up ranges from three years[97] to 40 years[98]. The number of subjects included ranged from 131[99] to 379,843[100].

The earliest study included in the review was published in 1980 by Dyer et al.[101] and included one group of middle-aged white men with no known heart disease from the Chicago Peoples Gas Company study. After adjustment for age, cholesterol, blood pressure, weight and smoking, an elevated baseline resting heart rate predicted an increase in the risk of sudden and all-cause death in the Gas Company cohort. Since then, elevated resting heart rate has also been found to be independently associated with an increase in the risk of all-cause death in middle-aged French[102], Jewish-Israeli[103], Italian[104], Japanese[105] and Danish men[106]. Shaper et al. 1993 further examined the risk of sudden death in middle-aged British men with and without pre-existing CHD, and found that an elevated heart rate predicted an increase in risk in those with no evidence of CHD, but was not associated with risk in those with pre-existing CHD[107].

Dyer et al. 1980 did not find any significant associations between heart rate and CV death or CHD death in any of the three cohorts[101]. Similarly, Shaper et al. 1993 found no association between heart rate and risk of CHD death, or major CHD events, in either group of subjects analysed[107]. However, Kristal-Boneh et al. 2000[103] and Seccareccia et al. 2001[104] found that a baseline resting heart rate ≥90bpm was associated with a 95%

(95% CI 10 to 280%) and a 154% (95% CI 25 to 416%) increase in the risk of CV death compared to a heart rate <70bpm, and <60bpm, respectively.

Batty et al. 2010 examined the risk of all-cause, CHD and stroke death in middle-aged government employees from London, but found no associations between heart rate and risk[98]. Compared to a heart rate ≤64bpm, a heart rate >75bpm was borderline significantly associated with an increase in risk of all-cause death (HR 1.17, 95% CI 0.99 to 1.37), so there may have been an insufficient number of events for the result to reach significance (n = 942). The number of CHD and stroke deaths were also relatively small (n = 307 and n = 90, respectively). Of the 42 studies, a total of 16 analysed outcomes in both men and women, but did so separately for each gender[100,108-122].

In contrast to the studies discussed previously, Benetos et al. 1999[112] and Tverdal et al. 2008[100] found that an elevated heart rate was associated with an increase in the risk of CHD death in middle-aged men from France, and Norway, respectively. For example, a 10bpm higher baseline heart rate was associated with a 12% increase in the risk of CHD death (95% CI 6 to 18%), after adjustment for cholesterol, triglycerides, DBP, smoking, physical activity and family history[100]. Both of these studies further confirmed that heart rate is associated with all-cause and CV death, but did not find significant associations with stroke death. Tverdal et al. 2008 also assessed risk of sudden death, but no increase in risk with higher heart rate was observed (note that the subjects had no history of CV disease)[100]. Reunanen et al. 2000 examined associations between heart rate and risk of all-cause, CV, CHD and stroke death in middle-aged Finnish men with and without pre-existing heart disease, and found that heart rate was not associated with any of the outcomes in men free of heart disease, but was associated with all-cause and CV death in men with heart disease, despite the number of events being much higher in those without heart disease[113].

The relationship between heart rate and risk has also been evaluated in older men. While some studies have found that an elevated heart rate is associated with an

increase in risk of all-cause death[111,122], CV death[111] and CHD death[118,122] in older men, others have not[110,114,115]. For example, Okamura et al. 2004 found that a heart rate ≥78bpm was associated with a 155% (p = 0.01), 299% (p = 0.03) and 45% (p = 0.02) increase in the risk of CV death, CHD or HF death, and all-cause death, respectively, in young to middle-aged men, but found no associations in older men, despite the number of events being higher in the older age group of men[115].

While earlier studies examined only fatal endpoints, and found no associations between heart rate and stroke death, the more recent study by Mao et al. 2010 found that an elevated heart rate was associated with an increase in risk of fatal and non-fatal CV disease, heart disease, CHD, and haemorrhagic stroke in a large population of Chinese men aged 40 years or older[120]. A 10bpm higher resting heart rate was associated with an 8% increase (95% CI 1 to 16%) in fatal or non-fatal haemorrhagic stroke after multivariate adjustment. The association between an elevated continuous heart rate and the risk of all fatal or non-fatal stroke was also borderline significant: a 10bpm increment was associated with a 4% increase (95% CI 0 to 8%) in risk. No significant association was observed in relation to fatal or non-fatal ischemic stroke, however the number of such events was much smaller than all of the other events analysed.

The association between heart rate and the risk of adverse outcomes are less consistent among women drawn from the general population. An elevated resting heart rate has been found to be associated with an increase in risk of all-cause death in younger to middle-aged women in some studies[100,110,112,115] but not in others[113,122]. Similarly, the majority of studies that have assessed the risk of CV death have not found any associations with heart rate[100,112,113,115]. Greenland et al. 1999, on the other hand, found that a 12bpm higher heart rate was associated with a 13% increase in the risk of CV death (95% CI 2 to 25%) in the middle-aged subgroup of women analysed[110]. The risk of CHD death has also been found to be related to heart rate in some studies of younger to middle-aged women[110,115,118], but not in others[100,112,113,122].

In older women, heart rate has similarly been associated with all-cause death in some studies[97,114,122,123] but not others. For example, in women aged 67 years or older who were referred for coronary angiography, but did not necessarily have CV disease, Vassalle et al. 2014 showed that a resting heart rate ≥76bpm was associated with a 70% increase in the risk of all-cause death ($p<0.05$)[122]. On the other hand, no significant association between heart rate and the risk of cardiac death was observed. In contrast, Kado et al. 2002 discovered that a 10bpm higher heart rate was associated with a 17% increase in the risk of CHD (95% CI 5 to 30%, $p = 0.003$) in white American women aged 65 or older[123]. However, other studies that have analysed the heart rate-risk relationship in older women found no association with any of the outcomes assessed[111,115,118].

The study by Mao et al. 2010, which included Chinese women aged 40 years or older, found that an elevated resting heart rate was associated with a higher risk of fatal and non-fatal CV disease, heart disease, and CHD after adjustment for multiple other covariates[120]. In addition, Cooney et al. 2010 demonstrated that heart rate was associated with all-cause, CV, and CHD death, as well as fatal and non-fatal CHD, in women aged 25 to 74 from Finland[119]. Hsia et al. 2009 further discovered that a heart rate ≥76bpm was associated with a 26% increase (95% CI 11 to 42%) in the risk of MI or coronary death[124]. So far, no significant associations between heart rate and the risk of sudden death[100], stroke death[100,112,113,123] or fatal or non-fatal stroke events[120,124] have been observed among women-only populations.

A reason why an association between heart rate and risk of outcome is often not found in women when it is in men may be because the number of events that occur in female subjects are often less than the number that occur in male subjects, because less females are included than males[100,110,112,113]. For example, in the study population of Benetos et al. 1999, 2036, 664, 370 and 125 all-cause, CV, CHD and stroke deaths,

respectively, occurred among the men, of whom there were 12123, whereas only 610, 180, 66 and 63 of each event occurred among the women, of whom there were 7263[112].

A total of 15 of the studies analysed outcomes in combined populations of men and women from the general population[66,99,125-136]. The first such study was carried out in 2007[125].

In such populations, heart rate has been shown to be associated with all-cause death[126,128,130-135], CV death[126,128,130,135], sudden death[137] and HF death[135]. For example, after adjustment for markers of inflammation as well as conventional risk factors, Jensen et al. 2012 found that a 10bpm higher resting heart rate was associated with a 9% (95% CI 5 to 14%) and 14% (95% CI 7 to 22%) increase in the risk of all-cause and CV death, respectively[128]. In a case-control study, Teodorescu et al. 2013[137] discovered that a 10bpm higher heart rate was associated with an 18% increase in the risk of sudden death ($p = 0.005$) after adjustment for risk factors including beta-blocker use and severe LVSD, and Woodward et al. 2014[135] found that an elevated heart rate was associated with a 106% (95% CI 5 to 302%) increase in the risk of HF death after adjustment for multiple variables.

Aladin et al. 2014[133] further examined the relationship between heart rate and the risk of major adverse cardiac events (all-cause death, MI, or revascularisation), MI and revascularisation in men and women without known CHD or AF, by gender, even though it presented results for all-cause death for both sexes analysed together. After adjustment for conventional risk factors, a heart rate ≥90bpm was associated with a higher risk of major CV events in both sexes, and of revascularisation in women. No significant associations between heart rate and the risk of MI were observed in either sex, which may have been due to a small number of events (n = 166 in men and n = 77 in women). Interestingly, no significant association with revascularisation was observed in men, even though the number of events was higher among men than women (n = 312 in men and n = 74 in women). When models were additionally adjusted for estimated

exercise capacity, all associations were attenuated. However, in a larger population of men and women from China, analysed together, a 10bpm higher heart rate was associated with a 10% increase in the risk of MI (95% CI 1 to 20%) in the most adjusted model[134]. The study also assessed the risk of all CV disease, any stroke, ischemic stroke, and haemorrhagic stroke, but no significant associations with heart rate were observed when the most adjusted model was used. In contrast, in an even larger study, Woodward et al. 2014 found that an elevated heart rate was associated with a higher risk of fatal and non-fatal CV disease, all stroke, haemorrhagic stroke, ischemic stroke, and unclassified stroke[135].

Jensen et al. 2011 investigated the association between heart rate and all-cause and CV death in relation to smoking status[127]. Time-dependent Cox models which accounted for changes in use of hypertensive medication, heart medication, and whether or not subjects had AF, revealed that a continuously higher heart rate was associated with a higher increase in risk of both all-cause and CV death in heavy, moderate and former smokers, compared to subjects who had never smoked. A 10bpm higher heart rate was associated with a 6%, 11% and 13% increase in the risk of all-cause death in subjects who had never smoked, were former smokers, and were current smokers, respectively. Similarly, a 10bpm increase was not found to be associated with risk of CV death in those who had never smoked (HR 1.06, 95% CI 0.99 to 1.13), but was associated with an 11%, 15% and 13% increase in risk in former, moderate and heavy smokers, respectively.

Cacciatore et al. 2007[125] and Pittaras et al. 2013[131] specifically evaluated the relationship between heart rate and all-cause death in older individuals. In a population of Italian subjects aged 65 years or older, Cacciatore et al. 2007 assessed whether the presence or absence of cognitive impairment affected the heart rate-risk relationship[125]. An elevated heart rate was not found to be associated with a higher risk of death in the whole study population (relative risk (RR) 0.69, 95% CI 0.27 to 1.73) or in those with cognitive impairment (RR 0.91, 95% CI 0.81 to 1.02). However, in those free

of cognitive impairment, an elevated heart rate was associated with a 10% increase in risk. Pittaras et al. 2013 found that subjects aged 60 years or older with a heart rate ≥70bpm were at a higher risk of death compared to those with a heart rate <60bpm[131].

Three recent studies focused on the risk of developing HF in relation to heart rate[129,66,136]. Pfister et al. 2012[129] and Opdahl et al. 2014[66] demonstrated that a 10bpm higher heart rate was associated with an 11% (95% CI 5 to 17%) and a 48% (95% CI 22 to 79%) increase in the risk of developing HF after multivariate adjustment, respectively. Opdahl et al. 2014 further found that a 10bpm increase was associated with a 97% ($p<0.001$) and 34% ($p = 0.028$) increase in risk in women and men, respectively[66].

Khan et al. 2015 was an interesting study[136]. In an individual participants pooled analysis of three population-based cohorts including some subjects on beta-blockers and with a history of CV disease, it was discovered that a 10bpm higher heart rate above 60bpm was associated with a 13% (95% CI 7 to 18%, $p<0.001$) increase in the risk of developing HF. Differences in the relationship between subjects with preserved and reduced ejection fraction (EF) were assessed, but none were found. A meta-analysis including the three population-based cohorts, as well as the results previously presented by Pfister et al. 2012[129] and Opdahl et al. 2014[66], and two other previously published studies (Nanchen et al. 2013[138] included in Section 2.3.1.9 and Nanchen et al. 2013[139] included in Section 2.3.2.1), was subsequently performed. This analysis showed that overall, an elevated heart rate was associated with a 40% increase in the risk of developing HF (95% CI 19 to 64%).

2.3.1.2 Subjects with Diabetes

Three of the studies found investigated the relationship between heart rate and adverse outcomes in subjects with diabetes. An overview of each of these studies is given in Table A1-5 provided in Appendix 1.

Stettler et al. 2007[140] and Hillis et al. 2012[141] demonstrated that an elevated baseline resting heart rate was associated with an increase in risk of all-cause and CV death in subjects with type 2 diabetes. In addition, Stettler et al. 2007 found that a 10bpm higher resting heart rate was associated with a 45% and 52% increase in the risk of cardiac death and CHD death, respectively, in subjects with type 2 diabetes[140]. Moreover, Hillis et al. 2012 found that the risk of a major CV event (CV death, non-fatal MI, or stroke) was 8% higher ($p = 0.009$) per 10bpm increment in heart rate[141].

While Stettler et al. 2007 found that an elevated heart rate was associated with an increase in risk of each of the endpoints analysed, no such associations were observed in the subjects with type 1 diabetes included in the study[140]. However, the number of events that occurred in the type 1 diabetes subjects, of whom there were 221, were smaller than those that occurred in the type 2 subjects, of whom there were 302, which may explain this. For example, the total number of deaths that occurred in type 2 subjects was 158, whereas the total number that occurred in type 1 subjects was 107; in regards to CHD death, the number of events that occurred in the type 2 subjects was more than double the number that occurred in the type 1 subjects.

Hillis et al. 2012 also performed competing risk analyses which adjusted for all-cause death as the competing event[140]. In this case, the sub-distribution HRs of CV death and all major CV events were 1.15 (95% CI 1.07 to 1.25, $p<0.001$) and 1.07 (95% CI 1.01 to 1.13, $p = 0.01$), respectively. Miot et al. 2012 similarly assessed whether resting heart rate was a predictor of the cumulative incidence of the combined primary outcome of CV death, non-fatal MI, non-fatal stroke, hospitalisation for HF, or onset of end-stage renal disease, adjusting for non-CV death as a competing risk, in type 2 diabetes subjects[142]. The analysis was stratified by whether or not subjects had CV disease at baseline, and the Fine and Gray model[143] was used. A baseline resting heart rate ≥70bpm was found to be associated with a higher risk of the primary endpoint in patients with CV disease ($p = 0.026$) but not in those without ($p = 0.628$).

2.3.1.3 Subjects with Hypertension

Four of the studies found evaluated the relationship between heart rate and adverse outcomes in subjects with hypertension. An overview of each of these studies is given in Table A1-6 provided in Appendix 1.

In a population of hypertensive subjects not taking anti-hypertensive medication at baseline, Gillman et al. 1993 assessed the association of heart rate with all-cause death, CV disease death, CHD death, sudden death, and incidence of CV disease and CHD[144]. The male and female subjects were analysed separately. The analysis demonstrated that a 40bpm higher heart rate was associated with a 98% (95% CI 52 to 159%) and an 87% (95% CI 37 to 156%) increase in the risk of all-cause death in men and women, respectively. An higher risk of CV disease death and CHD death was only observed in the male subjects. This may have been because the numbers of events among the women were smaller than those among the men: the number of CV disease and CHD deaths among the men were 267 and 187, respectively, whereas among the women there were only 151 and 78. In addition, elevated heart rate was not associated with sudden death, CV disease, or CHD in either sex, but again the numbers of events were small.

King et al. 2006 further analysed the risk of incident CHD and all-cause mortality in subjects with pre-hypertension with no evidence of CHD[145]. Pre-hypertension is defined as an SBP between 120 and 139mmHg or a DBP between 80 and 89mmHg, and can be seen as a warning that you may become hypertensive in the future. A heart rate ≥80bpm was found to be associated with a 47% increase (95% CI 2 to 114%) in the risk of all-cause mortality. Due to differences in hypertension and prognosis between men and women, the analysis was subsequently stratified by gender. However, the association was not maintained when men and women were analysed separately. Conversely, a heart rate ≥80bpm was associated with a 188% increase (95% CI 8 to 342%) in the risk of incident CHD in women, but not in men or when both sexes were analysed together.

In a small population of 528 subjects with resistant hypertension (already stable on three or more antihypertensive treatment drugs), Salles et al. 2013 analysed the association between both slow (<60bpm) and fast (>75bpm) ECG and clinic (pulse) heart rates and the risk of all-cause death, CV death and the composite of all fatal or non-fatal CV events[146]. Compared to a heart rate between 60 and 75bpm, only a slow ECG heart rate was associated with a higher risk of the combined endpoint after multivariate adjustment (HR 4.40, 95% CI 1.06 to 8.37). However, only a small number of events occurred in the population (n = 94, 62 and 44 of the combined endpoint, all-cause death, and CV death respectively) which may be a reason for no other associations being observed.

In elderly subjects with isolated systolic hypertension, a baseline heart rate >79bpm has been shown to be associated with an 89% increase in risk of all-cause death ($p<0.001$) and a 60% increase in the risk of CV death ($p<0.05$)[147].

2.3.1.4 Subjects with CHD

Four of the studies found examined the relationship between baseline resting heart rate and adverse outcomes in subjects with CHD. An overview of these studies is given in Table A1-7 provided in Appendix 1.

Both Diaz et al. 2005[148] and Ho et al. 2010[149] found that an elevated resting heart rate at baseline was associated with a higher risk of all-cause death and HF hospitalisation in subjects with CHD. A small percentage of the subjects included in the study by Ho et al. 2010 had a history of HF, but models were adjusted for this[149]. Neither study found an association between heart rate and the risk of MI or stroke, and Diaz et al. 2005 found no association between heart rate and hospitalisation due to angina. On the other hand, Diaz et al. 2005 established that a heart rate ≥83bpm was associated with a 31% (95% CI 15 to 48%) and a 14% (95% CI 2 to 27%) increase in the risk of CV death and CV hospitalisation (hospitalisation due to MI, angina, stroke, revascularisation or rhythm disturbance), respectively[148]. Similarly, Ho et al. 2010 ascertained that a 10bpm higher

baseline heart rate was associated with an 8% (p = 0.01) increase in the risk of major CV events, defined as CHD death, non-fatal MI, stroke, or a resuscitated cardiac arrest[149].

Anselmino et al. 2010 assessed the association with risk of all-cause death and CV events (all-cause death, non-fatal MI or stroke) in subjects with CHD with or without diabetes, some of whom had prior congestive HF[150]. A 10bpm higher heart rate was shown to be associated with a 34% (p = 0.015) increase in the risk of all-cause death in subjects with diabetes after adjustment for confounding variables, but not in those without. However, the number of deaths was slightly less in subjects without diabetes (49 in subjects with diabetes and 37 in those without). No associations between heart rate and the risk of the CV events endpoint were observed in either group of subjects.

In a broad unselected population of patients with stable CHD, Ortiz et al. 2010 found no associations between heart rate and the risk of major CV events (all-cause death, ACS, coronary revascularisation, stroke or admission to hospital for HF), coronary events (ACS or revascularisation) or all-cause death[151]. This may have been because the population was at low risk of CV events, or because the number of events was too small for significant differences to be detected (222 major CV events, 161 coronary events, and 33 all-cause deaths).

2.3.1.5 Post-MI/ACS Subjects

The risk associated with heart rate measured at a single point in time was evaluated in 19 studies of subjects who had experienced an ACS, six of which were conducted in the pre-PCI era[152-157]. The term ACS refers to any event that is caused by the blood supply to the heart muscle becoming suddenly blocked, and includes unstable angina, non-ST-elevation MI (NSTEMI), and ST-elevation MI (STEMI)[158]. An overview of each of these studies is given in Table A1-8 provided in Appendix 1.

A total of 15 of the 19 studies assessed the predictive value of admission heart rate[152-155,157,159-168,]. Elevated admission heart rate has been shown to be associated with a

higher risk of in-hospital mortality in patients hospitalised with MI[153,154,157,164,165] and ACS[160]. Honda et al. 2010, for example, demonstrated that an admission heart rate ≥93bpm was associated with an increased risk of in-hospital mortality (odds ratio (OR) 8.5, 95% CI 1.4 to 49, p = 0.018), in patients hospitalised within 24 hours of acute MI[157]. In patients who were hospitalised with non-ST-segment elevation ACS, and were part of the CRUSADE study, which encompassed 550 hospitals across the US, Bangalore et al. 2010 found that a heart rate >130bpm was associated with a 93% increase in the risk of in-hospital mortality (compared to an admission heart rate between 60 and 69bpm), using generalised estimating equations to account for within-hospital clustering[160].

Bangalore et al. 2010 also discovered that a heart rate <50bpm was associated with a 61% increase in the risk of in-hospital mortality[160]. Similarly, Asaad et al. 2014 showed that an admission heart rate <60bpm was associated with a higher risk of in-hospital mortality in patients diagnosed with unstable angina, NSTEMI or STEMI/left bundle branch block[167].

In addition, elevated admission heart rate has been shown to be associated with an increase in risk of some other in-hospital endpoints in patients hospitalised for MI and ACS. Salwa et al. 2015 showed that an elevated admission heart rate was associated with a higher risk of in-hospital CV mortality (OR 1.51, 95% CI 1.25 to 1.82), in patients with STEMI (it is not clear from the publication what cut-off value of heart rate was associated with this result)[168]. Honda et al. 2010[157] demonstrated that an admission heart rate ≥93bpm was associated with a higher risk of poor LV function (left-ventricular ejection fraction (LVEF) <50% before discharge) (OR 2.2, 95% CI 1.1 to 4.7, p = 0.033), while Asaad et al. 2014[167] discovered that a heart rate >89bpm was associated with a higher risk of in-hospital HF (OR 2.2, 95% CI 1.39 to 3.32, p = 0.001). Moreover, Bangalore et al. 2010 found that both high and low admission heart rates were associated with an elevated risk of in-hospital stroke[160]. For example, a heart rate <50bpm was associated with a 98% increase in the risk of in-hospital stroke, and a heart

rate >130bpm was associated with a 79% increase in risk. The study also evaluated the relationship between heart rate and the risk of in-hospital re-infarction, but no significant associations were observed.

The risk of post-discharge mortality has also been shown to increase with elevated admission heart rate in patients hospitalised with MI[152-154,159,162,164,166] and ACS[155,161,163]. For example, Parodi et al. 2010 showed that a 5bpm higher admission heart rate was associated with a 32% increase in the risk of 6-month post-discharge mortality in a population of patients with STEMI undergoing PCI[159]. In a population of patients with ACS, Facila et al. 2012 found that an admission heart rate (measured three to seven days after the occurrence of ACS) ≥70bpm was associated with a 150% increase in the risk of 1-year post-discharge mortality (95% CI 26 to 397%, p = 0.009), independent of other known risk factors[163].

The relationship between admission heart rate and risk has further been examined specifically in patients with AF, and with and without diabetes. Li et al. 2013 studied the association between admission heart rate and the risk of one-year post-discharge mortality in post-STEMI and non-STEMI patients in AF[166]. The analysis found that patients with an admission heart rate ≥95bpm were at 4.69 times (95% CI 1.47 to 15.01, p = 0.01) the risk of 1-year mortality compared to patients with a heart rate <95bpm after adjustment for confounders. In patients with anterior wall STEMI without diabetes, Davidovic et al. 2013 demonstrated that an admission heart rate ≥80bpm was associated with an 8% increase in the risk of in-hospital mortality (95% CI 1 to 15%, p = 0.033)[165]. Han et al. 2012 examined the association between admission heart rate and 30-day all-cause mortality, and CV events (all-cause mortality, re-infarction or stroke) in relation to the presence of type 2 diabetes, in patients admitted to hospital for STEMI[162]. In patients without type 2 diabetes, each of the three heart rate groups above 66bpm (67-76bpm, 77-88bpm, and >88bpm) were associated with a higher risk of both 30-day mortality and CV events. In patients with type 2 diabetes, only heart rates

between 77 and 88bpm, and >88bpm, were associated with a higher risk of 30-day events. Only a heart rate >88bpm was associated with an increased risk of 30-day mortality. The insignificance of the other heart rate groups may have been due to the small number of diabetic subjects included in the analysis (820 with diabetes, 6474 without). However, a significant interaction between heart rate and diabetes was observed for 30-day CV events ($p = 0.035$). This indicated that an elevated heart rate had greater adverse effect in subjects with type 2 diabetes, since the HRs in each heart rate group were larger in those subjects, than in those without diabetes. For example, a heart rate >88bpm was associated with a 130% increase in 30-day CV events in those without diabetes (95% CI 87 to 183%, $p<0.001$), and a 200% increase in those with diabetes (95% CI 76 to 414%, $p<0.001$). No significant interaction was observed for 30-day all-cause mortality ($p = 0.126$).

The remaining four of the 19 studies evaluated the predictive value of discharge heart rate[156,169-171]. Antoni et al. 2012[169] and Seronde et al. 2014[171] discovered that an elevated discharge heart rate was associated with a higher risk of post-discharge mortality in patients admitted to hospital with MI. For example, a 10bpm higher discharge heart rate was associated with a 9% increase in the risk of 5-year post-discharge mortality ($p = 0.015$)[171]. In subjects with stable or unstable ACS treated with PCI followed-up for two years, Jensen et al. 2013 further demonstrated that a 1bpm higher discharge heart rate was associated with a 4.1% ($p<0.001$) increase in mortality post-discharge[170].

The risk of other post-discharge outcomes has also been evaluated in relation to discharge heart rate. Mauss et al. 2005 revealed that elevated discharge heart rate was an independent predictor of the combined endpoint of all-cause mortality and arrhythmic events (such as sudden death and resuscitated ventricular fibrillation) ($p = 0.008$) in patients presenting with acute MI[156]. The risk of CV mortality at one and four years after discharge has been shown to increase by 29% and 26% (both $p<0.001$) in

relation to a 5bpm higher heart rate in patients admitted with STEMI treated with PCI[169]. Jensen et al. 2013 further discovered that a 1bpm higher heart rate was associated with a 2.9% increase in risk of the composite of CV mortality or non-fatal MI ($p = 0.011$)[170].

Finally, subgroup analyses performed by Seronde et al. 2014 showed significant differences in the association between discharge heart rate and risk of death in STEMI and non-STEMI patients ($p = 0.002$), and patients with LV dysfunction ($p < 0.001$)[171]. A heart rate ≥75bpm was associated with an 82% (95% CI 39 to 138%, $p<0.001$) increase in the risk of 5-year post-discharge mortality in non-STEMI patients, whereas no association between heart rate and risk was observed in STEMI patients ($p = 0.62$). Similarly, a heart rate ≥75bpm was associated with a 79% (95% CI 49 to 115%, $p<0.001$) increase in risk in patients with LV dysfunction, whereas no association was observed in those with preserved LV function ($p = 0.89$).

2.3.1.6 Subjects with HF

The risk associated with elevated heart rate measured at the beginning of follow-up was analysed in ten studies of subjects with HF. An overview of each of these studies is given in Table A1-9 provided in Appendix 1.

Of the ten studies, five evaluated the heart rate-risk association in subjects with chronic HF[172-176]. Among subjects with chronic HF in sinus rhythm with preserved EF, an elevated baseline resting heart rate has been shown to be associated with an increase in the risk of all-cause death[172,174-176], CV death[175,176], HF death[176] and HF hospitalisation[174,175]. For example, Takada et al. 2014 demonstrated that the highest third of the distribution of heart rate was associated with an 82% (95% CI 23 to 169%) and a 96% (95% CI 5 to 272%) increase in the risk of all-cause and CV death, respectively[176]. The middle third of heart rate was found to be associated with a 229% (95% CI 5 to 933%) increase in the risk of HF death, and the highest third was borderline significantly associated with an increase in risk (HR 3.16, 95% CI 0.99 to 10.10). There

were only 32 HF deaths in the total study population, however, (including the subjects with reduced EF) which may explain the large CIs and borderline significant association. The study did not observe any association between elevated heart rate and risk of HF hospitalisation. On the other hand, Bohm et al. 2014 illustrated that a 12.4bpm (one standard deviation) higher heart rate was associated with an 18% (p = 0.001) increase in the risk of HF hospitalisation[175].

An elevated baseline resting heart rate has also been discovered to be associated with an increase in the risk of all-cause death[174,176] and HF hospitalisation[174] among subjects with chronic HF in sinus rhythm with reduced EF. For example, Maeder and Kaye 2012 found that a heart rate >87bpm was associated with a 16% (p = 0.02) and a 31% (p<0.001) increase in the risk of all-cause death and HF hospitalisation, respectively, compared to a heart rate <71bpm[174]. In addition, Takada et al. 2014 established that the highest third of the distribution of heart rate was associated with an 80% (% CI 17 to 178%) increase in the risk of all-cause death[176]. However, no associations between heart rate and the risk of CV death, HF death or HF hospitalisation were observed.

Castagno et al. 2012 further discovered that a 10bpm higher heart rate was associated with a 6% (95% CI 2 to 10%) and a 7% (95% CI 3 to 10%) increase in the risk of all-cause death, and the combined endpoint of CV death or HF hospitalisation, respectively, in a population of subjects in either sinus rhythm or AF, with an LVEF ≤40%[173]. No association between heart rate and risk of all-cause death was observed in subjects with an LVEF >40%, and a borderline significant association between heart rate and the combined endpoint was found (HR 1.06, 95% CI 1.00 to 1.12). The interaction of effect between heart rate and LVEF was tested, but no significant interaction was discerned (p = 0.80 for all-cause death; p = 0.88 for CV death or HF hospitalisation).

Castagno et al. 2012 additionally stratified subjects by whether they were in sinus rhythm or AF[173]. In subjects in sinus rhythm with either reduced or preserved EF, a 10bpm higher heart rate was associated with an 8% (95% CI 4 to 12%) and a 10% (95% CI 6

to 13%) increase in the risk of all-cause death, and CV death or HF hospitalisation, respectively. Conversely, no associations between heart rate and the risk of either endpoint were established in subjects in AF. A significant interaction of effect between heart rate and rhythm was observed for both outcomes ($p<0.001$ for both). Bohm et al. 2014 also analysed the relationship between heart rate and outcome in subjects specifically in AF with a preserved EF[175]. In this population, no associations between heart rate and risk of any of the endpoints assessed were observed. In contrast, an elevated heart rate was found to be associated with a higher risk of all of the endpoints in the subjects in sinus rhythm. However, the number of subjects in AF included in the analysis (n = 696) was less than a quarter of the number of subjects in sinus rhythm (n = 3,271) which may be a reason for such a result.

The other five studies yet to be discussed evaluated the heart rate-risk relationship in patients with acute HF[177-181]. Admission heart rate was analysed by three of the studies[177,179,180] and discharge heart rate was analysed by the remaining two[178,181].

Elevated admission heart rate has been shown to be associated with an increase in the risk of in-hospital mortality in acute HF patients in sinus rhythm or AF, analysed as a combined group[177,179], and in subjects in sinus rhythm[177,180] and AF[177] analysed separately. For example, Bui et al. 2013 demonstrated that a 10bpm higher heart rate, in subjects with an admission heart rate between 70 and 105bpm, was associated with a 23% (95% CI 19 to 27%) increase in the risk of in-hospital mortality in patients in either AF or sinus rhythm[177]. Similarly, a 10bpm increase was associated with a 21% (95% CI 15 to 28%) increase in risk in sinus rhythm patients, and was associated with a 20% (95% CI 14 to 27%) increase in risk in AF patients. Kaplon-Cieslicka 2014 similarly established that a 10bpm higher admission heart rate was associated with a 59.4% (95% CI 6.1 to 139.5%) increase in the risk of in-hospital HF in a population of Polish patients in either AF or sinus rhythm[179]. However, when the sinus rhythm and AF patients were analysed

separately, heart rate was not found to be associated with risk. This may have been due to the fact that only 21 in-hospital deaths occurred.

In patients hospitalised for HF in sinus rhythm, Habal et al. 2014 discovered that a discharge heart rate >90bpm was associated with a 56% (p = 0.007), 65% (p = 0.017), 26% (p = 0.021) and 29% (p = 0.004) increase in the risk of 30-day post-discharge all-cause death, CV death, readmission for HF, and readmission for CV disease, respectively[178]. The risks of the same outcomes at 1-year post-discharge were also evaluated. A discharge heart rate >90bpm was similarly associated with a 41% (p<0.001) and 47% (p = 0.005) increase in the risk of all-cause and CV death, respectively, but no significant associations were observed for readmission for HF or CV disease. The risk of 30-day and 1-year post-discharge readmission for CHD was also evaluated, but no associations between heart rate and risk were observed at either time point.

Laskey et al. 2015 assessed the relationship between discharge heart rate and risk in patients hospitalised for HF either in sinus rhythm or AF[181]. A 10bpm higher heart rate in patients in sinus rhythm with a discharge heart rate ≥75bpm was associated with an 18.5% (p<0.001) and 6.3% (p<0.001) increase in the risk of 1-year post-discharge all-cause death, and all-cause readmission, respectively. Similarly, a 10bpm increase in patients in AF with a discharge heart rate ≥75bpm was associated with an 8.8% (p<0.001) and a 3.3% (p = 0.0046) increase in each of the endpoints, respectively. The effect of LVEF was also explored in the sinus rhythm and AF patients separately. No significant interactions between heart rate and LVEF were observed in the sinus rhythm patients in relation to either of the endpoints. On the other hand, significant interactions between heart rate and LVEF were observed in the AF patients for both of the endpoints (p = 0.01 for all-cause death and p = 0.003 for all-cause readmission).

2.3.1.7 Subjects with LV Dysfunction

Three of the studies found assessed the relationship between baseline resting heart rate and risk of adverse outcomes in subjects all of whom had LV dysfunction. An overview of each of these studies is given in Table A1-10 provided in Appendix 1.

In subjects with LV dysfunction, an elevated resting heart rate at baseline has been found to be associated with an increase in the risk of all-cause death[182,183], CV death[182,184], and hospital admission for HF[182,184]. Bohm et al. 2010, for example, ascertained that a baseline heart rate ≥87bpm was associated with an 86% ($p<0.001$), an 85% ($p<0.001$), and a 199% ($p<0.001$) increase in the risk of all-cause death, CV death, and hospital admission for HF, respectively, compared to a heart rate <72bpm[182]. The study also showed that a heart rate ≥87bpm was associated with a 134% ($p<0.001$) increase in the risk of death due to HF. Fox et al. 2008 previously demonstrated that the risk of hospital admission for MI and coronary revascularisation are also related to resting heart rate. A baseline resting heart rate ≥70bpm was associated with a 46% ($p = 0.0066$) and a 38% ($p = 0.037$) increase in the risk of hospital admission for MI, and coronary revascularisation, respectively, compared to a heart rate <70bpm[184].

Fosbol et al. 2010 assessed differences in the effect of resting heart rate on long-term mortality (follow-up was at least ten years) in patients with LVEF ≤35% who had previously been hospitalised due to an MI or HF[183]. A 10bpm higher heart rate was associated with a 16% ($p<0.001$) increase in the risk of mortality in the subgroup of post-MI patients, and a 9% ($p<0.001$) increase in the subgroup of patients with HF. No significant interaction of effect between resting heart rate and HF or MI was observed in relation to long-term mortality ($p = 0.2$). Conversely, when one-year mortality was investigated, a significant interaction effect was observed ($p<0.001$). While an elevated heart rate remained associated with an increase in the risk of one-year mortality in the MI patients, no such association was observed in the HF patients.

2.3.1.8 CABG Subjects

Three of the studies found analysed the association between heart rate measured at a single point in time and risk in subjects who were about to have, or had previously underwent, CABG surgery. An overview of each of these studies is given in Table A1-11 provided in Appendix 1.

In patients about to undergo CABG surgery, Fillinger et al. 2002 discovered that an elevated pre-induction heart rate was associated with an increase in the rate of in-hospital mortality (p for trend < 0.001)[185]. The risk of intra- or post-operative stroke was also assessed, but no association with heart rate was observed (p = 0.091). In a similar population of patients, Aboyans et al. 2008 demonstrated that a 10bpm higher pre-operative admission heart rate was associated with a 17% (p = 0.029) increase in the risk of experiencing the primary endpoint of the study (all-cause death, non-fatal MI or non-fatal stroke or transient ischemic attack (TIA)) within 30-days after CABG, after adjustment for age, sex, SBP, LVEF and beta-blocker use[186]. No association between an elevated admission heart rate and risk of the secondary endpoint (all-cause death or non-fatal stroke or TIA) was observed. This may have been because of the smaller number of events.

In patients who had recently undergone CABG surgery, followed-up for just over 3 years, Frank et al. 2010 found that a post-operative heart rate (measured at the first outpatient visit after surgery) ≥90bpm was associated with a 316% (p = 0.04) and a 128% (p = 0.04) increase in the risk of all-cause mortality, and the composite secondary endpoint of the study (all-cause death, secondary coronary revascularisation, non-fatal ACS, non-fatal stroke or TIA, or vascular surgery), respectively[187]. After adjustment for additional risk factors such as off-pump surgery and use of statins, the association with all-cause death was was no longer significant (HR 3.57, 95% CI 0.90 to 14.17, p = 0.07), but remained in regards to the composite secondary endpoint (HR 2.26, 95% CI 1.04 to 4.91, p = 0.04).

2.3.1.9 Subjects with Vascular Disease

Three of the studies were carried out in mixed populations of subjects with some form of vascular disease. An overview of each of these is given in Table A1-12 provided in Appendix 1.

An elevated resting heart rate at baseline has been shown to be associated with an increase in the risk of all-cause death[188,189], CV death[138,188], vascular events[188] and HF hospitalisation[138] in such populations. For example, Bemelmans et al. 2013 demonstrated that a 10bpm higher heart rate was associated with a 15% increase in both the risk of all-cause (95% CI 8 to 22%) and CV (referred to as vascular in the publication) death (95% CI 6 to 25%), and an 8% (95% CI 1 to 15%) increase in the risk of vascular events, in a mixed group of subjects with CHD, cerebrovascular disease, PAD, or abdominal aortic aneurysm, in sinus rhythm[188]. Additionally, van Kruijsdijk et al. 2014 showed that a 10bpm increase was associated with a 13% (95% CI 8 to 19%) increase in the risk of all-cause death after adjustment for competing mortality, using the Fine and Gray model[143], in the same population[189]. Bemelmans et al. 2013 found no association between heart rate and the risk of ischemic stroke or MI[188]. Nanchen et al. 2013 further discovered that a baseline heart rate in the highest third of the distribution was associated with a 62% (95% CI 9 to 141%)and a 48% (95% CI 3 to 113%) increase in the risk of HF hospitalisation and CV death, respectively, compared to a heart rate in the lowest third, in subjects with CHD, cerebral disease, or PAD, or who had hypertension, diabetes or were smokers, after adjustment for conventional risk factors and markers of inflammation and endothelial dysfunction[138].

2.3.1.10 Post-Stroke Subjects

The relationship between heart rate measured at a single time point and risk was evaluated in four studies that included subjects all of whom had recently experienced some form of stroke. An overview of each of these studies in given in Table A1-13 provided in Appendix 1.

An elevated baseline resting heart rate has been found to be associated with an increase in the risk of all-cause death[190,191], vascular death[190,191] and recurrent stroke[191,192] in subjects who had previously had a stroke or TIA. For example, Bohm et al. 2012 revealed that a heart rate >82bpm at baseline was associated with a 74% (95% CI 48 to 106%) and a 78% (95% CI 44 to 122%) increase in the risk of all-cause and vascular death, respectively, when compared to a heart rate ≤64bpm[190]. The risk of any type of recurrent stroke, MI, and chronic HF were also evaluated, but no associations with heart rate were observed. On the other hand, Fox et al. 2013 discovered that a baseline heart rate ≥70bpm, compared to one <70bpm, was associated with a 32% (p = 0.029) and an 11% (p = 0.040) increase in the risk of all fatal or non-fatal MI, and all fatal or non-fatal stroke, respectively[191]. No associations with a heart rate ≥70bpm were observed for non-fatal MI, all fatal or non-fatal ischemic stroke, or non-fatal ischemic stroke. However, a 5bpm higher heart rate was associated with a 9% increase in the risk of non-fatal MI.

Erdur et al. 2014 assessed the association between admission heart rate and the risk of in-hospital mortality in a population of ischemic stroke patients admitted to hospital within 72 hours after onset of symptoms, and found that a 10bpm higher admission heart rate was associated with a 40% (p = 0.003) increase in the risk of in-hospital mortality[193].

2.3.1.11 Subjects with Kidney Disease

Three of the studies found assessed the relationship between baseline heart rate and risk in subjects who had kidney disease. An overview of each of these studies is given in Table A1-14 provided in Appendix 1.

After adjustment for demographics, comorbidities, haemoglobin, physical activity, estimated glomerular filtration rate (eGFR) and baseline medications, Beddhu et al. 2009 showed that a heart rate ≥90bpm was associated with a 264% (95% CI 83 to 612%) increase in the risk of all-cause death in American subjects with chronic kidney

disease[194]. When the same model was used to evaluate the risk of CV events, no association with heart rate was observed. However, only a small number of CV events occurred (n = 110) which may explain this. In a much larger study, including 147,702 Japanese subjects receiving haemodialysis three times a week, Iseki et al. 2011 demonstrated that subjects with a heart rate ≥70bpm were at a higher risk of death compared to those with a heart rate between 60 and 69bpm[195]. For example, patients with a heart rate between 80 and 89bpm were at a 46% ($p<0.001$) higher risk of mortality.

In a similar but much smaller study of Japanese subjects receiving haemodialysis three times a week, Inoue et al. 2012 found that a heart rate ≥80bpm was associated with a 101% (95% CI 1 to 322%) increase in the risk of the composite of all-cause death, ACS, stroke or any other CV event (the secondary endpoint of the study)[196]. The primary endpoint was the same, excluding any other CV events. No association between heart rate and the primary endpoint was observed. However, this may again have been due to the very small number of events that occurred: a total of 14 primary and 18 secondary endpoints.

2.3.2 Multiple Heart Rate Measurement Studies

Of the 118 studies chosen for inclusion in the review, 20 analysed the risk associated with at least one additional heart rate measurement obtained after the beginning of the study, and are thus referred to as multiple heart rate measurement studies. They were grouped into those which included a general population of subjects, and those which included subjects all of whom had a specific pre-existing disease or condition, and are discussed accordingly. The quality of each study, appraised using the Newcastle-Ottawa Scale[96], is given in Table A1-15 provided in Appendix 1. Study quality was high, ranging from 7 to 9 stars.

2.3.2.1 General Populations

A total of eleven of the multiple heart rate measurement studies investigated the association between heart rate and risk in subjects from the general population, often with no existing CV disease or CHD. An overview of each of these studies is given in Table A1-16 provided in Appendix 1.

Five of the studies analysed the prognostic value of a change in resting heart rate[197-201]. Jouven et al. 2009, for example, assessed the magnitude and direction of change in resting heart rate from baseline to 5-years post-baseline in middle-aged French men who had no known CV disease[198]. Compared to subjects with a baseline heart rate between 64 and 70bpm whose heart rate was unchanged after five years (had decreased by at the most 4bpm or had increased by at the most 3bpm), subjects with an elevated heart rate at baseline (>70bpm) that had increased by at least 4bpm over the five years were at a 64% (95% CI 34 to 100%, $p<0.001$) higher risk of mortality. In contrast, subjects who had a low heart rate at baseline (<64bpm) that had decreased by at least 5bpm were at a 29% (95% CI 11 to 44%, $p = 0.003$) lower risk.

The association between change in resting heart rate and death was further explored by Nauman et al. 2011 in a population of Norwegian men and women aged 20 years or older who had participated in both the first and second waves of the HUNT study (HUNT-1 and HUNT-2), the second of which occurred approximately 10 years after the first[199]. Compared to participants who had a heart rate <70bpm at both HUNT-1 and HUNT-2, participants who had a heart rate <70bpm at HUNT-1 that had increased to >85bpm by HUNT-2 were at a 50% (95% CI 20 to 90%) higher risk of all-cause death. Moreover, participants with a heart rate >85bpm at both waves of the study were at a 30% (95% CI 10 to 50%) higher risk. Similarly, compared to participants with a low heart rate at both waves, participants whose heart rate was between 70 and 85bpm at HUNT-1 that had increased to >85bpm by HUNT-2 were at an 80% (95% CI 20 to 180%) higher risk of CHD death.

On the other hand, in a population of unselected primary care patients from Germany without known CV disease, Leistner et al. 2012 found that neither baseline or change in resting heart rate over the following year were associated with risk of all-cause mortality, CV mortality, major CV events (non-fatal MI, revascularisation or CV mortality), or CV events (non-fatal MI or revascularisation)[200]. However, the number of events was small (137 deaths and 121 CV events, for example), so there may have been insufficient statistical power to detect associations.

Both Jouven et al. 2001[202] and Floyd et al. 2015[203] evaluated the relationship between the mean of five heart rate measurements gathered annually over time and the risk of adverse events in subjects without any known CV disease. Jouven et al. 2001 found that a 10.2bpm higher baseline heart rate was associated with a 28% ($p = 0.003$) increase in the risk of sudden death in middle-aged French men, and while the result obtained using mean heart rate was not explicitly stated, it was said to be very similar to the baseline result[202]. Floyd et al. 2015 found that a 10bpm higher mean heart rate was associated with a 12% (95% CI 5 to 20%) increase in the risk of all-cause death in American men and women[203]. Neither study found an association between heart rate and the risk of MI, but this may have been due to an insufficient number of events. For example, in the population studied by Floyd et al. 2015, there were only 262 MI events compared to 1,326 all-cause deaths[203]. Ho et al. 2014 also investigated the relationship between the mean of multiple heart rate measurements obtained over time and risk in American men and women with no evidence of prior MI, HF or AF[204]. In this case, the heart rate measurements were gathered over 8 years prior to baseline. After multivariable adjustment, a 10bpm higher baseline heart rate was associated with a 17% ($p<0.001$), 18% ($p = 0.001$), 15% ($p<0.001$) and 32% ($p<0.001$) increase in the risk of all-cause death, CV death, CV disease and HF, respectively. Similar to Jouven et al. 2001, the results obtained using mean heart rate were not explicitly provided, but were stated as showing similar associations to baseline. No associations between baseline or mean heart rate and the risk of CHD or stroke were observed.

Four of the studies assessed the prognostic value of multiple heart rate measurements entered into the extended Cox model[205] as a single time-updated variable, referred to as time-updated heart rate[139,204,206,207]. Legeai et al. 2011[206], Ho et al. 2014[204], and O'Hartaigh et al. 2015[207] each found that an elevated time-dependent heart rate was associated with an increase in the risk of all-cause death. Ho et al. 2014, for example, found that an 11bpm higher time-updated heart rate was associated with an 18% ($p<0.001$) increase in the risk of all-cause death[204]. The study also found that an 11bpm higher time-updated heart rate was associated with an 18% ($p = 0.005$), 22% ($p<0.001$) and 41% ($p<0.001$) increase in the risk of CV death, CV disease, and HF, respectively. While no association between baseline or mean heart rate and the risk of CHD was observed, an 11bpm higher time-updated heart rate was associated with a 19% ($p<0.001$) increase in risk of CHD. No association between time-updated heart rate and the risk of stroke was observed. Nanchen et al. 2013 further explored the association between time-updated heart rate and risk of HF in men and women separately[139]. A 10bpm higher time-updated heart rate was associated with a 13% ($p = 0.017$) increase in the risk of HF in men, but no such association was observed in women.

2.3.2.2 Disease-Specific Populations

The remaining nine of the multiple heart rate measurement studies examined the relationship between heart rate and risk in subjects who had some form of pre-existing disease or condition. An overview of each of these studies is given in Table A1-17 provided in Appendix 1.

Five of the studies included subjects all of whom had hypertension[208-212]. In a population of subjects with stable CHD as well as hypertension, Kolloch et al. 2008 demonstrated that an increase in the mean of multiple heart rate measurements gathered over follow-up was associated with an increase in the risk of the composite of all-cause death, non-fatal MI, or non-fatal stroke, even after adjustment for baseline heart rate[208]. Paul et al. 2010 investigated the relationship between baseline heart

rate, final visit heart rate, and change in heart rate from baseline to the final visit, and all-cause, CV, and CHD death in Scottish men and women with hypertension, in sinus rhythm[209]. No associations between baseline heart rate and risk of any of the endpoints were observed. A final visit heart rate between 81 and 90bpm was associated with a 64% ($p = 0.026$) increase in the risk of all-cause death, compared to a final visit heart rate ≤60bpm, but again no associations between final visit heart rate and the risk of CV or CHD death were observed. Conversely, a 1bpm increase in heart rate from baseline to the final visit was associated with a 1% increase in the risk of all-cause death ($p = 0.028$), CV death ($p = 0.035$) and CHD death ($p = 0.007$). Furthermore, compared to subjects who had a heart rate <80bpm at both baseline and the final study visit, those who had a heart rate ≥80bpm at both visits were at a 78% ($p<0.001$), 92% ($p = 0.004$) and 94% ($p = 0.035$) higher risk of all-cause, CV and CHD death, respectively. Subjects with a heart rate <80bpm at baseline that had increased to ≥80bpm by the final study visit were additionally found to be at a 91% ($p = 0.025$) higher risk of CV death.

Both Okin et al. 2010[210] and Okin et al. 2012[211] assessed the association between time-updated resting heart rate and risk of adverse events in patients with hypertension and ECG LV hypertrophy who took part in the LIFE study. Okin et al. 2010 revealed that a 10bpm higher time-updated heart rate was associated with a 25% ($p<0.001$) and 16% ($p<0.001$) increase in the risk of all-cause and CV death, respectively, after adjustment for conventional risk factors as well as baseline heart rate[210]. Excluding subjects with prior HF, Okin et al. 2012 further showed that a 10bpm higher time-updated heart rate was associated with a 45% ($p<0.001$) increase in the risk of developing HF[211].

In a population of patients hospitalised for MI in sinus rhythm who survived the first year, Jabre et al. 2014 determined that both an elevated admission heart rate, and an elevated heart rate measured during the first year of follow-up, were associated with an increase in the risk of all-cause and CV death[213]. For example, an admission heart rate ≥90bpm was associated with a 62% (95% CI 25 to 109%) and a 66% (95% CI 14 to

142%) increase in the risk of all-cause and CV death, respectively, compared to an admission heart rate ≤60bpm. Similarly, a heart rate ≥90bpm measured during the first year was associated with a 116% (95% CI 64 to 184%) and a 93% (95% CI 27 to 194%) increase in risk, respectively, compared to a heart rate ≤60bpm within the first year.

Two of the studies included subjects all of whom had HF[214,215]. In a population of patients hospitalised for worsening HF, with LVEF ≤40% in sinus rhythm, no association between baseline (admission) heart rate and all-cause death was observed[214]. However, a 5bpm increase in heart rates ≥70bpm measured at one and four weeks after discharge were associated with a 13% (p = 0.002) and 12% (p = 0.001) increase in the risk of death, respectively. Furthermore, a 5bpm increase in heart rate from baseline to discharge was associated with a 6% (p = 0.046) increase in risk.

Vazir et al. 2014 examined the association between baseline heart rate, time-updated heart rate, and time-updated change in heart rate, and risk of a number of adverse outcomes, in subjects with chronic HF, in sinus rhythm or AF[215]. Time-updated change in heart rate was the difference in heart rate from one visit to the next, entered as a single time-dependent variable in the extended Cox model[205]. An elevated baseline heart rate was found to be associated with an increase in the risk of all-cause death, CV death and hospitalisation for HF. However, no associations between baseline heart rate and the risk of fatal or non-fatal MI, and fatal or non-fatal stroke were observed. On the other hand, a 5bpm higher time-updated heart rate, additionally adjusted for baseline heart rate, was associated with a 9% (p<0.001), 8% (p<0.001), 7% (p<0.001), 5% (p = 0.031) and 8% (p = 0.002) increase in the risk of all-cause death, CV death, hospitalisation for HF, fatal or non-fatal MI, and fatal or non-fatal stroke, respectively. Similarly, a 5bpm increase in time-updated change in heart rate, additionally adjusted for the previous heart rate measurement, was associated with a 9% (p<0.001), 9% (p<0.001), 6% (p<0.001), 6% (p = 0.014) and 7% (p = 0.009) increase in the risk of all-

cause death, CV death, hospitalisation for HF, fatal or non-fatal MI, and fatal or non-fatal stroke, respectively.

Finally, Lonn et al. 2014 evaluated the relationship between baseline and mean follow-up resting heart rate (referred to as "in-trial heart rate" in the publication), and risk, in subjects with CHD, PAD, cerebrovascular disease, or diabetes with end-stage organ damage[216]. An elevated continuous baseline heart rate was associated with an increase in the risk of major vascular events (CV death, MI, stroke or hospitalisation for HF), all-cause death, CV death and hospitalisation for HF. No associations between baseline heart rate and risk of MI or stroke were observed. Conversely, a 10bpm higher mean follow-up heart rate was associated with a 12% ($p = 0.0006$) increase in the risk of stroke, and a 22%, 33%, 33%, and 48% (all $p<0.0001$) increase in the risk of major vascular events, all-cause death, CV death and hospitalisation for HF, respectively. Again, no association between mean follow-up heart rate and risk of MI was observed.

2.4 Discussion

2.4.1 Baseline Heart Rate Studies

A total of 118 studies were included in the review, 98 of which analysed the risk associated with heart rate measured at a single point in time at the beginning of follow-up, referred to as 'baseline heart rate' studies. The majority of these studies used Cox proportional hazards regression models to estimate the association between heart rate and risk, and demonstrated that an elevated heart rate was associated with an increase in the risk of death and adverse CV outcomes, regardless of the population of subjects, independent of other risk factors. Table 2-1 provides a simplified illustration of the evidence in relation to each of the main adverse outcomes and population of subjects, as discussed in Section 2.3.1. The cells that contain a black rectangle indicate where an association between baseline resting heart rate and risk has been established, using a multivariate-adjusted model; the blank cells indicate where an association has yet to be established using such a model.

Table 2-1: A summary of the evidence presented by the 'baseline heart rate' studies, on the association between baseline resting heart rate and each of the main adverse outcomes in the populations of subjects discussed in Section 2.3.1.

Outcome	Category of Subjects										
	General 42 Studies	Diabetes 3 Studies	Hypertension 4 Studies	CHD 4 Studies	Post-MI/ACS 19 Studies	HF 10 Studies	LV Dysfunction 3 Studies	CABG 3 Studies	Vascular Disease 3 Studies	Post-Stroke 4 Studies	Kidney Disease 3 Studies
Deaths											
All-cause death	■	■	■	■	■	■	■	■	■	■	■
CV/vascular death	■	■	■	■	■	■	■		■	■	
Cardiac death	■	■									
CHD death	■	■	■								
HF death	■					■	■				
Sudden death	■										
Other											
CV disease/event	■			■	■	■	■		■		■
CHD	■		■								
MI	■						■			■	
Revascularisation							■				
HF	■			■	■	■	■		■		
Stroke	■				■					■	

The cells that contain a black rectangle indicate where an association between baseline resting heart rate and risk has been established, using a multivariate-adjusted model; the blank cells indicate where an association has yet to be established using such a model. The 'Other' events include combinations of both fatal and non-fatal events, and non-fatal events only.

ACS = Acute Coronary Syndrome; CABG = Coronary Artery Bypass Graft; CHD = Coronary Heart Disease; CV = Cardiovascular; HF = Heart Failure; LV = Left-Ventricular; MI = Myocardial Infarction.

2.4.2 Multiple Heart Rate Measurement Studies

Only 20 of the 118 studies analysed the risk associated with baseline and at least one additional heart rate measurement obtained after the beginning of the study, referred to as 'multiple heart rate measurement' studies. Table 2-2 provides a summary of the evidence presented by these studies, in relation to each of the main adverse outcomes and populations of subjects, as discussed in Section 2.3.2. The cells that contain one or more black shapes indicate where an association between some form of resting heart rate variable and risk has been established, using a multivariate-adjusted model; the blank cells indicate where an association has yet to be established using such a model. Each shape represents a different resting heart rate variable: a rectangle represents baseline resting heart rate; a circle represents a change in resting heart rate over time; a triangle represents the mean of multiple resting heart rate measurements gathered over time; and a star represents time-updated resting heart rate.

A number of the multiple heart rate measurement studies demonstrated that multiple heart rate measurements predicted outcomes that were not found to be associated with baseline heart rate. Paul et al. 2010, for example, did not observe any associations between baseline heart rate and risk of any of the endpoints assessed, which were all-cause death, CV death, and CHD death[209]. Conversely, a 1bpm increase in heart rate from baseline to the final visit was associated with a 1% increase in risk of each of the endpoints (all $p<0.04$). Similarly, while Lonn et al. 2014 demonstrated that an elevated baseline heart rate was associated with an increase in the risk of major vascular events, all-cause death, CV death and CHD death, no association between baseline heart rate and risk of stroke was observed[216]. On the other hand, a 10bpm increase in the mean of multiple heart rate measurements gathered over follow-up was associated with a 12% ($p = 0.0006$) increase in the risk of stroke.

Table 2-2: A summary of the evidence presented by the 'multiple heart rate measurement studies', on the association between both baseline and multiple resting heart rate measurements, and each of the main adverse outcomes in the populations of subjects discussed in Section 2.3.2.

	Category of Subjects				
Outcome	**General**	**Hypertension**	**Post-MI/ACS**	**HF**	**Vascular Disease**
	11 Studies	**5 Studies**	**1 Studies**	**2 Studies**	**1 Study**
Deaths					
All-cause death	■●▲★	■●★	■	■★	■▲
CV/vascular death	■▲★	●★	■	■★	■▲
Cardiac death					
CHD death	●	●			
HF death					
Sudden death		■			
Other					
CV disease/event	■▲★				■▲
Cardiac event		■			
CHD	★				
MI		■		★	
Revascularisation					
HF	■▲★	■★		■★	■▲
Stroke		■		★	▲

The cells that contain one or more black shapes indicate where an association between some form of resting heart rate variable and risk has been established, using a multivariate-adjusted model; the blank cells indicate where an association has yet to be established using such a model. Each shape represents a different resting heart rate variable: a rectangle represents baseline resting heart rate; a circle represents a change in resting heart rate over time; a triangle represents the mean of multiple resting heart rate measurements gathered over time; and a star represents time-updated resting heart rate. The 'Other' events include combinations of both fatal and non-fatal events, and non-fatal events only.

ACS = Acute Coronary Syndrome; CABG = Coronary Artery Bypass Graft; CHD = Coronary Heart Disease; CV = Cardiovascular; HF = Heart Failure; LV = Left-Ventricular; MI = Myocardial Infarction.

Seven of these studies assessed the prognostic value of multiple heart rate measurements entered into the extended Cox model[205] as a single time-dependent variable, often referred to as time-updated heart rate[139,204,206,207,210,211,215]. Some of them also showed that time-updated heart rate was able to predict events where baseline heart rate was not. Vazir et al. 2014, for example, found no association between baseline heart rate and the risk of fatal or non-fatal MI, or fatal or non-fatal stroke[215]. In contrast, a 5bpm higher time-updated heart rate, adjusted for baseline heart rate, was associated with a 5% ($p = 0.031$) and an 8% ($p = 0.002$) increase in the risk of MI and stroke, respectively. Furthermore, while Ho et al. 2014 observed no association between baseline heart rate or mean follow-up heart rate and risk of CHD, an 11bpm higher time-updated heart rate was associated with a 19% ($p<0.001$) increase in risk[204]

2.4.3 Findings in Relation to Practice and Research

Despite the abundance of evidence and the fact that it is straightforward and easy to measure, resting heart rate as a risk marker is given less consideration in clinical practice than perhaps it should be. The ESC guidelines relating to CV disease prevention in clinical practice[31], diabetes[217], arterial hypertension[218], stable CHD[219], STEMI[220], and HF[221], as well as the ACC/AHA guidelines for stable CHD[222] and CABG surgery[223], currently recognise elevated heart rate as an indicator of risk. However, only the ESC guidelines for CV disease prevention in clinical practice, and the management of arterial hypertension, recommend that heart rate be measured as part of the routine physical examination for risk assessment[31,218]. In addition, only the NICE guidelines for the management of ACS, and unstable angina and NSTEMI, mention that formal assessment of risk should include a physical examination where heart rate is measured, alongside blood pressure[224,225].

One of the reasons physicians may overlook heart rate is because it is influenced by factors such as stress, physical activity and illness. A single baseline heart rate

measurement may not sufficiently predict the risk of experiencing an adverse event many years in the future. Taking updated measurements of heart rate into account could provide a more reliable estimate of the risk, which may be more closely related to newly measured levels, as has been illustrated. The prognostic value of time-updated heart rate measurements may therefore be more relevant to clinical practice than that of a single heart rate measurement.

Compared to the number of studies that have investigated the risk associated with a single resting heart rate measurement, few have assessed the prognostic value of time-updated measurements. In the current review, no time-updated heart rate measurement studies were identified of specific groups of subjects with diabetes, CHD, ACS, or who had previously experienced an MI, LV dysfunction, who had undergone, or were about to undergo, CABG surgery, had some form of vascular disease, had previously experienced a stroke or TIA, or who had kidney disease. Further studies of the relationship between time-updated heart rate measurements and risk could encourage health care providers to give more consideration to routine monitoring of heart rate as an indicator of risk.

Another reason that heart rate may not be given much consideration in clinical practice is perhaps because studies often include very specific populations of subjects, and so general conclusions about its effect as a risk marker cannot be made. Moreover, studies that did not find an association between heart rate and risk of certain outcomes often included only a small number of events, and hence may have lacked the statistical power required to detect significant differences. Meta-analysis, defined as the statistical analysis of a collection of analytic results for the purpose of integrating findings[226], can be used to help overcome both of these issues. It can be used to calculate a single more powerful estimate of the effect of a risk marker for example, by combining the results from different studies, and also look for consistency of effect across sub-populations.

Khan et al. 2015 was the only study found in the current review that used meta-analysis techniques to assess the association between heart rate and risk[136]. Combining and re-analysing individual patient data from three previous cohort studies in what is known as an individual patient meta-analysis, Khan et al. 2015 discovered that a 10bpm increase in heart rate above 60bpm was associated with a 13% ($p<0.001$) increase in the risk of developing HF, in a large population of subjects from the general population, some of whom had a history of CV disease and some of whom were taking beta-blockers. A aggregate data meta-analysis was subsequently performed, which extracted results from the previously published Pfister et al. 2012[129], Opdahl et al. 2014[66], and Nanchen et al. 2013[138,139], and combined them with the results from the three previous cohort studies. It demonstrated that overall, an elevated resting heart rate was associated with a 40% increase in the risk of developing HF (95% CI 19 to 64%). Further meta-analyses of heart rate could lead to more general conclusions about its effect as a risk marker being drawn, thus emphasising its potential for assessing risk in both healthy individuals, and those with pre-existing conditions.

The majority of studies of single and multiple heart rate measurements analysed the risk associated with an elevated heart rate in subjects from the general population, often with no evidence of existing CV disease or CHD. Thus, further analyses of subjects with specific conditions could be informative.

2.4.4 Strengths and Limitations

The review has several strengths and limitations. Firstly, it was limited to full-text articles that were available in English, and made no attempt to include unpublished material. Further, it did not search for, or include, studies of risk models that may have included heart rate, but did not highlight its inclusion in the title of the paper. In addition, there was no review protocol, and the objectives and methods of the review were not formally pre-specified: not having a protocol increases the likelihood of bias, such as selective outcome reporting[95]. Moreover, MEDLINE and Embase were the only

databases searched initially for studies, and while they are two of the most comprehensive sources of healthcare information worldwide, like any database, their coverage is somewhat limited. However, reference and citation lists of include studies were searched for additional relevant publications, by hand and through Web of Science, respectively. The literature search, eligibility assessment, selection of studies, and data extraction process, was carried out by only one investigator. Ideally, two or more independent investigators take part in each of these steps, so that objectivity is enhanced, and disagreements can be explored and resolved by consensus. The contribution of at least two investigators can decrease the probability of rejecting relevant studies[227]. When only one investigator conducts each stage of the review, mistakes in study selection and data extraction, and bias, are much more likely. Furthermore, no data extraction sheet was formally developed or piloted before the review began. The studies included in the review were also considerably heterogeneous with respect to definition of outcomes, length of follow-up, variables adjusted for in multivariate models applied, and methods used to measure subjects' heart rate. Heterogeneity also existed in regard to the types of heart rate measurements and variables used to evaluate associations between resting heart rate and risk: for example, some studies assessed the risk associated with resting heart rate as a continuous variable, some compared risk between subjects in two different heart rate groups, and some compared risk between subjects in multiple different heart rate groups. Additionally, the studies that compared risk between subjects in different heart rate groups used varying cut-off points to define the groups. The review did, however, follow the PRISMA guidelines[94,95] as extensively as possible. The search was extensive, the quality of studies was high, and a number of studies that found no association between heart rate and risk were included: thus bias should be limited. The discussion of studies by patient population, and whether single or multiple heart rate measurements were used, should aid in accentuating where knowledge is lacking, thus helping researchers extend previous analysis and develop the field.

2.4.5 Chapter Summary and Conclusions

This chapter presented a review of observational studies and post-hoc clinical trial analyses that evaluated resting heart rate as a risk marker for mortality and adverse CV outcomes, in a variety of populations, distinguishing between studies that used a single heart rate measurement to predict risk from those that used multiple heart rate measurements.

The majority of studies included in this systematic review demonstrated that an elevated heart rate is associated with an increase in the risk of adverse events. Despite this, heart rate is not routinely used as a risk marker for CV disease. The relatively recent findings that time-updated heart rate measurements have increased prognostic value, may encourage physicians to give more consideration to regular assessment of heart rate as an indicator of risk. Further multiple heart rate measurement studies, meta-analyses of heart rate as a risk marker, and additional analyses of subjects with specific conditions would be instructive.

Accordingly, the role of resting heart rate as a risk marker is further explored in Chapters 4 to 8; new analyses of data from nine clinical trials was undertaken. Following on from this review, meta-analyses of the risk of death from any cause and death from CV causes are presented in Chapter 9, including the published prospective evidence identified in the review as well as the results from Chapters 4 to 8. Chapter 3 details the specific methods of analysis that were applied, and the trials which were newly explored.

Chapter 3

Materials and Methods

3.1 Introduction

This chapter describes the trials which were newly analysed in this thesis, and the methods of analysis that were employed. Specifically, new analyses of nine trials are presented in Chapters 4 to 8 and these trials are described in Section 3.2. The role of resting heart rate as a risk marker for death and other adverse outcomes is further investigated in Chapters 4 to 9. In Chapter 4, Section 4.3, and Chapters 5 to 8, both the original[74] and extended Cox model[205] were employed to explore the predictive value of baseline and time-updated resting heart rate for adverse outcomes in a number of different patient populations. In Chapter 4, Section 4.2, and Chapter 8, Section 8.4, pooled individual patient meta-analyses are described. The discrimination and calibration of the models applied in Chapters 4 to 8 were evaluated using Harrell's C-statistic[228,229] and likelihood ratio tests, respectively. Finally, following on from the systematic review presented in Chapter 2, meta-analyses of the risk of death from any cause and death from CV causes are presented in Chapter 9 Sections 9.2 and 9.3. Since similar methods of analysis were applied in Chapters 4 to 8, they are presented in Section 3.3. Finally, Section 3.4 describes the methods used to conduct the meta-analyses presented in Chapter 9. All analyses were executed using the statistical software package R[230].

3.2 Datasets and Trials

Nine trials are newly analysed in this thesis in Chapters 4 to 8. Table 3-1 provides an overview of the main features of each of these trials: they are described in greater detail in Sections 3.2.1 to 3.2.6.

Table 3-1: Main features of the nine trials newly analysed in this thesis.

Trial and Section Where Described	CAPRICORN Section 3.2.1.1	EPHESUS Section 3.2.1.2	OPTIMAAL Section 3.2.1.3	VALIANT Section 3.2.1.4	EUROPA Section 3.2.2	PROSPER Section 3.2.3	PERFORM Section 3.2.4	BEAUTIFUL Section 3.2.5	SHIFT Section 3.2.6
Trial Characteristics									
No. of patients randomised	1959	6632	5477	14703	12218	5804	19100	10917	6505
Length of follow-up	1.3 years	1.3. years	2.7 years	2.1 years	4.2 years	3.2 years	2.4 years	1.6 years	1.9 years
Study treatments	Carvedilol and placebo	Eplerenone and placebo	Losartan and captopril	Valsartan and captopril	Perindopril and placebo	Pravastatin and placebo	Terutroban and aspirin	Ivabradine and placebo	Ivabradine and placebo
Patient Characteristics									
Main inclusion criteria	Post-MI with LVEF ≤40%, aged at least 18 years	Post-MI with LVEF ≤40%, and HF or diabetes, aged at least 21 years	Post-MI with LVEF <35% or HF, aged at least 50 years	Post-MI with HF, LVEF ≤40%, or both, aged at least 18 years	Stable CHD (without HF) aged at least 18 years	Pre-existing vascular disease, or hypertension, diabetes, or currently smoking, without HF, aged 70 to 82 years	Post-stroke or TIA aged at least 55 years	CHD with LVEF <40%, and resting heart rate ≥60bpm, in sinus rhythm, aged at least 55 years	Chronic HF with LVEF ≤35%, and resting heart rate ≥70bpm, in sinus rhythm, aged at least 18 years
Mean age	63 years	64 years	67 years	65 years	60 years	75 years	67 years	65 years	60 years
Percentage of men	74%	71%	71%	69%	85%	48%	63%	83%	77%

Table continued and footnote provided on the following page.

Table 3-1 (Cont.): Main features of the nine trials newly analysed in this thesis.

Trial and Section Where Described	CAPRICORN Section 3.2.1.1	EPHESUS Section 3.2.1.2	OPTIMAAL Section 3.2.1.3	VALIANT Section 3.2.1.4	EUROPA Section 3.2.2	PROSPER Section 3.2.3	PERFORM Section 3.2.4	BEAUTIFUL Section 3.2.5	SHIFT Section 3.2.6
Information on Resting Heart Rate									
Resting heart rate measurements available	Baseline and at visits throughout follow-up	Baseline only	Baseline only	Baseline only	Baseline and at visits throughout follow-up	Baseline and at visits throughout follow-up	Baseline and at visits throughout follow-up	Baseline and at visits throughout follow-up	Baseline and at visits throughout follow-up
Method of heart rate measurement	Information on method not available	Information on method not available	Information on method not available	Information on method not available	Information on method not available, but likely pulse palpation (see Section 3.2.2)	ECG	ECG, auscultation, or pulse palpation, according to decision of investigator	ECG	ECG

The follow-up duration is the mean length of follow-up in regards to CAPRICORN, EPHESUS, OPTIMAAL, EUROPA, PROSPER and PERFORM, and the median length in regards to VALIANT, BEAUTIFUL and SHIFT.

CHD = Coronary Heart Disease; ECG = Electrocardiography; HF = Heart Failure; LVEF = Left-Ventricular Ejection Fraction; MI = Myocardial Infarction; TIA = Transient Ischemic Attack.

3.2.1 Patients Included in the High Risk MI Database

The individual patient meta-analysis presented in Chapter 4 Section 4.2 was carried out using the High Risk MI Database. The High Risk MI Database Initiative[231] created a database that pooled data of the CAPRICORN, EPHESUS, OPTIMAAL and VALIANT trials, each of which was a double-blind, randomised, controlled trial that enrolled patients after acute MI, with HF, LVSD, or both. The database contains a total of 28,771 patients, followed-up for a mean of 2.7 years. The mean age of the patients was 65 years and 70% were male. Patients' heart rates were recorded in each of the four trials at baseline: details of the method of measurement used in each trial are given in Sections 3.1.1.1 to 3.1.1.4.

3.2.1.1 CAPRICORN

The Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) study was a multi-centre, double blind, randomised controlled trial of carvedilol versus placebo involving 17 countries and 163 centres worldwide, which investigated whether carvedilol improved outcomes in patients with LV dysfunction after acute MI[232,233]. Eligible patients were aged 18 years or older with a stable, definite MI occurring 3-21 days before randomisation, with LVEF ≤40%. Participants were receiving concurrent treatment with angiotensin converting enzyme (ACE) inhibitors for at least 48 hours, and with a stable dose for more than 24 hours, unless there was a proven intolerance of ACE inhibitors. The trial included 1,959 patients who were followed-up for a mean of 1.3 years. The mean age of the patients was 63 years, 73.5% were men, and mean LVEF was 32.8%. There was no evidence of a difference between carvedilol and placebo for the first primary endpoint, which was the composite of all-cause mortality or CV cause hospital admission ($p = 0.30$). However, treatment with carvedilol did reduce the frequency of the second primary endpoint of all-cause mortality by 23% (95% CI 2 to 40%, $p = 0.031$).

Resting heart rate was recorded at baseline, and was also measured at 3-month intervals during the first year of follow-up, and at 4-month intervals thereafter. The method of heart rate measurement is not stated in the original trial publication[233], or the design and methodology publication[232]. Chapter 4 Section 4.3 presents an analysis of data from the CAPRICORN trial.

3.2.1.2 EPHESUS

The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) was a multi-centre, double-blind, randomised controlled trial involving 37 countries and 674 centres worldwide that evaluated the effect of eplerenone on adverse outcomes among patients with acute MI, complicated by LV dysfunction and HF, who were receiving optimal medical therapy[234,235]. Eligible patients had experienced an acute MI 3-14 days before randomisation, were aged 21 years or older, with an LVEF ≤40%, along with documented HF or diabetes. The trial included 6,632 patients who were followed-up for a mean of approximately 1.3 years. The mean age of the patients was 64 years, 71% were male, 14.5% had HF, 32% had diabetes, and mean LVEF was 33%. The majority of patients received optimal medical therapy for acute MI complicated by LV dysfunction and HF, including ACE inhibitors or angiotensin-II receptor blockers (ARBs) (in 87% of the patients), diuretics (in 60%), beta-blockers (in 75%), and aspirin (in 88%). The two primary endpoints of the trial were all-cause death, and CV death or hospitalisation for a CV event (including HF, recurrent acute MI, stroke, or ventricular arrhythmia). Eplerenone reduced the risk of all-cause death by 15% (95% CI 4 to 25%, p = 0.008), and CV death or hospitalisation for a CV event by 13% (95% CI 5 to 21%, p = 0.002).

Resting heart rate was measured at baseline; the method of heart rate measurement is not stated in the original trial publication[235], or the background, design, and organisation of the trial publication[234].

3.2.1.3 OPTIMAAL

The Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) was an investigator-initiated, multinational, double-blind, randomised, parallel-group trial involving seven European countries and 320 centres, which compared the effects of the ARB losartan with those of the ACE inhibitor captopril on adverse events in patients with acute MI and evidence of HF or LV dysfunction[236,237]. Eligible patients were 50 years or older with an acute MI occurring 10 days before randomisation, with signs or symptoms of HF during the acute phase, or an LVEF <35%, a new Q-wave anterior infarction or re-infarction. The trial included 5,477 patients who were followed-up for a mean of 2.7 years. The mean age of the patients was 67 years, 71% were male, and 6.2% had congestive HF. A non-significant difference in total mortality with a trend in favour of captopril was observed (p = 0.07), although losartan was better tolerated, and was associated with significantly fewer discontinuations (p<0.001).

Resting heart rate was measured at baseline; the method of heart rate measurement is not stated in the original trial publication[237], or the trial design publication[236].

3.2.1.4 VALIANT

The Valsartan in Acute Myocardial Infarction (VALIANT) trial was a multi-centre, international, double-blind, randomised clinical trial involving 931 centres in 24 countries, that compared the effect of valsartan, captopril, and the combination of the two on mortality in patients with MI complicated by LVSD, HF or both[238,239]. Eligible patients were aged 18 years or older with an acute MI occurring between 12 hours and 10 days prior to randomisation with evidence of HF, evidence of LVSD (an LVEF ≤35% on echocardiography or contrast angiography, and ≤40% as assessed by radionuclide scan), or both. The trial included 14,703 patients who were followed-up for a median of approximately 2.1 years. The mean age of the patients was 65 years, 69% were male, 15% had HF and mean LVEF was 35%. The trial revealed that valsartan was as effective

as captopril, but that combining valsartan with captopril increased the rate of adverse events without improving survival[239].

Resting heart rate was measured at baseline; the method of heart rate measurement is not stated in the original trial publication[239], or the rationale and design of the trial publication[238].

3.2.2 EUROPA

Data from the EUropean trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease (EUROPA) trial is analysed in Chapter 5. EUROPA was a randomised, double-blind, placebo controlled, multi-centre trial involving 424 centres in 24 countries, that assessed the ability of the ACE inhibitor perindopril to reduce CV events in a broad, low-risk population of patients with stable CHD without HF[240,241]. Men and women aged at least 18 years without clinical evidence of HF and with evidence of CHD, documented by previous MI (>3 months before screening), percutaneous or surgical coronary revascularisation (>6 months before screening), or angiographic evidence of at least 70% narrowing of one or more major coronary arteries, were eligible for inclusion in the trial. Men could also be recruited if they had a history of chest pain and a positive ECG, echo, or nuclear stress test. The trial included 12,218 patients who were followed-up for a mean of 4.2 years. The mean age of the patients was 60 years, 85% were male, and a total of 92%, 62% and 58% were taking platelet inhibitors, beta-blockers, and lipid-lowering therapies, respectively. Treatment with perindopril was associated with a 20% (95% CI 9 to 29%, p = 0.0003) reduction in the primary endpoint, which was the composite of CV mortality, non-fatal MI, or cardiac arrest with successful resuscitation.

Patients underwent a run-in period, where they received 4mg oral perindopril twice daily, in the morning, for 2 weeks in addition to their normal medication, followed by 8mg oral perindopril once daily, in the morning, for 2 weeks if the lower dose was well

tolerated. Patients aged 70 years or older were given 2 mg perindopril in the first week of screening, followed by 4mg daily in the second week, and 8mg daily in the last 2 weeks. At the end of the run-in period, patients were randomly assigned to receive perindopril 8mg (two tablets) or placebo once daily for at least 3 years. If this dose was not tolerated, it could be reduced to 4mg once daily or matching placebo. Heart rate was measured twice during the run-in period (at Study Visits 1 and 2) and at randomisation (Study Visit 3) in the supine position. The method of heart rate measurement is not stated in the original trial publication, but the publication does state that it was measured in the sitting position[240]. This suggests that heart rate may have been measured by pulse palpation, since it is normally performed with the subject in the sitting position, whereas ECG is performed with the subject lying down[72]. Follow-up visits took place at 3, 6 and 12 months after randomisation, and at 6-monthly intervals thereafter, at which heart rate was also recorded if possible.

3.2.3 PROSPER

Chapter 6 analyses data from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) trial. The PROSPER trial was a randomised, double-blind, placebo controlled trial that recruited elderly men and women with existing, or at high risk of developing, vascular disease from Scotland, Ireland and the Netherlands. The aim of the trial was to determine if pravastatin reduced the risk of cardiac events, stroke, cognitive decline, and disability in this cohort of patients[242,243]. Eligible patients were aged 70-82 years old with pre-existing vascular disease (coronary, cerebral, or peripheral) or raised risk of such disease because of smoking, hypertension, or diabetes. Participants with symptomatic congestive HF (New York Heart Association (NYHA) class III or IV) or evidence of AF were excluded, as well as those with poor cognitive function (Mini Mental State Examination score <24). The trial included 5,804 patients who were followed-up for a mean of 3.2 years. The mean age of the patients was 75 years and 48% were male. Treatment with pravastatin reduced the incident of the primary

endpoint, which was the composite of death from CHD, non-fatal MI, or fatal or non-fatal stroke, by 15% (95% CI 3 to 26%, p = 0.014).

Resting heart rate was measured from a 12-lead ECG at baseline (as part of the first enrolment visit), and annually thereafter.

3.2.4 PERFORM

Data from the Prevention of cerebrovascular and cardiovascular Events of ischaemic origin with teRutroban in patients with a history oF ischaemic strOke or tRansient ischaeMic attack (PERFORM) trial is analysed in Chapter 7. The PERFORM trial was an international, multi-centre, randomised, double-blind, parallel-group trial that was undertaken in 802 centres in 46 countries that compared terutroban with aspirin in the prevention of cerebral and CV ischemic events in patients who had experienced a recent non-cardioembolic ischemic event[244,245]. Eligible patients were men or women, aged 55 years or older, who had experienced an ischemic stroke or arterial retinal ischemic event more than 48 hours and less than 3 months preceding inclusion, or a TIA in the previous 8 days. The trial included 19,100 patients followed-up for a mean of approximately 2.4 years. The mean age of the patients was 67.2 years and 63% were men. The trial was stopped prematurely on the grounds of futility[245]. There was no evidence of a difference between terutroban and aspirin for the primary endpoint, which was the composite of fatal or non-fatal ischemic stroke, fatal or non-fatal MI, or other vascular death (excluding haemorrhagic death), or for any of the other endpoints assessed.

Heart rate was measured at baseline after a 10-minute rest in the supine position by palpation, auscultation, or 12-lead ECG, according to the investigator's decision. Follow-up visits took place at 1, 3 and 6 months after randomisation and at 6-monthly intervals thereafter until closure of the study, and heart rate was recorded at each of these visits if possible.

3.2.5 BEAUTIFUL

Chapter 8 analyses data from the morBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction (BEAUTIFUL) trial. The BEAUTIFUL trial was a randomised, double-blind, placebo-controlled, parallel-group trial, across 781 centres in 33 countries that assessed whether the addition of ivabradine (a pure heart-rate-lowering drug) to standard treatment could reduce adverse CV events in patients with CHD and LVSD[246-248]. Eligible patients were men and women aged 55 years or older with CHD, LVEF of less than 40% and end-diastolic short-axis internal dimension larger than 56mm, identified by echocardiography. Patients had to be in sinus rhythm, with a resting heart rate of 60bpm or greater. Any angina or symptoms of HF should have been stable for at least three months and patients should have received appropriate conventional CV medication at stable doses for at least one month. The trial included 10,917 patients, followed-up for a median of approximately 1.6 years. The mean age of the patients was 65.2 years, 83% were male, 87% were receiving beta-blockers, mean LVEF was 32.4% and mean resting heart rate was 71.6bpm. After one year, ivabradine had reduced heart rate by 6bpm. Reduction in heart rate with ivabradine did not reduce risk of the primary endpoint, which was the composite of CV death or admission to hospital for MI or new-onset or worsening HF (HR 1.00, 95% CI 0.91 to 1.10, p = 0.94), or any of the other endpoints. However, in a pre-specified subgroup of patients with baseline heart rate ≥70bpm, the risk of admission to hospital for MI, admission to hospital for MI or unstable angina, and coronary revascularisation was reduced by 36% (p = 0.001), 22% (p = 0.023) and 30% (p = 0.016), respectively.

Resting heart rate was measured at baseline and follow-up visits in the supine position by 12-lead ECG. After randomisation, visits were scheduled at 2 weeks; 1, 3 and 6 months; and every 6 months thereafter and heart rate measurements were recorded at each of these visits if possible.

3.2.6 SHIFT

Results from the Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT) are also presented in Chapter 8. SHIFT was a randomised, double-blind, placebo-controlled, multinational trial across 677 centres in 37 countries, that assessed whether the addition of ivabradine to guidelines-based treatment could reduce adverse events in patients with chronic HF and LVSD[32,249]. Men and women aged 18 years or older, with symptomatic chronic HF, an LVEF of 35% or lower, who were in sinus rhythm with a heart rate of 70bpm or higher, had been admitted to hospital for HF within the previous year before randomisation, and were on stable background treatment including a beta-blocker if tolerated, were eligible for inclusion in the study. The trial included a total of 6,505 participants followed-up for a median of approximately 1.9 years. The mean age of the patients was 60 years, 76.5% were male, 89.5% were taking beta-blockers, and mean LVEF was 29%. Treatment with ivabradine was associated with an 18% reduction (95% CI 10 to 25%, $p<0.001$) in the primary endpoint, which was the composite of CV death or hospital admission for worsening HF.

Resting heart rate was measured at baseline and follow-up visits in the supine position by 12-lead ECG. After randomisation, visits were scheduled at 28 days post-baseline, and every four months thereafter, and heart rate was recorded at each of these visits if possible.

3.3 Methods of Analysis Applied in Chapters 4 to 8

3.3.1 Heart Rate Groups

Firstly, the study populations were divided into groups according to their baseline heart rate values. In the previously published PERFORM and BEAUTIFUL baseline heart rate analyses[191,184], the populations of patients were divided into two groups according to whether their baseline resting heart rates were less than, or greater than or equal to, 70bpm. In each case, the cut-off of 70bpm was selected on the basis that it was very

close to the median heart rate of each population, and because published evidence has suggested that the risk associated with heart rate rises greatly above this value[148,156,208]. Thus, to make the current results as comparable as possible to the previously published results, the heart rate cut-off of 70bpm was also used in the current analyses of the PERFORM and BEAUTIFUL populations. For consistency of approach, in each of the other analyses that involved a single trial, excluding the analysis of the PROSPER patient population, the study population was divided into two groups, according to whether baseline resting heart was less than, or greater than or equal to, a certain baseline heart rate cut-off value that was chosen individually for each trial in a similar manner to that of PERFORM and BEAUTIFUL. The median heart rate of each population was found, and was rounded up or down to the nearest multiple of five or ten. In CAPRICORN, the median heart rate of the placebo population was 76bpm, which was rounded down to 75bpm; in EUROPA, the median heart rate was 65bpm, but because risk has been shown to increase above 70bpm, it was rounded up to 70bpm; and in SHIFT, the median heart rate of the placebo population was 77bpm, which was rounded up to 80bpm, since the SHIFT patients with a heart rate greater than the median had previously been found to be at higher risk of an event[32].

In the PROSPER analysis, the study population was divided into three groups according to the tertiles of the distribution of baseline heart rate values, since this was the method employed in the original PROSPER baseline heart rate publication[138]. This was done separately for women and men because women have a higher resting heart rate than men[250]. The male participants were divided into 'low', 'medium' and 'high' baseline heart rate groups according to the tertiles of their distribution of baseline heart rate, and the female participants were divided in the same way. The participants in the 'low', 'medium', and 'high' groups were then combined to produce three groups of subjects both male and female.

In the analysis that involved pooling individual patient data from two or more trials, it was not appropriate to divide the pooled population into two groups based on the median heart rate value of the population, since the distribution of baseline heart rate in each trial population differed. The patients in BEAUTIFUL, for example, were required to have a heart rate of at least 60bpm to be enrolled in the trial, whereas in SHIFT they were required to have a heart rate of at least 70bpm. Thus, it was decided that the pooled study population would be divided into multiple baseline heart rate groups, which also allowed the observation of a finer relationship between heart rate and risk. The heart rate distributions of the pooled populations were explored, and it was decided that each would be divided into six groups, as this resulted in a similar number of patients being assigned to each category. Again, for consistency of approach, both pooled populations were categorised into the same six heart rate groups: <65bpm, 65-69bpm, 70-74bpm, 75-79bpm, 80-84bpm, and ≥85bpm.

3.3.2 Comparison of Baseline Characteristics

Baseline characteristics were compared between the subjects in each of the baseline heart rate groups. For continuous variables, unpaired two-sample t-tests or analysis of variance (ANOVA) were used depending on whether baseline characteristics were being compared between two groups, or more than two groups, respectively. For categorical variables, chi-squared tests were used. Continuous variables are reported as means along with the corresponding standard deviation, and categorical variables are reported as counts along with the corresponding percentage.

3.3.3 Cox Proportional Hazards Regression Analysis

3.3.3.1 Associations Between Elevated Baseline Heart Rate and Risk

In each individual analysis presented in Chapters 4 to 8, associations between baseline resting heart rate and risk of certain outcomes were assessed using the standard Cox proportional hazards regression model[74], adjusted for a number of other covariates, specified in each individual section or chapter. Since associations between baseline

resting heart rate and risk had been previously examined in the PROSPER, PERFORM, BEAUTIFUL and SHIFT populations, the Cox regression models applied in the analyses of these populations were adjusted for the same variables adjusted for in the respective baseline heart rate studies[138,191,184,182] to make the current results as comparable as possible to the previously published results. In the PROSPER and SHIFT baseline analyses[138,182], along with the majority of other studies identified in the review of Chapter 2, the variables adjusted for in the models appeared to be selected purely at the discretion of the researchers, based on their clinical relevance and potential influence on outcome. In the PERFORM and BEAUTIFUL baseline analyses[191,184], on the other hand, subjects were divided into groups according to their heart rate values at baseline, and the models were adjusted for the variables which were significantly different between the groups. Thus, for consistency of approach, the Cox models applied in the analyses of the CAPRICORN and EUROPA populations, and the pooled populations of patients included in the High Risk MI Database and placebo patients from BEAUTIFUL and SHIFT, were similarly adjusted for the variables which were significantly different between the heart rate groups at baseline.

Standard Cox proportional hazards regression models allow the effect that a baseline measurement has on the risk of a future event to be estimated. The model allows for other prognostic variables to be adjusted for to take into account potential confounding factors.

The hazard function for the Cox proportional hazards model is

$$h(t, \boldsymbol{X}) = h_0(t) exp(\sum_{i=1}^{n} \beta_i X_i) \qquad (3\text{-}1)$$

where $\boldsymbol{X} = (X_1, X_2, \ldots, X_n)$ are the prognostic variables and $h_0(t)$ is the baseline hazard.

It is a semi-parametric model, because the form of the baseline hazard does not need to be specified to estimate the effect of the coefficients. On the other hand, the coefficients themselves have to satisfy certain assumptions: firstly, that they are independent of time (the proportional hazards assumption); and secondly, that they are linear.

The HR of an individual with covariates $\boldsymbol{X}$ compared to an individual with covariates $\boldsymbol{X}^*$ is

$$\frac{h(t,\boldsymbol{X})}{h(t,\boldsymbol{X}^*)} = \frac{h_0(t)exp(\sum_{i=1}^{n}\beta_i X_i)}{h_0(t)exp\left(\sum_{i=1}^{n}\beta_i X_i^*\right)}$$

$$= \frac{exp\left(\sum_{i=1}^{n}\beta_i X_i\right)}{exp\left(\sum_{i=1}^{n}\beta_i X_i^*\right)}$$

$$= exp(\sum_{i=1}^{n}\beta_i(X_i - X_i^*)) \qquad (3\text{-}2)$$

The HR does not depend on time.

Risk was compared between subjects in the baseline heart rate groups with the lowest heart rate group used as the reference group. The risk associated with baseline heart rate as a continuous variable was also assessed and presented as HRs associated with a 5bpm higher heart rate. To obtain the HR associated with a 5bpm higher baseline heart rate, the exponential of the coefficient for a 1 unit (i.e. 1bpm) higher baseline heart rate from the Cox model was raised to the power of 5; to obtain the HR associated with a 10 or 20bpm higher heart rate, it would be raised to the power of 10 or 20, and so on. In each analysis, estimated HRs were calculated with associated 95% CIs and p-values, calculated using the Wald test[251].

3.3.3.2 Associations Between Elevated Time-Updated Resting Heart Rate and Risk

In Chapter 4, Section 4.3, and Chapters 5 to 8, associations between time-updated resting heart rate and risk was assessed using the extended Cox proportional hazards regression model[205], adjusted for the same covariates as in the baseline heart rate analysis. This was not done in Chapter 4, Section 4.2, because multiple heart rate measurements gathered over follow-up were not available in the High Risk MI Database[231].

The extended Cox proportional hazards regression model allows for multiple measurements of a variable gathered over a prolonged period of time to be entered into the model as a single time-dependent variable.

The hazard function for the extended Cox model is

$$h\big(t, \boldsymbol{X}(t)\big) = h_0(t) exp\Big[\sum_{i=1}^{m} \beta_i X_i + \sum_{j=1}^{n} \delta_j X_j(t)\Big] \qquad (3\text{-}3)$$

where $\boldsymbol{X}(t) = \big(X_1, X_2, \dots, X_m, X_1(t), X_2(t), \dots, X_n(t)\big)$ denotes all of the prognostic variables, X_i denotes the i^{th} time-fixed variable (the form that all variables take in the standard Cox proportional hazards model described previously), $X_j(t)$ denotes the j^{th} time-dependent variable, and $h_0(t)$ is the baseline hazard.

The extended HR of an individual with covariates $\boldsymbol{X}$ in relation to an individual with covariates $\boldsymbol{X}^*$ at time t is

$$\frac{h(t,\boldsymbol{X}(t))}{h(t,\boldsymbol{X}^*(t))} = \frac{h_0(t)exp\left(\sum_{i=1}^{m}\beta_i X_i - \sum_{j=1}^{n}\delta_j X_j(t)\right)}{h_0(t)exp\left(\sum_{i=1}^{m}\beta_i X_i^* - \sum_{j=1}^{n}\delta_j X_j^*(t)\right)}$$

$$= \frac{exp\left(\sum_{i=1}^{m}\beta_i X_i - \sum_{j=1}^{n}\delta_j X_j(t)\right)}{exp\left(\sum_{i=1}^{m}\beta_i X_i^* - \sum_{j=1}^{n}\delta_j X_j^*(t)\right)}$$

$$= exp\left[\sum_{i=1}^{m}\beta_i\left(X_i - X_i^*\right) + \sum_{j=1}^{n}\delta_j\left(X_j(t) - X_j^*(t)\right)\right] \qquad (3\text{-}4)$$

Time-updated heart rate represents the most recent available heart rate value for each patient at any point over the course of follow-up. A patient's baseline heart rate is carried forward until the day of the first follow-up visit, at which time the new 'current' value is used, and then subsequently carried forward until the next visit, and so on across all visits. Since resting heart rate is evaluated as a time-updated risk marker, the most immediate value is consistently used for prognostic estimation, thereby potentially enhancing clinical relevance.

Risk was compared between the time-updated heart rate groups, and the risk associated with continuous time-updated heart rate was also assessed. Relating this back to Equation 3-3, $X_1(t_{visit_k})$ was included as the only heart rate variable, and the only time-dependent variable, in the model, where $visit_k$ denotes the heart rate measurement obtained at the k^{th} visit during the trial. For heart rate as a categorical outcome, the heart rate group a subject was in was updated each time they had their heart rate measured throughout follow-up. Estimated HRs of each higher time-updated heart rate group relative to the lowest heart rate group, and a 5bpm higher time-updated heart rate (the exponential of the coefficient for a 1 unit (i.e. 1bpm) higher

time-updated heart rate from the Cox model raised to the power of 5), were again calculated with associated 95% CIs and p-values, calculated using the Wald test[251].

Additional models were fitted with adjustment for (i) baseline resting heart rate group or baseline heart rate as appropriate, and (ii) the previous heart rate group or the previous measurement. In other words, in relation to Equation 3-3, additional models were fitted where (i) $X_1(t_{visit_k})$ was included as the only time-dependent variable in the model, where $visit_k$ denotes the heart rate measurement obtained at the k^{th} visit during the trial, and $X_{baseline}$ was also included as a time-fixed variable in the model, where $baseline$ denotes the baseline heart rate measurement; and (ii) $X_1(t_{visit_k})$ was included as a time-dependent variable, and $X_2(t_{visit_{k-1}})$ was also included as a time-dependent variable, where $visit_{k-1}$ denotes the heart rate measurement obtained at the visit immediately prior to the k^{th} visit during the trial. This was done to determine whether the updated heart rate measurements added prognostic value to the information already provided by the baseline or previous heart rate measurement.

3.3.3.3 Associations Between Time-Updated Categorical Heart Rate Patterns and Risk

Finally, in order to assess the risk associated with the direction of change in heart rate at each follow-up visit, in a similar manner to previous studies such as Jouven et al. 2009[198], Paul et al. 2010[209], and Nauman et al. 2011[199], models were fitted for 'time-updated categorical heart rate patterns'. Subjects were classified into a group at each time point, depending on their current and previous heart rate measurement. Those whose heart rate had: remained below a defined cut-off (such as 70bpm) were classified as being in the 'low-low' group; decreased from above the cut-off to below the cut-off were classified as being in the 'high-low' group; increased from below the cut-off to above the cut-off were classified as being in the 'low-high' group; and remained above the cut-off were classified as being in the 'high-high' group. This analysis takes into account the change in heart rate between visits, while also adjusting for the previous

visit measurement (which is absorbed into the grouping). Estimated HRs for a time-updated high-high, low-high, and high-low heart rate relative to a low-low heart rate were calculated with associated 95% CIs and p-values, calculated using the Wald test[251].

3.3.4 Linearity

The linearity of effect for each continuous heart rate variable was evaluated by plotting the Martingale residuals (a linear transformation of Cox-Snell residuals)[252,253] of each model against the heart rate values. This is the recommended method for assessing the linearity of a variable in a Cox proportional hazards regression model[252].

3.3.5 Model Discrimination and Calibration

While associations between resting heart rate and risk of death and adverse CV outcomes have been well studied, as illustrated by the review of Chapter 2, information on the prognostic value of resting heart rate beyond measures of association is lacking. Lonn et al. 2014[216] appeared to be the only study included in the review that examined both associations between heart rate and risk of adverse events, and the discrimination and calibration of the models applied. The discrimination of a model is its ability to differentiate between subjects who experience an event from those who do not; the calibration of a model is how accurately its predictions match the observed event rates[254].

It is important to assess model discrimination and calibration, since a risk marker that is strongly and significantly associated with risk of an outcome may not necessarily be adept at predicting risk of that outcome[255]. Thus, in a similar manner to Lonn et al. 2014[216], the discrimination and calibration of the models applied in Chapters 4 to 8 were evaluated using Harrell's C-statistic[228,229] and likelihood ratio tests, respectively. Specifically, Harrell's C-statistic was calculated for each resting heart rate model, as well as for the model excluding resting heart rate. Harrell's C-statistic can range from 0 to 1, with a value of 0 indicating that the model has no predictive ability, a value of 1

indicating that the model has perfect predictive ability, and a value of 0.5 indicating that the model has average predictive ability, equivalent to that of random prediction[256]. Similarly, the likelihood ratio test statistic of each heart rate model compared to the model excluding resting heart rate was calculated and tested for significance using the likelihood ratio X^2 test. A significant likelihood ratio X^2 value indicates that the addition of the heart rate variable of interest to the model notably improves the calibration (or goodness-of-fit) of the model. The C-statistics were only observationally, and not computationally, compared between models – Harrell recommends against the computational comparison of competing models by their C-statistics due to the lack of statistical power in such tests, and states instead that comparison of models using the powerful likelihood ratio test is both sufficient and ideal[257,258].

3.3.6 Subgroup Analyses

In the pooled individual patient meta-analyses presented in Chapter 4 Section 4.2, and Chapter 8 Section 8.4, interactions between heart rate and study were added to the Cox models and tested for significance using likelihood ratio tests to check whether the relationships between heart rate and outcome were different between the studies.

Similarly, in the PROSPER analysis presented in Chapter 6, interactions between time-updated heart rate and use of anti-arrhythmic drugs (details of the specific drugs included in this category were not available) and/or beta-blockers were added to the models that were additionally adjusted for baseline heart rate, and tested for significance. Patients were classified as 'taking anti-arrhythmic drugs and/or beta-blockers' if they were taking an anti-arrhythmic drug, a beta-blocker, or both at randomisation. This was done in order to examine whether the relationships between heart rate and outcome were different in patients who were or were not taking anti-arrhythmic drugs and/or beta-blockers at randomisation (drugs which can directly affect heart rate). HRs, 95% CIs, and p-values were also estimated for a 5bpm higher time-

updated heart rate adjusted for baseline heart rate, separately in patients who were or were not taking anti-arrhythmic drugs and/or beta-blockers.

3.3.7 Proportionality of Hazards

A key assumption of the Cox model is that proportionality of hazards is maintained over time, as mentioned in Section 3.3.3.1. Although there are visual methods for the diagnosis of non-proportionality of hazards, a standard diagnostic is a residuals-based test[259]. Therneau, Grambsch and Fleming 1990 developed a test based on the absolute value of the summed Schoenfeld residuals[253], which are the residuals from a Cox model defined as the value of each covariate minus its expected value, for each individual who experienced an event[259].

Grambsch and Therneau 1994 modified this test by using scaled Schoenfeld residuals[260]. In principle, the scaled Schoenfeld residuals are the Schoenfeld residuals adjusted by the inverse of their covariance matrix[261]. Grambsch and Therneau 1994, however, proposed that this adjustment could be executed using the variance-covariance matrix of the parameter estimates, divided by the number of events, under the assumption that the distribution of the covariates is similar in each of the different risk sets[260,261]. This test has both a global and covariate specific form, and is the standard diagnostic test for non-proportionality of hazards in the Cox model. The covariate specific test statistic is

$$T_k = \frac{\left\{\sum_{i=1}^{n}\left(\delta_{k_i} g_{k_i} - \bar{g}\right) s_k^*\right\}^2}{d I_k \sum_{i=1}^{n}\left(\delta_{k_i} g_{k_i} - \bar{g}\right)^2} \qquad (3\text{-}5)$$

where δ_{k_i} and g_{k_i} are the indicator variable and time of the event for the i^{th} observation (with n representing the total number of observations), respectively, s_k^* are the scaled Schoenfeld residuals for covariate k, $\bar{g}$ is the average pre-defined time scale (either linear or log-linear), d is the number of events, and I_k is the information matrix

of variance estimates of the parameter estimates for covariate k[261,262]. Under the null hypothesis, this test statistic follows a chi-squared distribution with one degree of freedom for the covariate-specific version of the test. It can be interpreted as a measure of the correlation between the covariate-specific residual, and event times. Test statistics that exceed 5% critical values are viewed as possible evidence that the non-proportional hazards assumption has been violated.

The assumption of proportionality of hazards was tested for each of the models fitted in Chapters 4 to 8 using the Grambsch and Therneau 1994 test. If the test showed evidence of non-proportionality, the smoothed curve and corresponding 95% CIs of the Schoenfeld residuals were plotted and examined to determine how the effect of heart rate on risk changed over the period of follow-up.

3.4 Methods used in the Meta-Analyses Presented in Chapter 9

Available HRs and 95% CIs for all-cause mortality and CV mortality were converted to the HR and 95% CI associated with a 5bpm higher heart rate (either 'baseline' or 'time-updated'). HRs were then combined using random-effects meta-analysis with inverse variance weighting - where weights are assigned to each study based on the inverse of their within-study variance - to compensate for expected heterogeneity between studies[226].

Fixed-effects meta-analysis assumes that all the studies included in the analysis are essentially identical. Thus, the results of a fixed-effects meta-analysis only apply to the specific population studied, and are not generalisable to other populations[263]. Differences between studies, such as the types of subjects included, are better taken into account using random-effects models. Random-effects models allow the size of the effect of interest to differ between studies, but assumes that they are drawn from a common distribution of effect sizes. This distribution is usually assumed to be the Normal distribution, with a variance determined by the data[226,263,264]. Thus, random-

effects meta-analysis is the more suitable method when the aim is to generalise the results across a variety of populations or circumstances, which is more often the case[263]. Generally, a test for heterogeneity is performed before conducting a random-effects meta-analysis, such as the Q and I^2 statistic[265-267]. Both of these statistics were used in Chapter 9 to assess heterogeneity across the studies.

Three of the most commonly used methods for fitting random-effects models are the DerSimonian and Laird method[226], and the maximum and restricted maximum likelihood methods[265,268,269]. Regardless of which model is used, the between-study variance τ^2 is approximated first, followed by the overall effect estimate, $\hat{\mu}$[263]. The key difference between each of these methods is their calculation of τ^2 [265]. The DerSimonian and Laird method uses a non-iterative technique to approximate τ^2, whereas the maximum and restricted maximum likelihood methods use an iterative technique[265,268,269]. Additionally, while both the maximum and restricted maximum likelihood methods assume that the within and between-study effects are normally distributed, the DerSimonian and Laird method does not[263,269].

It would appear that the restricted maximum likelihood method is increasingly being used in published meta-analyses over the DerSimonian and Laird method[269]. Moreover, Thompson and Sharp 1999 recommended its use over the maximum likelihood method[265]. The log-likelihood function for the maximum likelihood method is:

$$log_{ML}(\theta, \tau^2) = -\frac{1}{2}\left[\sum_{i=1}^{k} log\left\{2\pi\left(\hat{\sigma}_i^2 + \tau^2\right)\right\} + \sum_{i=1}^{k} \frac{(\hat{\theta}_i - \theta)}{(\hat{\sigma}_i^2 + \tau^2)}\right] \qquad (3\text{-}6)$$

where k is the number of studies being combined, $\hat{\theta}_i$ and $\hat{\sigma}_i^2$ are the effect and variance estimates from study i, and θ is the overall effect[268]. It assumes that θ is known, when in actual fact it is estimated from the data, and thus does not take into consideration the degrees of freedom used in the estimation of θ[263,265,270]. This results in a tendency

of the maximum likelihood method to underestimate τ^2 and standard errors, especially when there are only a small number of studies included in the analysis[263,265,270]. The restricted maximum likelihood method, on the other hand, does not assume that θ is known, and excludes it from the estimation - in this way, it is restricted[271]. The log-likelihood function for the restricted maximum likelihood is:

$$log_{REML}(\theta, \tau^2)$$

$$= -\frac{1}{2}\left[\sum_{i=1}^{k} log\{2\pi(\hat{\sigma}_i^2 + \tau^2)\} + \sum_{i=1}^{k} \frac{(\hat{\theta}_i - \hat{\theta})}{(\hat{\sigma}_i^2 + \tau^2)}\right] - \frac{1}{2} log \sum_{i=1}^{k} \frac{1}{(\hat{\sigma}_i^2 + \tau^2)} \quad (3\text{-}7)$$

where k is the number of studies being combined, $\hat{\theta}_i$ and $\hat{\sigma}_i^2$ are the effect and variance estimates from study i, and $\hat{\theta}$ is the overall effect estimate with

$$\hat{\theta} = \frac{\sum_{i=1}^{k}[\theta_i/(\hat{\sigma}_i^2 + \tau^2)]}{\sum_{i=1}^{k}[1/(\hat{\sigma}_i^2 + \tau^2)]}. \quad (3\text{-}8)$$

Non-negativity for τ^2 is enforced at each iteration, and iteration continues until convergence or until the maximum number of iterations is reached[269]. It is considered an improvement over maximum likelihood, since it does adjust for the degrees of freedom used in the estimation of the overall effect θ[226,263]. Thus, the random-effects restricted maximum likelihood method was applied in Chapter 9[226,269].

In the meta-analysis of baseline resting heart rate, presented in Chapter 9 Section 9.2, publication bias was assessed using the random-effects version of Egger's test[272,273], and funnel plots. If publication bias was observed, trim and fill analysis was carried out to determine the possible impact of missing studies, using both the L_0 and R_0 estimators of the number of missing studies[274]. Duval and Tweedie 2000 recommend using both estimators to optimally evaluate the number of studies that are potentially missing[274]. It was not appropriate to assess publication bias in the time-updated heart rate meta-

analysis, presented in Section 9.3, since too few published studies were included – tests for publication bias should only be applied when ten or more studies are included in the analysis[275].

Study quality was assessed using the 9-star Newcastle-Ottawa Scale[96], which is widely used for assessing the quality of observational studies and post-hoc clinical trial analyses. It awards a maximum of nine stars to each study being assessed, with higher quality studies attaining a greater number of stars. Stars are awarded in relation to the following three categories: selection (4 stars); comparability (2 stars); and outcome (3 stars).

3.5 Chapter Summary

This chapter began by outlining the analyses that were carried out in the following Chapters 4 to 9. As the analyses involved new investigation of data from nine clinical trials, an overview of their main features was provided in Table 3-1, and each were described in greater detail in Section 3.2. The rest of the chapter set out the specific methods of analyses that were employed. As similar methods were used in Chapters 4 to 8, they were presented in Section 3.3. Lastly, Section 3.4 detailed the methods used to conduct the meta-analyses presented in Chapter 9.

The first analysis chapter, Chapter 4, explores the associations between baseline and time-updated resting heart rate, and long-term adverse events, in post-MI patients with HF, LVSD, or both.

Chapter 4

Heart Rate and Risk in Post-Acute MI Patients

4.1 Introduction

A raised resting heart rate measured at a single point in time has been associated with an increase in the risk of all-cause death[164,169-171,183,213], CV death[169,213], the combinations of all-cause death and arrhythmic events[156], and CV death or non-fatal MI[170], in patients with ACS followed-up for more than one year. However, information on the relationship between resting heart rate and other endpoints, such as hospitalisation for HF, subsequent MI, and stroke, does not yet appear to be available in this population of patients.

Previous studies have indicated that the association between heart rate and risk may be stronger in patients with LVSD[171,173]. However, the systematic review of Chapter 2 identified only one study that evaluated the heart rate-risk relationship in post-MI patients with LVSD[183]. None of the studies assessed the prognostic value of resting heart rate in post-MI patients with HF, LVSD, or both.

Using the High Risk MI Database[231], an individual patient meta-analysis of the association between baseline resting heart rate and risk of death and a number of adverse CV outcomes in post-MI patients with HF, LVSD, or both was performed. Differences between the CAPRICORN[233], EPEHSUS[235], OPTIMAAL[237] and VALIANT[239] trials that made up the database, in relation to the effect of baseline heart rate, were also examined.

Since CAPRICORN patients also had their heart rates measured throughout follow-up, additional data from the trial made it possible to further investigate the prognostic value of baseline and time-updated heart rate for long-term adverse outcomes in post-MI patients specifically with LVSD. The systematic review of Chapter 2 did not identify any studies of time-updated heart rate in post-MI patients.

4.2 A Pooled Analysis of the Predictive Value of Baseline Resting Heart Rate in Patients after Acute MI, with HF, LVSD or Both

The pooled analysis of individual trial data from the CAPRICORN, EPHESUS, OPTIMAAL and VALIANT trials included 28,691 patients (99.7% of the 28,771 randomised in total) who had a baseline heart rate measurement available (1,955 from CAPRICORN (99.8% of the 1,959), 6,606 from EPHESUS (99.5% of the 6,642), 5,461 from OPTIMAAL (99.7% of the 5,477) and 14,669 from VALIANT (just less than 100% of the 14,703 randomised)). Ideally, only the placebo group of CAPRICORN would have been included in the analysis, since carvedilol has heart rate lowering effects, however the High Risk MI Database did not contain the randomised study treatment[231] so it was not possible to exclude the treatment group subjects.

The publications reporting the primary results of each trial included in the database did not report the same outcomes. However, the High Risk MI Database provided simplified information on the following 12 endpoints, all of which were evaluated in the current analysis: (1) all-cause death; (2) CV death; (3) CV hospitalisation; (4) HF hospitalisation; (5) fatal or non-fatal MI; (6) fatal or non-fatal stroke; (7); CV death or non-fatal MI; (8) CV death or non-fatal stroke; (9) CV death or HF hospitalisation; (10) CV death, non-fatal MI or non-fatal stroke; (11) CV death, non-fatal MI, non-fatal stroke or HF hospitalisation; and (12) CV death or CV hospitalisation.

Table 4-1 shows the characteristics and inclusion criteria of each trial. CAPRICORN was the smallest trial in terms of number of patients randomised, which was just under 2,000; EPHESUS and OPTIMAAL were larger, randomising on average approximately 6,000 patients each; and VALIANT randomised over seven times the number of patients randomised in CAPRICORN, and was by far the largest of the four trials. CAPRICORN and EPHESUS had similar lengths of follow-up of approximately just over one year, while OPTIMAAL had the longest of approximately three years. CAPRICORN, EPHESUS and VALIANT were similar in that they accepted young patients into the trial, whereas

OPTIMAAL included only middle-aged or older subjects. CAPRICORN included the highest percentage of men. Patients in all four trials had very recently experienced an acute MI prior to randomisation: OPTIMAAL and VALIANT randomised subjects as little as 12 hours after the event, while the subjects randomised to CAPRICORN and EPHESUS had experienced the event at least three days prior.

Table 4-1: Characteristics and inclusion criteria of the CAPRICORN, EPHESUS, OPTIMAAL and VALIANT trial populations.

n = 28691	**CAPRICRON n = 1955**	**EPHESUS n = 6606**	**OPTIMAAL n = 5461**	**VALIANT n = 14669**
Trial Characteristics				
No. of patients randomised	1959	6632	5477	14703
Follow-up (months)	15.6	16.0	32.4	25.9
Study treatments	Carvedilol and placebo	Eplerenone and placebo	Losartan and captopril	Valsartan and captopril
Patient Characteristics				
Mean age (years)	63	64	67	65
Percentage of males	75%	71%	71%	69%
Mean LVEF	33%	33%	-	35%
Inclusion Criteria				
Primary diagnosis	Acute MI	Acute MI	Acute MI	Acute MI
Age	≥18 years	>21 years	≥50 years	≥18 years
MI criteria	LVEF ≤40%	Clinical evidence of HF, or diabetes, and LVEF ≤40%	Clinical evidence of HF or evidence of LV dysfunction (LVEF ≤35%) or new Q-wave anterior infarct	Clinical evidence of HF or evidence of LV dysfunction (LVEF ≤40%)
Randomisation after onset of symptoms	3 to 21 days	3 to 14 days	12h to 10 days	12h to 10 days

The number of subjects given in the first row of the table are the number that had baseline heart rate measurements available who are included in the present analysis. The follow-up duration is the mean length of follow-up in regards to CAPRICORN, EPHESUS, and OPTIMAAL, and the median length in regards to VALIANT. Mean LVEF was not reported in the OPTIMAAL trial publication and OPTIMAAL did not collect information about patients' LVEF.

HF = Heart Failure; LVEF = Left-Ventricular Ejection Fraction; MI = Myocardial Infarction.

Patients were categorised into the following six heart rate groups: <65bpm, 65-69bpm, 70-74bpm, 75-79bpm, 80-84bpm, and ≥85bpm. The baseline characteristics of the patients in each of the six baseline heart rate groups are shown in Table 4-2.

Not all patients had every baseline measurement available. CAPRICORN did not report any information on whether patients were taking beta-blockers at randomisation. EPHESUS did not report any information on whether patients had previously undergone a percutaneous transluminal coronary angiography (PTCA) or CABG procedure, or were taking anti-aldosterone agents at randomisation. OPTIMAAL did not report any information about patients' LVEF, or whether they were on antiplatelet agents (excluding aspirin), ACE inhibitors, ARBs, anti-aldosterone agents, or other lipid lowering medications (excluding statins) at randomisation. VALIANT did not report any information on whether patients were taking anti-aldosterone agents at randomisation. Therefore, percentages and means were calculated using the number of subjects with non-missing data as the denominator.

There were significant differences between the six groups of patients for all of the baseline characteristics except renal insufficiency, cerebrovascular accident, previous PTCA, SBP, and intake of calcium channel blockers (CCBs). Patients in the highest heart rate group (≥85bpm) were more likely to be younger, with a higher BMI and a lower LVEF. They were also more likely to be female and black, and have diabetes (in terms of both type 1 and type 2), AF, HF, chronic obstructive pulmonary disease, and a Killip class of above 2. They were less likely to have angina, or have previously experienced an MI (prior to the most recent one). In terms of intake of drugs at randomisation, those in the highest heart rate group were less likely to be taking aspirin and beta-blockers, and were more likely to be taking other antiplatelets (excluding aspirin), vitamin K antagonists, diuretics and cardiac glycosides.

Table 4-2: Baseline characteristics of the pooled population of patients included in the High Risk MI Database by heart rate group.

n = 28691	Group 1 <65bpm n = 5724	Group 2 65-69bpm n = 3278	Group 3 70-74bpm n = 5250	Group 4 75-79bpm n = 3740	Group 5 80-84bpm n = 4558	Group 6 ≥85bpm n = 6141	P-Value
Demographic Characteristics							
Age (years)	65.7 (11.2)	64.9 (11.2)	64.9 (11.4)	64.9 (11.6)	64.7 (11.6)	64.6 (11.6)	<0.001
Sex (male)	4306 (75%)	2345 (72%)	3726 (71%)	2583 (69%)	3091 (68%)	4086 (67%)	<0.001
Race							**<0.001**
Caucasian	5461 (95%)	3111 (95%)	4914 (94%)	3496 (93%)	4258 (93%)	5675 (92%)	-
Black	68 (1%)	50 (2%)	77 (1%)	66 (2%)	81 (2%)	161 (3%)	-
Asian	41 (1%)	28 (1%)	58 (1%)	41 (1%)	41 (1%)	78 (1%)	-
Other	154 (3%)	89 (3%)	201 (4%)	137 (4%)	178 (4%)	227 (4%)	-
BMI (kg/m^2)	27.2 (4.5)	27.4 (4.5)	27.4 (4.7)	27.6 (4.9)	27.6 (4.7)	27.7 (5.5)	<0.001
Smoking history							**<0.001**
Never	1879 (33%)	1191 (36%)	1956 (37%)	1463 (39%)	1693 (37%)	2294 (37%)	-
Current	1960 (34%)	1094 (33%)	1679 (32%)	1172 (31%)	1461 (32%)	1809 (29%)	-
Past	1881 (33%)	993 (30%)	1607 (31%)	1105 (30%)	1398 (31%)	2053 (33%)	-
Medical History							
Diabetes	**1146 (20%)**	**783 (24%)**	**1273 (24%)**	**1026 (27%)**	**1258 (28%)**	**1878 (31%)**	**<0.001**
Type 1 diabetes	207 (4%)	171 (5%)	280 (5%)	213 (6%)	292 (6%)	517 (8%)	
Type 2 diabetes	939 (16%)	612 (19%)	993 (19%)	813 (22%)	966 (21%)	1361 (22%)	
Hypertension	2972 (52%)	1811 (55%)	2906 (55%)	2116 (57%)	2442 (54%)	3294 (54%)	<0.001
Angina	2561 (45%)	1494 (46%)	2374 (45%)	1620 (43%)	1978 (43%)	2395 (39%)	<0.001
Previous MI	1617 (28%)	931 (28%)	1357 (26%)	979 (26%)	1097 (24%)	1483 (24%)	<0.001
AF	695 (12%)	345 (11%)	660 (13%)	453 (12%)	614 (13%)	969 (16%)	<0.001
Dyslipidaemia	2833 (50%)	1482 (45%)	2387 (46%)	1734 (46%)	2106 (46%)	2856 (47%)	<0.001
Renal insufficiency	187 (3%)	96 (3%)	181 (3%)	112 (3%)	159 (3%)	199 (3%)	0.63
Heart failure	1906 (33%)	1212 (37%)	1984 (38%)	1440 (39%)	1864 (41%)	2748 (45%)	<0.001
COPD	379 (7%)	244 (7%)	387 (7%)	320 (9%)	422 (9%)	630 (10%)	<0.001
Cerebrovascular accident	455 (8%)	243 (7%)	408 (8%)	283 (8%)	375 (8%)	492 (8%)	0.77
Previous CABG	315 (6%)	157 (5%)	241 (5%)	185 (5%)	216 (5%)	397 (6%)	<0.001
Previous PTCA	803 (14%)	458 (14%)	726 (14%)	553 (15%)	759 (17%)	1107 (18%)	0.21

Table continued and footnote provided on the following pages.

Table 4-2 (Cont.): Baseline characteristics of the pooled population of patients included in the High Risk MI Database by heart rate group.

n = 28691	Group 1 <65bpm n = 5724	Group 2 65-69bpm n = 3278	Group 3 70-74bpm n = 5250	Group 4 75-79bpm n = 3740	Group 5 80-84bpm n = 4558	Group 6 ≥85bpm n = 6141	P-Value
Cardiac Parameters							
SBP (mm HG)	121.6 (17.0)	121.8 (17.0)	121.7 (16.5)	122.1 (16.5)	121.8 (17.1)	121.6 (17.3)	0.89
DBP (mm Hg)	70.8 (11.0)	71.8 (11.0)	72.4 (10.6)	72.5 (10.8)	73.0 (10.7)	72.6 (11.7)	<0.001
Heart rate (bpm)	59.5 (4.3)	67.1 (1.3)	71.6 (1.4)	76.6 (1.2)	81.3 (1.6)	94.2 (8.7)	-
Killip Class							**<0.001**
1	1983 (35%)	1037 (32%)	1503 (29%)	1064 (28%)	1175 (26%)	1398 (23%)	-
2	2975 (52%)	1717 (52%)	2783 (53%)	1953 (52%)	2440 (54%)	3154 (51%)	-
3	574 (10%)	405 (12%)	741 (14%)	571 (15%)	737 (16%)	1181 (19%)	-
4	166 (3%)	107 (3%)	205 (4%)	137 (4%)	184 (4%)	448 (7%)	-
LVEF	35.3 (8.9)	35.0 (8.5)	34.9 (9.1)	34.3 (8.4)	33.9 (8.8)	32.9 (9.1)	<0.001
Medication at Randomisation							
Aspirin	5101 (89%)	2892 (88%)	4567 (87%)	3251 (87%)	3939 (86%)	5262 (86%)	<0.001
Antiplatelet (excluding aspirin)	1117 (20%)	626 (19%)	1093 (21%)	815 (22%)	977 (21%)	1465 (24%)	<0.001
ACE inhibitor	2510 (44%)	1504 (46%)	2488 (47%)	1710 (46%)	2035 (45%)	2642 (43%)	<0.001
ARB	60 (1%)	47 (1%)	49 (1%)	56 (1%)	54 (1%)	79 (1%)	<0.001
Anti-aldosterone agents	2 (0.03%)	1 (0.03%)	4 (0.08%)	6 (0.2%)	10 (0.2%)	9 (0.1%)	<0.001
Beta-blocker	4152 (73%)	2230 (68%)	3386 (64%)	2236 (60%)	2683 (59%)	3080 (50%)	<0.001
Statin	2226 (39%)	1062 (32%)	1761 (34%)	1224 (33%)	1499 (33%)	2016 (33%)	<0.001
Other lipid lowering agent (excluding statin)	71 (1%)	44 (1%)	84 (2%)	49 (1%)	63 (1%)	90 (1%)	<0.001
Vitamin K antagonist	508 (9%)	292 (9%)	531 (10%)	375 (10%)	479 (11%)	707 (12%)	<0.001
CCB	475 (8%)	279 (9%)	403 (8%)	270 (7%)	383 (8%)	542 (9%)	0.058
Any diuretic	2176 (38%)	1381 (42%)	2296 (44%)	1666 (45%)	2168 (48%)	3284 (53%)	<0.001
Cardiac glycosides	410 (7%)	245 (7%)	518 (10%)	350 (9%)	587 (13%)	1027 (17%)	<0.001

This table shows the clinical and demographic characteristics of the patients in each of the six baseline heart rate groups, including only patients who had their baseline resting heart rate measured. Data are the number of patients with the corresponding percentage, or the mean with the standard deviation, depending on whether the variable was categorical or continuous, respectively. The values of each characteristic were compared between the six baseline heart rate groups of patients using ANOVA and chi-square tests for continuous and categorical variables, respectively.

ACE = Angiotensin-Converting Enzyme; AF = Atrial Fibrillation; ARB = Angiotensin II Receptor Blocker; BMI = Body Mass Index; CABG = Coronary Artery Bypass Graft; CCB = Calcium Channel Blocker; COPD = Chronic Obstructive Pulmonary

Disease; DBP = Diastolic Blood Pressure; LVEF = Left-Ventricular Ejection Fraction; MI = Myocardial Infarction; PTCA = Percutaneous Transluminal Coronary Angioplasty; SBP = Systolic Blood Pressure.

Not all patients had every baseline measurement available. CAPRICORN did not report any information on whether patients were taking beta-blockers at randomisation. EPHESUS did not report any information on whether patients had previously undergone a PTCA or CABG procedure, or were taking anti-aldosterone agents at randomisation. OPTIMAAL did not report any information about patients' LVEF, or whether they were on antiplatelet agents (excluding aspirin), ACE inhibitors, ARBs, anti-aldosterone agents, or other lipid lowering medications (excluding statins) at randomisation. VALIANT did not report any information on whether patients were taking anti-aldosterone agents at randomisation. Therefore, percentages and means were calculated using the number of subjects with non-missing data as the denominator.

The number of events that occurred in each of the six baseline heart rate groups, as well as in the total pooled population, is presented in Table 4-3.

Table 4-3: The number of first events that occurred in the pooled population of patients included in the High Risk MI Database and each of the baseline heart rate groups.

	Subjects Separated by Baseline Heart Rate						
	Pooled Population	**Group 1 <65bpm**	**Group 2 65-69bpm**	**Group 3 70-74bpm**	**Group 4 75-79bpm**	**Group 5 80-84bpm**	**Group 6 ≥85bpm**
	n = 28691	**n = 5724**	**n = 3278**	**n = 5250**	**n = 3740**	**n = 4558**	**n = 6141**
Mortality-Related Endpoints							
All-cause death	5108 (18%)	780 (14%)	494 (15%)	836 (16%)	658 (18%)	864 (19%)	1476 (24%)
CV death	4387 (15%)	650 (11%)	426 (13%)	700 (13%)	570 (15%)	746 (16%)	1295 (21%)
Hospitalisation-Related Endpoints							
CV hospitalisation	13111 (46%)	2623 (46%)	1488 (45%)	2327 (44%)	1698 (45%)	2051 (45%)	2924 (48%)
HF hospitalisation	3375 (12%)	484 (8%)	343 (10%)	554 (11%)	439 (12%)	582 (13%)	973 (16%)
Other Individual Endpoints							
Subsequent MI (fatal or non-fatal)	3116 (11%)	619 (11%)	368 (11%)	520 (10%)	383 (10%)	474 (10%)	752 (12%)
Stroke (fatal or non-fatal)	937 (3%)	179 (3%)	99 (3%)	164 (3%)	133 (6%)	147 (3%)	215 (4%)
Composite Endpoints							
CV death or non-fatal MI	6104 (21%)	1050 (18%)	642 (20%)	1019 (19%)	763 (20%)	1001 (22%)	1629 (27%)
CV death or non-fatal stroke	4939 (17%)	757 (13%)	492 (15%)	794 (15%)	659 (18%)	757 (17%)	1417 (23%)
CV death or HF hospitalisation	6646 (23%)	986 (17%)	655 (20%)	1091 (19%)	855 (23%)	1130 (25%)	1929 (31%)
cv death, non-fatal MI, or non-fatal stroke	6597 (23%)	1146 (20%)	699 (21%)	1103 (21%)	843 (23%)	1066 (23%)	1740 (28%)
CV death, non-fatal MI, non-fatal stroke or HF hospitalisation	8457 (29%)	1413 (25%)	884 (27%)	1434 (27%)	1074 (29%)	1397 (31%)	2255 (37%)
CV death or CV hospitalisation	15017 (52%)	2880 (50%)	1649 (50%)	2630 (50%)	1943 (52%)	2379 (52%)	3536 (58%)

This table shows the total number of patients included in the High Risk MI Database with available baseline resting heart rate data who experienced any pre-specified events of interest, as well as the number in relation to baseline heart rate group. Data are number of patients who experienced each event as a first event, with the corresponding percentage. Note that first event refers to the first event of each type: for example, a patient may have been hospitalised for a CV cause, and then subsequently been hospitalised for HF at a later date.

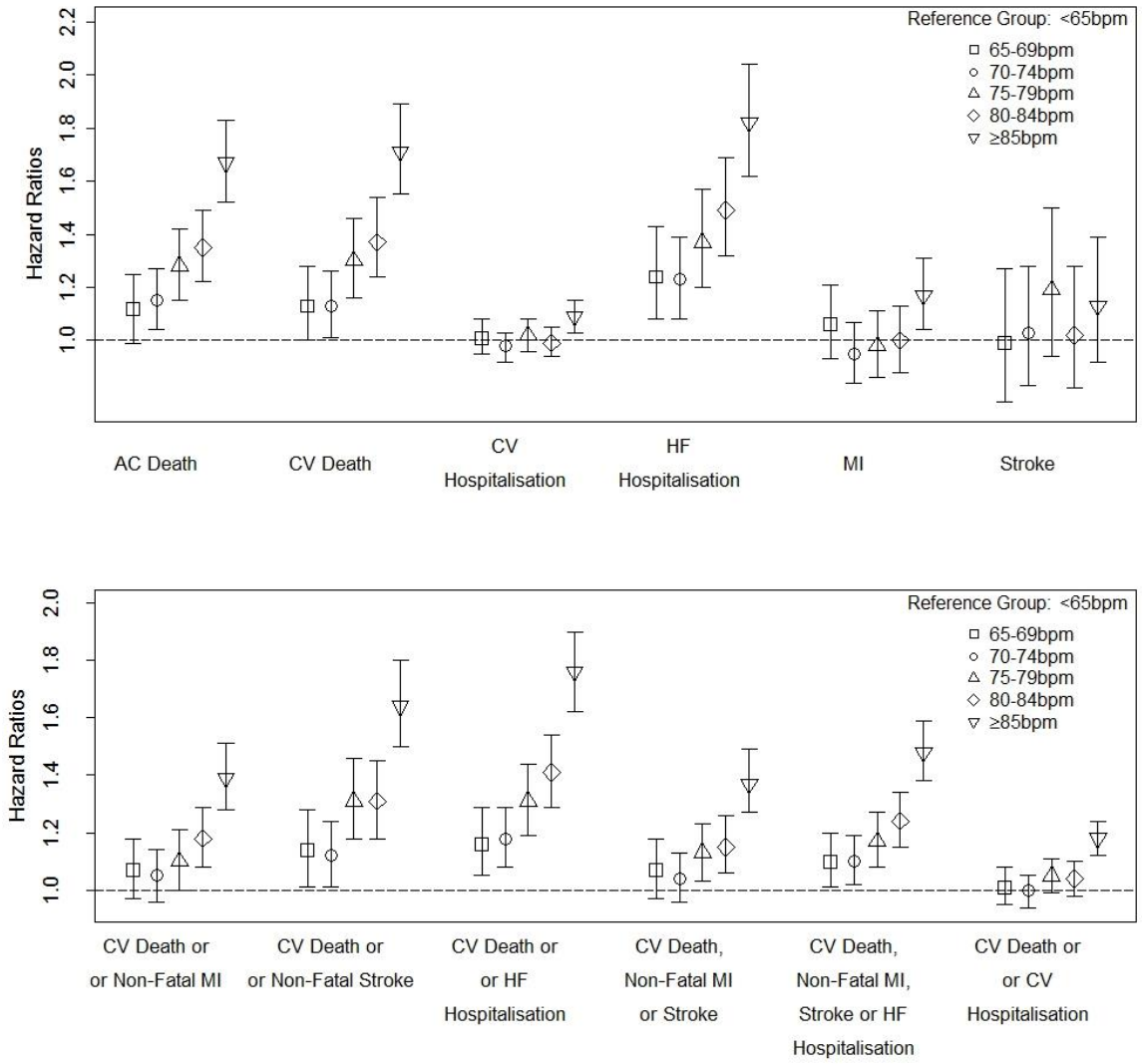
CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction.

The Cox models were adjusted for the variables which were significantly different between the heart rate groups at baseline ($p<0.05$), and were available for all four individual studies: age; sex; race; BMI; smoking history; diabetes; hypertension; angina; prior MI; AF; dyslipidaemia; HF; chronic obstructive pulmonary disease; DBP; Killip class; and intake of certain drugs at randomisation which were aspirin, statins, vitamin K antagonists, diuretics and cardiac glycosides. Models were also adjusted for study.

The linearity of effect for each continuous heart rate variable was evaluated by plotting the Martingale residuals (a linear transformation of Cox-Snell residuals)[252,253] of each model against the heart rate values. No violations of the linearity assumption were observed.

Comparing the risk of the outcomes between the heart rate groups greater than or equal to 65bpm, versus <65bpm, produced the HRs, 95% CIs and p-values shown by Figure 4-1 and in Table A2-1 provided in Appendix 2. Compared to patients with a baseline heart rate <65bpm, patients in each of the baseline heart rate groups ≥65bpm were at a higher risk of HF hospitalisation, and the combined endpoints CV mortality or non-fatal stroke, CV death or HF hospitalisation, and CV mortality, non-fatal MI, stroke or HF hospitalisation. Patients in each heart rate group ≥70bpm were at a higher risk of all-cause and CV death. Those in each heart rate group ≥75bpm were at a higher risk of the combined endpoints CV death or non-fatal MI, and CV death, non-fatal MI or stroke. Finally, patients with a baseline heart rate ≥85bpm were at a higher risk of CV hospitalisation, fatal or non-fatal MI, and the combined endpoint of CV death or CV hospitalisation. No significant increases in risk of fatal or non-fatal stroke were observed.

Figure 4-1: Results of fitting Cox proportional hazards models. Hazard ratios with corresponding 95% confidence intervals for each of the five baseline heart rate groups greater than or equal to 65bpm, relative to a baseline heart rate <65bpm in the pooled population of patients included in the High Risk MI Database.

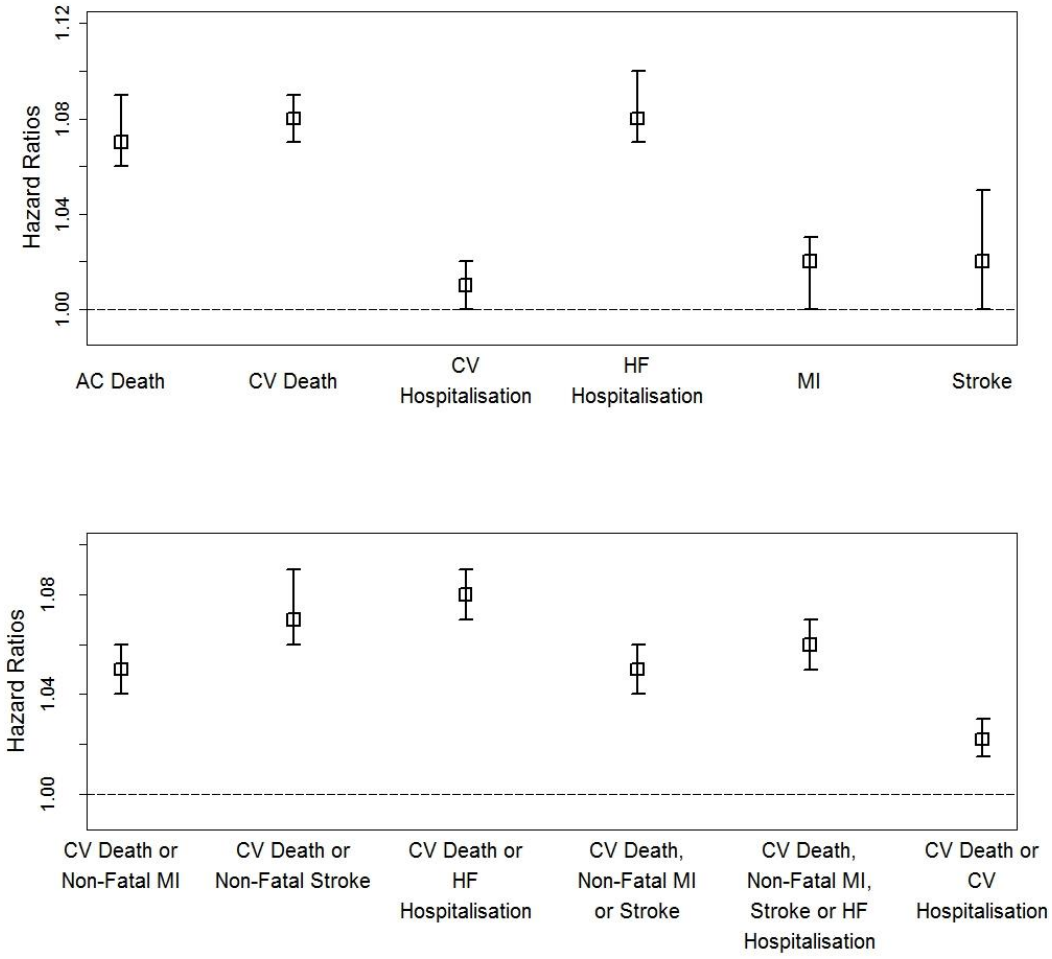


AC = All-Cause; CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction.

Models were additionally adjusted for: age; sex; race; body mass index (BMI); smoking history; diabetes; hypertension; angina; prior myocardial infarction (MI); atrial fibrillation (AF); dyslipidaemia; heart failure (HF); chronic obstructive pulmonary disease; diastolic blood pressure (DBP); Killip class; intake of certain drugs at randomisation which were aspirin, statins, vitamin K antagonists, diuretics and cardiac glycosides; and study.

Analysing continuous baseline heart rate produced the HRs, 95% CIs and p-values shown by Figure 4-2 and in Table A2-2 provided in Appendix 2. Elevated baseline heart rate was associated with an increase in risk of all of the endpoints except fatal or non-fatal stroke (p = 0.062). The smallest increases in risk were observed for CV hospitalisation and fatal or non-fatal MI. A 5bpm higher baseline heart rate was associated with a 1% (p = 0.0059) and 2% (p = 0.0086) increase in the risk of CV hospitalisation and fatal or non-fatal MI, respectively. The largest increase in risk was observed for CV death, HF hospitalisation, and the composite of the two. A 5bpm higher heart rate was associated with an 8% increase in risk of each of these endpoints.

Figure 4-2: Results of fitting Cox proportional hazards models. Hazard ratios with corresponding 95% confidence intervals for a 5bpm higher baseline heart rate in the pooled population of patients included in the High Risk MI Database.



AC = All-Cause; CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction.

Models were additionally adjusted for: age; sex; race; body mass index (BMI); smoking history; diabetes; hypertension; angina; prior myocardial infarction (MI); atrial fibrillation (AF); dyslipidaemia; heart failure (HF); chronic obstructive pulmonary disease; diastolic blood pressure (DBP); Killip class; intake of certain drugs at randomisation which were aspirin, statins, vitamin K antagonists, diuretics and cardiac glycosides; and study.

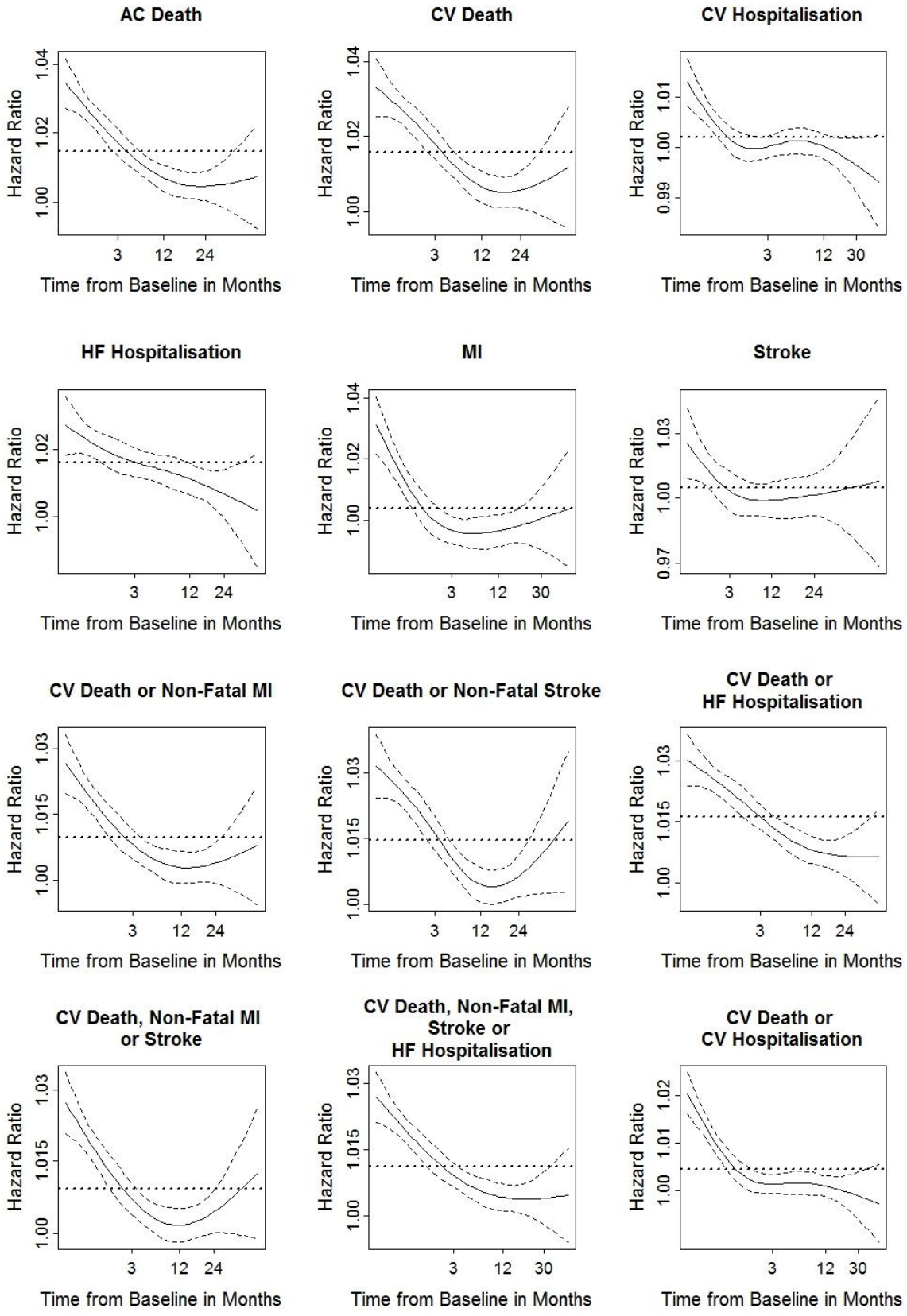
The discrimination and calibration of the models were evaluated using Harrell's C-statistic and likelihood ratio tests, respectively. Table A2-3 provided in Appendix 2 shows Harrell's C-statistics for the model excluding resting heart rate, and the model including the baseline heart rate group variable, for each outcome. Regardless of whether resting heart rate group was included, the models had the greatest predictive ability for all-cause death, CV death, HF hospitalisation, and the combined endpoints of CV death or non-fatal stroke, and CV death or HF hospitalisation: the C-statistics of the models both excluding and including resting heart rate ranged from 0.703 to 0.735 for these outcomes. On the other hand, the models had the least predictive ability for CV hospitalisation, and the combined endpoint of CV death or CV hospitalisation, with C-statistics ranging from 0.581 to 0.591. The addition of the baseline heart rate groups variable improved discrimination for all of the outcomes. The largest improvements in discrimination were observed for CV death and HF hospitalisation, with the C-statistics increasing from 0.715 to 0.723, and 0.727 to 0.735, respectively, when baseline heart rate group was added to the model. The smallest improvements were observed for CV hospitalisation, and fatal or non-fatal MI, with the C-statistics increasing from 0.581 to 0.582, and 0.650 to 0.652, respectively. The likelihood ratio test statistics and corresponding p-values for the addition of the baseline heart rate group variable to the models are also presented in Table A2-3. The addition of baseline heart rate group resulted in statistically significant improvements in the calibration of the models for all of the outcomes excluding fatal or non-fatal stroke.

Harrell's C-statistics for the model excluding resting heart rate, and the model including the continuous baseline heart rate variable, for each outcome, are shown in Table A2-4 provided in Appendix 2, along with the likelihood ratio test statistics and corresponding p-values for the addition of the continuous baseline heart rate variable to the models. The results were very similar to those observed for baseline resting heart rate group.

All of the models with the exception of the heart rate groups model for fatal or non-fatal stroke exhibited evidence of non-proportionality of the effect of heart rate on the hazard over time (see Table A2-5 and A2-6 in Appendix 2 for the p-values of the Grambsch and Therneau 1994 test for non-proportionality). The previously presented HRs therefore represent the 'average' effect of heart rate on the hazard over the duration of follow-up. Examination of the plots of the smoothed curve and corresponding 95% CIs of the Schoenfeld residuals for each model and outcome suggested that the effect of heart rate was highest at the beginning of follow-up, and then decreased over time. Figure 4-3 shows the Schoenfeld residual plots for a 5bpm higher baseline heart rate, along with the previously calculated 'average' hazard ratio of each outcome, represented by the horizontal dotted line, and provides an illustration of this finding.

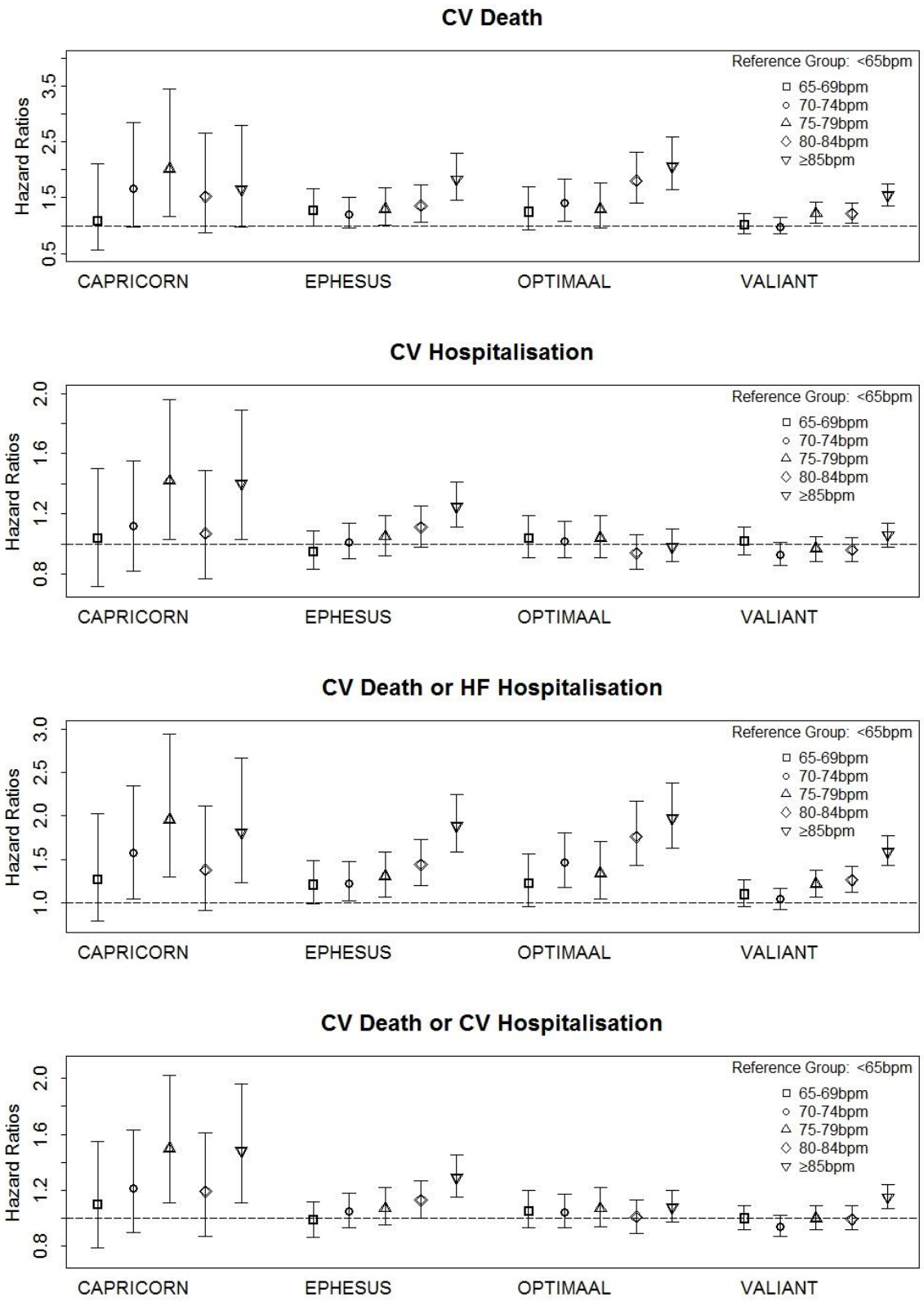
Table A2-1 and Table A2-2 in Appendix 2 also provide the p-values for the likelihood ratio tests for the interaction term of heart rate with study. Significant interactions between heart rate group and study were observed for CV death ($p = 0.040$), CV hospitalisation ($p = 0.0025$), and the combined endpoints CV death or HF hospitalisation ($p = 0.027$), and CV death or CV hospitalisation ($p = 0.034$). When continuous heart rate was analysed, significant interactions between heart rate and study were observed for CV hospitalisation ($p<0.001$), fatal or non-fatal MI ($p = 0.0045$) and CV death or CV hospitalisation ($p = 0.0027$). This indicates that the effect of heart rate is different depending on study for these outcomes. To gain insight into these differences, HRs for categorical heart rate were calculated for the four outcomes that showed significant interaction for each of the four individual trials. These are shown by Figure 4-4 and given in Table A2-7 provided in Appendix 2. Similarly, HRs for a 5bpm higher heart rate were calculated and are shown by Figure 4-5 and in Table A2-8 provided in Appendix 2.

Figure 4-3: The Schoenfeld residuals plots for a 5bpm higher baseline heart rate for each outcome in the pooled population of patients included in the High Risk MI Database.



The horizontal dotted lines represent the previously calculated 'average' hazard ratio of each outcome. AC = All-Cause; CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction.

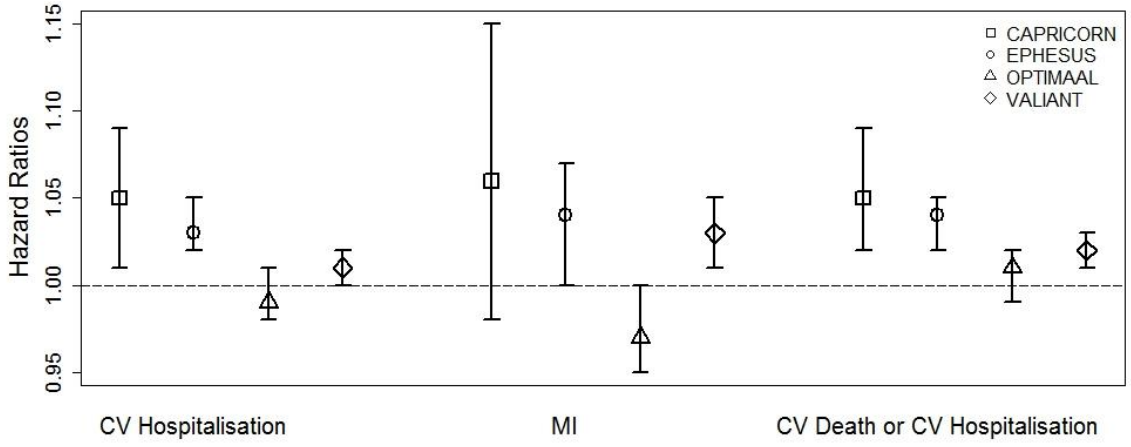
Figure 4-4: Results of fitting Cox proportional hazards models. Hazard ratios with corresponding 95% confidence intervals for each of the five baseline heart rate groups greater than or equal to 65bpm, relative to a baseline heart rate <65bpm, in the CAPRICORN, EPHESUS, OPTIMAAL and VALIANT populations, for the outcomes that showed significant interactions between heart rate and study.



CV = Cardiovascular; HF = Heart Failure.

Models were additionally adjusted for: age; sex; race; body mass index (BMI); smoking history; diabetes; hypertension; angina; prior myocardial infarction (MI); atrial fibrillation (AF); dyslipidaemia; heart failure (HF); chronic obstructive pulmonary disease; diastolic blood pressure (DBP); Killip class; and intake of certain drugs at randomisation which were aspirin, statins, vitamin K antagonists, diuretics and cardiac glycosides.

Figure 4-5: Results of fitting Cox proportional hazards models. Hazard ratios with corresponding 95% confidence intervals for a 5bpm higher baseline heart rate, in the CAPRICORN, EPHESUS, OPTIMAAL and VALIANT populations, for the outcomes that showed significant interactions between heart rate and study.



CV = Cardiovascular; MI = Myocardial Infarction.

Models were additionally adjusted for: age; sex; race; body mass index (BMI); smoking history; diabetes; hypertension; angina; prior myocardial infarction (MI); atrial fibrillation (AF); dyslipidaemia; heart failure (HF); chronic obstructive pulmonary disease; diastolic blood pressure (DBP); Killip class; and intake of certain drugs at randomisation which were aspirin, statins, vitamin K antagonists, diuretics and cardiac glycosides.

Patients in each of the heart rate groups were shown to be at a similar risk of CV death and the combined endpoint of CV death or HF hospitalisation across all four studies. The significant interactions observed are therefore likely to be due to a difference in the strength of the associations, with a suggestion of a significant but weaker gradient in the risk in the largest study, VALIANT. In contrast, for CV hospitalisation and the combination of CV death or CV hospitalisation, there was no evident association between heart rate and risk in OPTIMAAL, with a clear gradient of risk in EPHESUS and evidence of an association in the smaller CAPRICORN trial. While there was also no association between heart rate and risk of CV hospitalisation in the VALIANT population, VALIANT patients with a baseline heart rate ≥85bpm were found to be at a 15% higher risk of CV death or CV hospitalisation compared to those with a baseline heart rate <65bpm. Similar results were found when heart rate was analysed as a continuous variable for the outcomes of CV hospitalisation and CV death or CV hospitalisation. For the outcome of fatal or non-fatal MI, it appears that the OPTIMAAL study is an outlier with a trend to a negative association with risk for an elevated heart rate (a 5bpm

higher heart rate was associated with a borderline significant decrease in the risk of MI: HR 0.97, 95% CI 0.95 to 1.00, p = 0.077).

4.3 The Predictive Value of Time-Updated Heart Rate Measurements in the CAPRICORN Placebo Patients

A total of 981 of the patients assigned to the CAPRICORN placebo group (98.7% of the 984 placebo-assigned patients) had baseline heart rate measurements available and were included in the present analysis. Patients who were randomised to the treatment group were excluded since carvedilol has heart rate lowering effects and could possibly interfere with any association between heart rate and outcomes.

The current analysis evaluated all of the outcomes that were assessed in the original CAPRICORN trial publication[233]: all-cause death (the first primary endpoint of CAPRICORN); all-cause death or CV hospital admission (the second primary endpoint of CAPRICORN); sudden death; hospital admission for HF; CV death; HF death; non-fatal MI; and all-cause death or non-fatal MI.

The heart rate cut-off of 75bpm was selected on the basis that it was very close to the median heart rate of 76bpm of the CAPRICORN placebo population. The baseline characteristics of the placebo-assigned CAPRICORN patients, overall and categorised into groups depending on whether their baseline resting heart rate was less than, or greater than or equal to, 75bpm, are shown in Table 4-4. There were significant differences between the two groups of patients in terms of sex, whether or not they had diabetes, their LVEF (borderline), the site of their MI, and whether or not they were treated with intravenous diuretics post-MI. Patients in the higher heart rate group were more likely to be female and have diabetes. They were also more likely to have had an anterior MI, and to have been treated with intravenous diuretics.

Table 4-4: Baseline characteristics of the CAPRICORN placebo population.

	Baseline Heart Rate			
	All Subjects n = 981	**<75bpm n = 449**	**≥75bpm n = 532**	**p-value**
Demographic Characteristics				
Age (years)	63.2 (11.7)	63.0 (11.4)	63.3 (12.0)	0.62
Sex				**0.042**
Men	721 (74%)	344 (77%)	377 (71%)	
Women	260 (27%)	105 (23%)	155 (29%)	
Smoking				**0.64**
Current	319 (33%)	153 (34%)	166 (31%)	
Previous	242 (25%)	109 (24%)	133 (25%)	
Never	417 (43%)	186 (41%)	231 (43%)	
Medical History				
Previous MI	290 (30%)	131 (29%)	159 (30%)	0.81
Previous angina	531 (54%)	249 (55%)	282 (53%)	0.44
Previous hypertension	512 (52%)	231 (51%)	281 (53%)	0.67
Previous diabetes	229 (23%)	85 (19%)	144 (27%)	0.0027
Other vascular disease	159 (16%)	70 (16%)	89 (17%)	0.63
Previous revascularisation	107 (11%)	48 (11%)	59 (11%)	0.84
Hyperlipidaemia	322 (33%)	139 (31%)	183 (34%)	0.25
Infarct Characteristics				
LVEF (%)	32.7 (6.4)	33.1 (6.2)	32.3 (6.6)	0.050
SBP (mmHg)	120.7 (16.1)	121.4 (15.6)	120.1 (16.5)	0.21
DBP (mmHg)	73.4 (10.0)	73.7 (9.6)	73.1 (10.4)	0.39
Heart rate (bpm)	77.2 (11.3)	67.8 (4.3)	85.1 (9.0)	-
Site of MI				**0.025**
Anterior	533 (54%)	234 (52%)	299 (56%)	
Inferior	205 (21%)	111 (25%)	94 (18%)	
Other	243 (25%)	104 (23%)	139 (26%)	
Treatment for Index MI				
Nitrates	714 (73%)	331 (74%)	383 (72%)	0.54
Intravenous beta-blockers	99 (10%)	43 (10%)	56 (11%)	0.62
Intravenous heparin	632 (64%)	290 (65%)	342 (64%)	0.92
Subcutaneous heparin	481 (49%)	221 (49%)	260 (49%)	0.91
Intravenous diuretics	319 (33%)	110 (24%)	209 (39%)	<0.001
Thombolysis/primary angioplasty	463 (47%)	208 (46%)	255 (48%)	0.62
Medications at Time of Randomisation				
ACE inhibitor	953 (97%)	439 (98%)	514 (97%)	0.28
Aspirin	845 (86%)	382 (85%)	463 (87%)	0.38

This table shows the clinical and demographic characteristics of the CAPRICORN placebo patients who had baseline resting heart rate measurements available. Values are given for the total placebo population, as well as separately for patients who had a baseline resting heart rate <75bpm, and patients who had a baseline resting heart rate ≥75bpm. Data are the number of patients with the corresponding percentage, or the mean with the standard deviation, depending on whether the variable was categorical or continuous. Not all patients had every baseline measurement available. Therefore, percentages and means were calculated using the number of subjects with non-missing data as the denominator. The values of each characteristic were compared between the two different baseline resting heart rate groups using unpaired two-sample t-tests and chi-squared tests, for continuous and categorical variables, respectively.

ACE = Angiotensin-Converting Enzyme; DBP = Diastolic Blood Pressure; LVEF = Left-Ventricular Ejection Fraction; MI = Myocardial Infarction; SBP = Systolic Blood Pressure.

The total number of events that occurred in the placebo group is presented in Table 4-5, along with the number that occurred in each of the baseline heart rate groups of patients. The percentage of patients in the greater than or equal to 75bpm baseline heart rate group who experienced an event was higher for every event compared to the less than 75bpm baseline heart rate group of patients.

Table 4-5: The number of first events that occurred in the CAPRICORN placebo population.

		Subjects Separated by Baseline Heart Rate	
	Total Placebo Population n = 981	**<75bpm n = 449**	**≥75bpm n = 532**
Primary Endpoints			
All-cause mortality	150 (15%)	55 (12%)	95 (18%)
All-cause mortality or cardiovascular cause hospital admission	366 (37%)	141 (31%)	225 (42%)
Secondary Endpoints			
Sudden death	68 (7%)	26 (6%)	42 (8%)
Hospital admission for heart failure	138 (14%)	42 (9%)	96 (18%)
Other Endpoints			
Cardiovascular-cause mortality	138 (14%)	52 (12%)	86 (16%)
Death due to heart failure	30 (3%)	7 (2%)	23 (4%)
Non-fatal myocardial infarction	57 (6%)	19 (4%)	38 (7%)
All-cause mortality or non-fatal myocardial infarction	191 (19%)	70 (16%)	121 (23%)

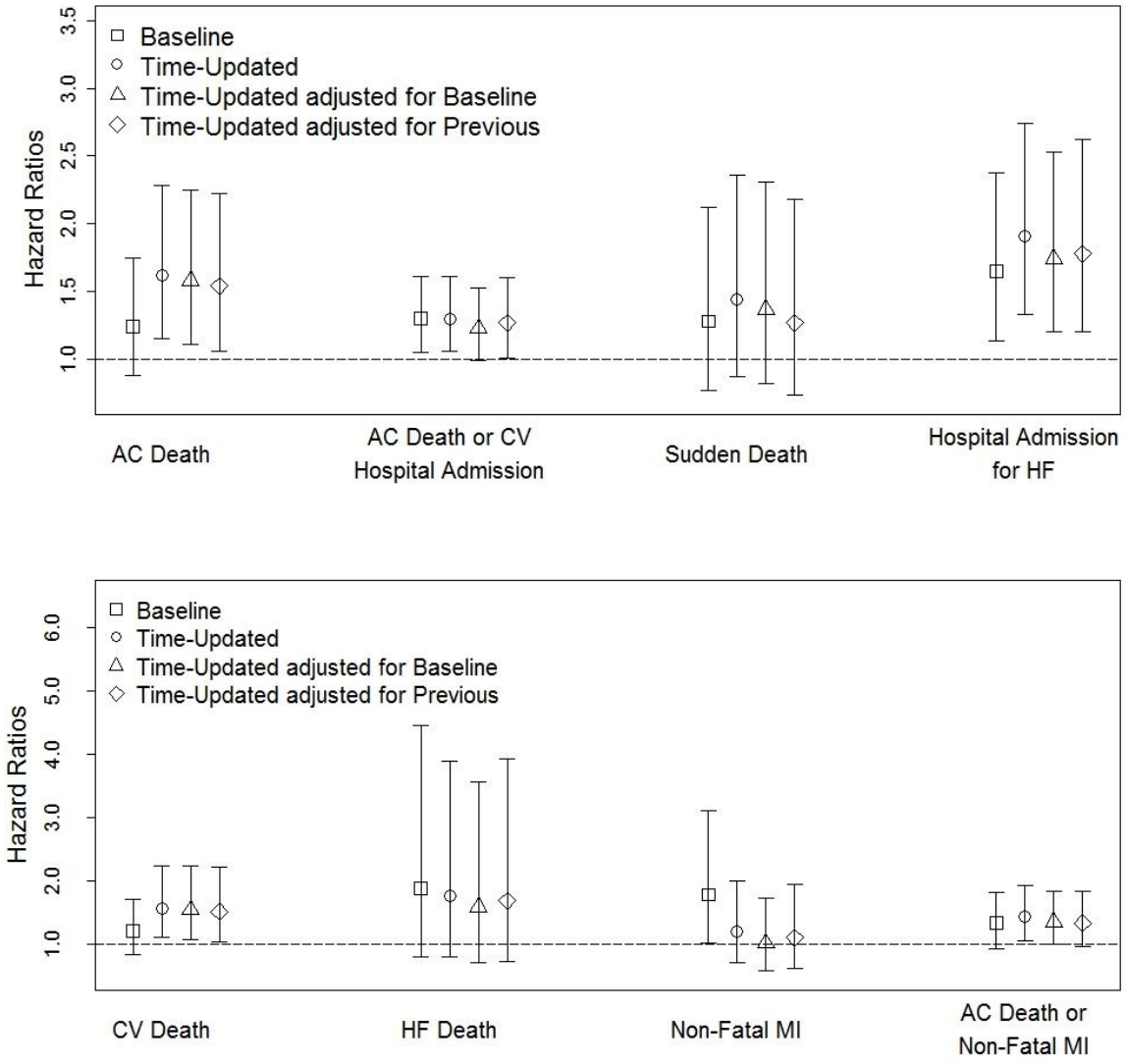
This table shows the total number of CAPRICORN placebo patients with available baseline resting heart rate data who experienced any pre-specified events of interest, as well as the number in relation to baseline heart rate, partitioned at 75bpm. Data are number of patients who experienced each event as a first event, with the corresponding percentage. Note that first event refers to the first event of each type: for example, a patient may have experienced a non-fatal MI, and then subsequently been admitted to hospital for HF at a later date.

The Cox regression models adjusted for the variables which were significantly different between the two baseline heart rate groups ($p \leq 0.05$); sex, previous diabetes, LVEF, site of MI, and in-hospital treatment with intravenous diuretics.

The linearity of effect for each continuous heart rate variable was evaluated by plotting the Martingale residuals (a linear transformation of Cox-Snell residuals)[252,253] of each model against the heart rate values. No violations of the linearity assumption were observed.

Comparing the risk of each of the outcomes between patients with a baseline or time-updated heart rate greater than or equal to 75bpm, or less than 75bpm, produced the HRs and CIs shown by Figure 4-6 and in Table A2-9 provided in Appendix 2.

Figure 4-6: Results of fitting Cox proportional hazards models. Hazard ratios with corresponding 95% confidence intervals for a heart rate ≥75bpm compared to a heart rate <75bpm in the CAPRICORN placebo population.



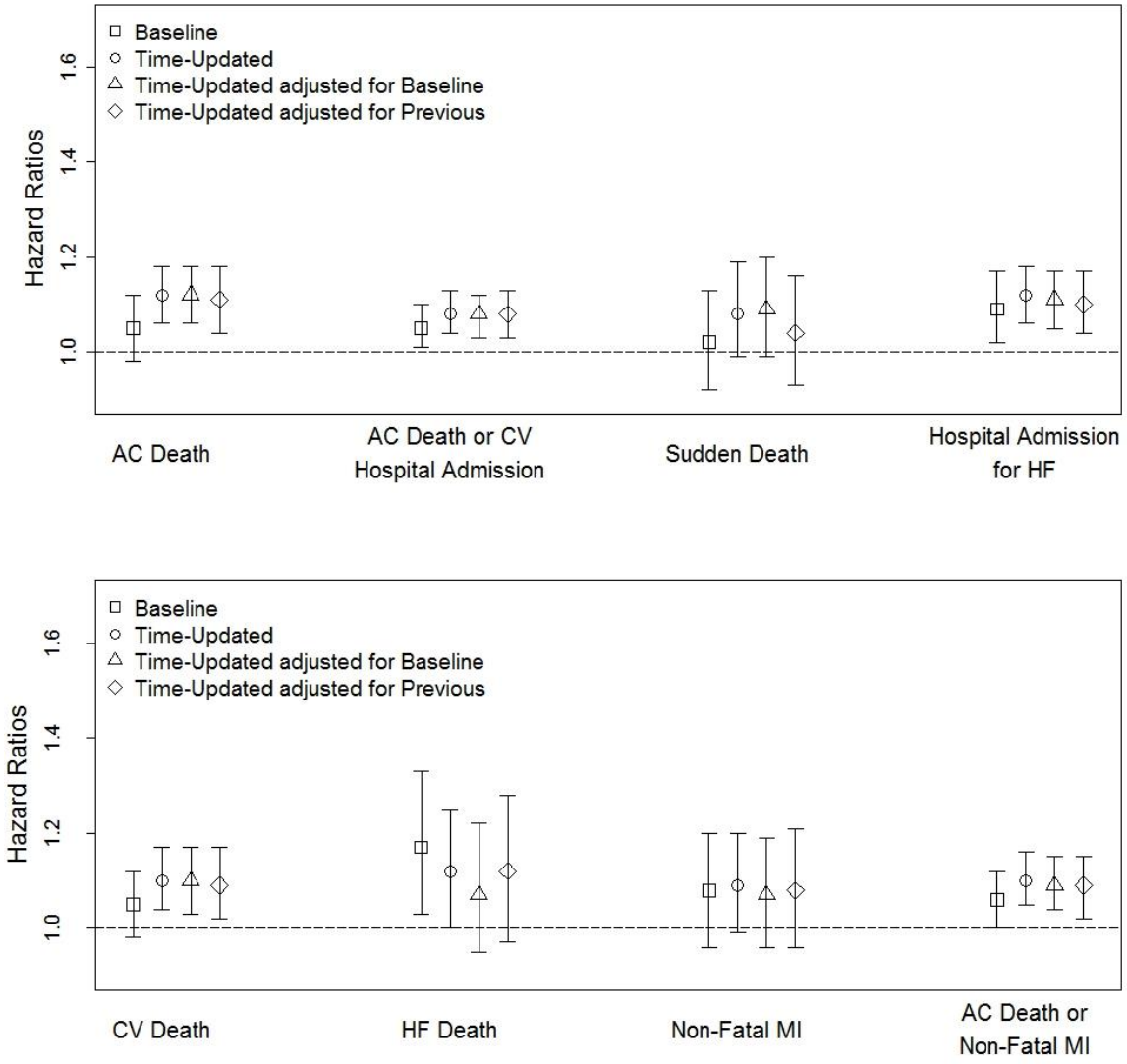
AC = All-Cause; CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction.

Models were additionally adjusted for: sex; previous diabetes; left-ventricular ejection fraction (LVEF); site of MI; and in-hospital treatment with intravenous diuretics.

A heart rate ≥75bpm was associated with an increase in risk of the combined endpoint of all-cause death or CV-cause hospital admission, and hospital admission for HF in all models fitted (time-updated heart rate adjusted for baseline was borderline significant for all-cause death or CV-cause hospital admission ($p = 0.067$)). A baseline resting heart rate ≥75bpm was not associated with an increase in risk of all-cause mortality, CV mortality or the combined endpoint of all-cause mortality or non-fatal MI. However, time-updated resting heart rate ≥75bpm was associated with a 62% ($p = 0.0058$) increase in risk of all-cause mortality, and a 57% increase in risk of CV mortality ($p = 0.013$), with the association remaining even after adjustment for baseline or the previous heart rate category. Similarly, time-updated heart rate ≥75bpm was associated with a 43% ($p = 0.019$) increase in risk of all-cause mortality or non-fatal MI, but after adjustment for baseline heart rate or the previous heart rate category, the association was attenuated slightly ($p = 0.058$ and $p = 0.082$ for adjustment for baseline, and the previous category, respectively). Conversely, a baseline heart rate ≥75bpm was associated with a 78% ($p = 0.042$) increase in risk of experiencing a non-fatal MI, while none of the time-updated heart rate variables were. No significant associations between heart rate and risk were observed for sudden death or death due to HF in any of the models.

Analysing continuous heart rate measurements produced the HRs and CIs shown by Figure 4-7 and in Table A2-10 provided in Appendix 2. The pattern of results was generally very similar to those for the categorical heart rate analysis, with the exceptions that baseline heart rate was no longer associated with risk of MI, and a 5bpm higher baseline heart rate was associated with a 17% ($p = 0.018$) increase in the risk of death due to HF.

Figure 4-7: Results of fitting Cox proportional hazards models. Hazard ratios with corresponding 95% confidence intervals for a 5bpm higher heart rate in the CAPRICORN placebo population.



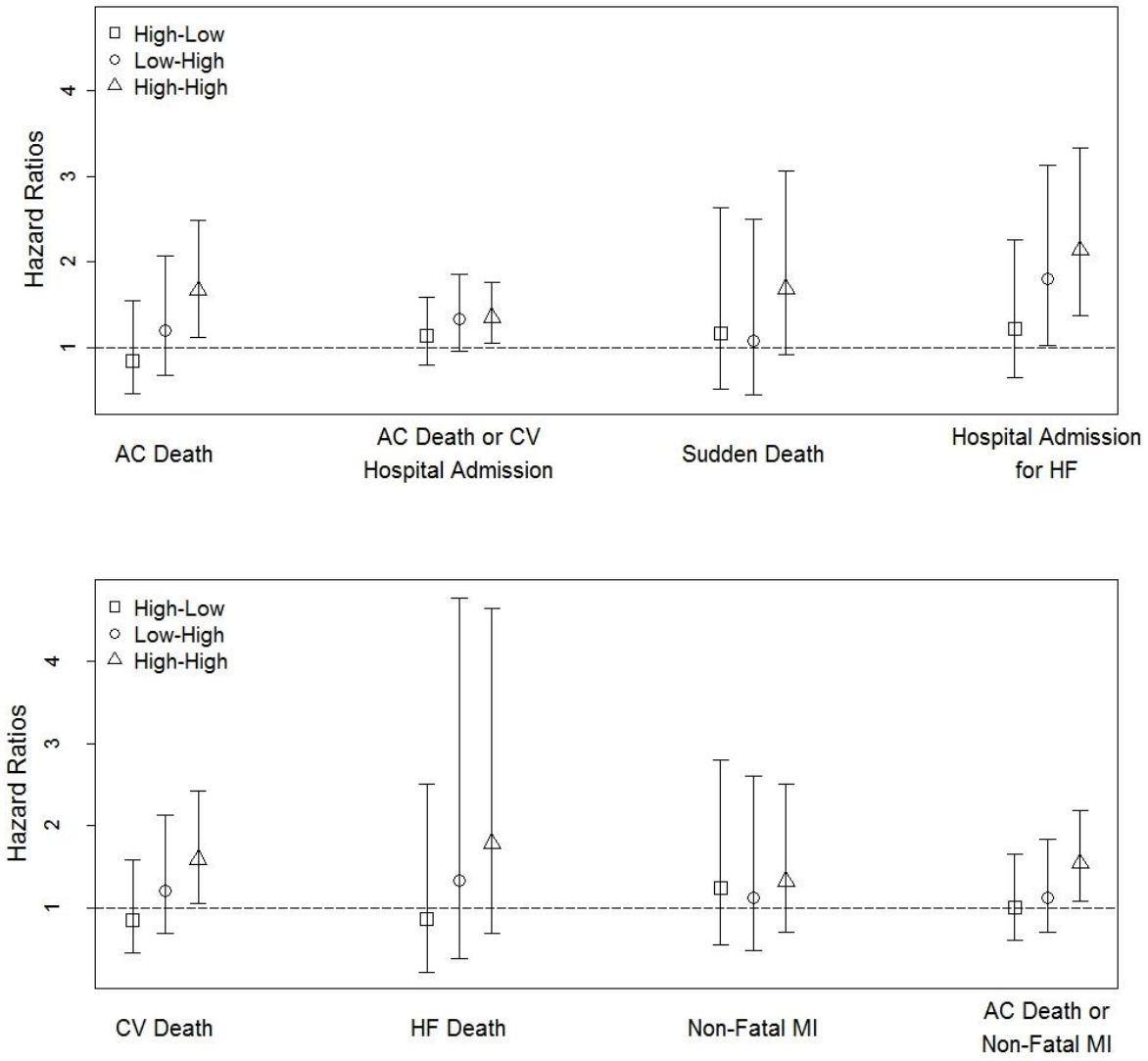
AC = All-Cause; CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction.

Models were additionally adjusted for: sex; previous diabetes; left-ventricular ejection fraction (LVEF); site of MI; and in-hospital treatment with intravenous diuretics.

Figure 4-8 and Table A2-11 show the adjusted HRs and 95% CIs estimated using the time-updated categorical heart rate patterns models. Comparing the current heart rate measurement at each visit to the previous heart rate measurement, those who had a heart rate ≥75bpm at both visits (high-high) were found to be at a higher risk of all-cause mortality (67%, 95% CI 12 to 149%, p = 0.012), the combined endpoint of all-cause mortality or CV cause hospital admission (36%, 95% CI 6 to 76%, p = 0.017), CV-cause mortality (59%, 95% CI 5 to 142%, p = 0.028), and all-cause death or non-fatal MI (54%, 95% CI 9 to 119%, p = 0.015), compared to those patients who had a heart rate <75bpm at both visits (low-low). Patients with a high heart rate at both visits (high-high), and an increase in heart rate from below 75bpm at the previous visit, to greater than or equal to 75bpm at the current visit (low-high), were at a significantly higher risk of hospital admission for HF compared to those patients with a low heart rate at both visits (low-high: 80%, 95% CI 3 to 213%, p = 0.038; high-high: 114%, 95% CI 38 to 233%, p<0.001). There were no significant increases in the risk of sudden death, death due to HF, or non-fatal MI.

The discrimination and calibration of the models were evaluated using Harrell's C-statistic and likelihood ratio tests, respectively. Table A2-12 provided in Appendix 2 shows Harrell's C-statistics for the model excluding resting heart rate, and the models including the heart rate variables that categorised subjects according to whether they had a heart rate less than, or greater than or equal to, 75bpm for each outcome. Regardless of whether any resting heart rate category variables were included, the models had the greatest predictive ability for hospital admission for HF and death due to HF: the C-statistics of the models both excluding and including resting heart rate ranged from 0.682 to 0.703, and 0.733 to 0.768 for each of these outcomes, respectively. The C-statistics of the models for the other outcomes ranged from 0.604 to 0.657. The addition of resting heart rate category improved discrimination for all of the outcomes compared to the model excluding heart rate. For all-cause death, hospitalisation for HF, death due to HF, and the combined endpoints of all-cause death

Figure 4-8: Results of fitting Cox proportional hazards models. Hazard ratios with corresponding 95% confidence intervals for the time-updated categorical heart rate patterns 'high-low', 'low-high' and 'high-high' relative to the category 'low-low' in the CAPRICORN placebo population.



Patients were classified as being in the low-low category if their heart rate measurement at both the current and previous visit was below 75bpm. Similarly, patients were classified as being in the high-high category if their heart rate measurement at both the current and previous visit was greater than or equal to 75bpm, and so on.

AC = All-Cause; CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction.

Models were additionally adjusted for: sex; previous diabetes; left-ventricular ejection fraction (LVEF); site of MI; and in-hospital treatment with intravenous diuretics.

or CV hospital admission, and all-cause death or non-fatal MI, the model including time-updated resting heart rate category additionally adjusted for baseline heart rate category had the best discrimination. The greatest improvement in discrimination was observed for death due to HF, with the C-statistic increasing from 0.733 to 0.768. The model including time-updated heart rate category additionally adjusted for the previous heart rate category had the best discrimination for sudden death, and both of the time-updated heart rate models adjusted for either baseline or the previous heart rate category had the best for CV death. Conversely, the model including baseline resting heart rate only, had the best predictive ability for non-fatal MI, which corresponds with the fact that a baseline heart rate ≥75bpm was associated with an increase in risk of MI, while none of the time-updated heart rate variables were. The likelihood ratio test statistics and corresponding p-values for the addition of the heart rate category variables to the models are also presented in Table A2-12. The addition of any of the heart rate category variables resulted in statistically significant improvements in the calibration of the models for all-cause death, the combined endpoint of all-cause death or CV hospital admission, and hospital admission for HF. Only the addition of the time-updated heart rate category variable, with or without adjustment for baseline or the previous heart rate category, improved the calibration of the models for CV death, and the combined endpoint of all-cause death or non-fatal MI. On the other hand, only the addition of baseline heart rate category improved the calibration of the model for non-fatal MI. There were no significant improvements in model calibration for sudden death or death due to HF with the addition of any of the heart rate category variables.

Harrell's C-statistics for the model excluding resting heart rate, and the models including the continuous heart rate variables, for each outcome, are shown in Table A2-13 provided in Appendix 2, along with the likelihood ratio test statistics and corresponding p-values for the addition of the different continuous heart rate variables. The results were very similar to those observed for the heart rate categories according to whether subjects had a heart rate less than, or greater than or equal to 75bpm, with

a few exceptions. First, the model including continuous time-updated heart rate additionally adjusted for baseline heart rate had the best discrimination for non-fatal MI, as opposed to the model including only baseline heart rate, but there were no significant improvements in model calibration for MI with the addition of any of the continuous heart rate variables. Second, the addition of baseline heart rate, or time-updated heart rate (but not in combination with baseline or previous heart rate) improved the calibration of the model for death due to HF.

Table A2-14 provided in Appendix 2 shows Harrell's C-statistics for the model excluding resting heart rate, and the models including the time-updated categorical heart rate patterns variable for each outcome. Again, irrespective of whether resting heart rate was included, the models had the greatest predictive ability for hospital admission for HF and death due to HF. The addition of time-updated categorical heart rate pattern improved discrimination for all of the outcomes. The largest improvements in discrimination were observed for sudden death and death due to HF, with the C-statistics increasing from 0.622 to 0.640, and 0.733 to 0.752, respectively, when time-updated heart rate pattern was added to the models. The smallest were observed for the composite of all-cause death or CV hospital admission, and non-fatal MI, with the C-statistics increasing from 0.604 to 0.611, and 0.632 to 0.638, respectively. The likelihood ratio test statistics and corresponding p-values for the addition of the heart rate patterns variable to the models are also presented in Table A2-14. The addition of heart rate pattern only resulted in statistically significant improvements in the calibration of the models for all-cause death and hospital admission for HF; there were no significant improvements in model calibration for any of the other outcomes.

Tables A2-15, A2-16 and A2-17 in Appendix 2 show the p-values of the Grambsch and Therneau 1994 test for non-proportionality of hazards for all of the models and outcomes. There were no violations of the proportional hazard assumption for any of the heart rate variables that were associated with risk of outcome.

4.4 Discussion

In the large pooled population of patients after MI with HF, LVSD, or both, an elevated baseline resting heart rate was associated with an increase in the risk of all of the endpoints evaluated, except for fatal or non-fatal stroke. The addition of baseline heart rate also resulted in statistically significant improvements in the calibration of the models for all of the outcomes except fatal or non-fatal stroke. However, adding baseline heart rate to the models improved discrimination for every outcome. The associations were similar for all-cause death, CV death, and HF hospitalisation, but were weaker for CV hospitalisation and subsequent MI. The models had the greatest predictive ability for the three former endpoints, and the least for CV hospitalisation. Evidence of non-proportionality of the effect of an elevated heart rate was observed for all outcomes (excluding higher heart rate group for fatal or non-fatal stroke). It appeared that the association between elevated heart rate and risk of each outcome was highest immediately after MI, and decreased over time.

When differences between each of the four cohorts were examined, it was discovered that the relationship between heart rate and CV hospitalisation, the combined endpoint of CV death or CV hospitalisation, and the individual endpoint of subsequent MI, were particularly different in the OPTIMAAL population. For example, a raised resting heart rate was associated with an increase in the risk of CV death or CV hospitalisation in all of the populations except OPTIMAAL, despite the fact that the number of CV death or CV hospitalisation events that occurred in OTPIMAAL (n = 3215) were similar to the number that occurred in EPHESUS (n = 3116). Similarly, a raised resting heart rate was associated with an increase in the risk of subsequent MI in the EPHESUS and VALIANT populations, but was not associated with risk in either CAPRICORN or OPTIMAAL. Few recurrent MI events occurred in CAPRICORN (n = 118), however, which could explain the insignificant association, whereas the number that occurred in OPTIMAAL (n = 657) was again similar to the number that occurred in EPHESUS (n = 604).

In the small placebo population of patients with MI and LVSD from CAPRICORN, an elevated resting heart rate was associated with an increase in the risk of all the endpoints evaluated, except for sudden death. The addition of resting heart rate also resulted in statistically significant improvements in the calibration of the models for all of the outcomes except sudden death. However, adding resting heart rate to the models improved discrimination for all of the endpoints.

Both an elevated baseline and time-updated heart rate, unadjusted and adjusted for the baseline or previous heart rate measurement, were associated with an increase in the risk of hospital admission for HF; the addition of any of the heart rate variables also resulted in statistically significant improvements in the calibration of the models.

While no associations between baseline heart rate and risk of all-cause or CV death were observed, an elevated time-updated heart rate was similarly associated with an increase in risk of both endpoints. When heart rate was treated as a continuous variable, only the addition of the time-updated heart rate variables, with or without adjustment for baseline or the previous heart rate measurement, improved the calibration of the models for all-cause and CV death (the addition of any of the heart rate category variables resulted in statistically significant improvements in the calibration of the models for all-cause death). Generally, the models including time-updated heart rate additionally adjusted for the baseline or previous heart rate measurement had the best discrimination for hospital admission for HF, all-cause death and CV death. This suggests that, despite knowing the baseline or previous heart rate measurement, the current measurement contributes significant additional information about risk of each of these endpoints.

Only an elevated continuous baseline heart rate, and a baseline heart rate ≥75bpm, were associated with an increase in the risk of death due to HF, and non-fatal MI, respectively. The model including baseline heart rate category also had the best discrimination for non-fatal MI, and was the only model found to have a significantly

better calibration than the model excluding heart rate. The model including continuous baseline heart rate was also found to have a significantly better calibration than the model excluding heart rate for death due to HF. Conversely, the time-updated heart rate model adjusted for baseline heart rate had the greatest discriminative ability for death due to HF, regardless of whether heart rate was treated as a categorical or continuous variable.

The results found using baseline heart rate in the pooled analysis were similar to those found using time-updated heart rate in the CAPRICORN placebo analysis for all-cause and CV death. Furthermore, using time-updated heart rate appeared to strengthen the associations, despite less than 200 deaths occurring in the CAPRICORN placebo population, compared to more than 4000 occurring in the pooled population. For example, in the pooled analysis, a 5bpm higher baseline heart rate was associated with a 7% ($p<0.001$) and an 8% ($p<0.001$) increase in risk of all-cause and CV death, respectively; in the CAPRICORN analysis, a 5bpm higher time-updated heart rate adjusted for baseline was associated with a 12% ($p<0.001$) and a 10% ($p = 0.0031$) increase in risk, respectively.

Previous studies of post-MI patients have found similar increases in the risk of all-cause death[164,171,183]. In addition, Fox et al. 2008[184] and Bohm et al. 2010[182] found that a 5bpm higher baseline heart rate was associated with a similar 8% ($p = 0.05$) and 16% ($p<0.001$) increase in the risk of CV death in patients with LVSD who had CHD, or HF, respectively. In contrast, Antoni et al. 2012 demonstrated that a 5bpm higher discharge heart rate was associated with a much higher 26% ($p<0.001$) and 24% ($p<0.001$) increase in the risk of all-cause death and CV death four years after discharge, respectively, in STEMI patients treated with PCI[169].

The results found using baseline heart rate in regards to hospital admission for HF were similar between the two analyses, despite only 138 events occurring in the CAPRICORN population compared to 3375 in the pooled population. Again, the association was

apparently strengthened when time-updated heart resting heart rate was used. For example, a 5bpm higher baseline heart rate was associated with an 8% ($p<0.001$) and a 9% ($p = 0.012$) increase in hospitalisation for HF in the pooled and CAPRICORN analysis, respectively, and a 5bpm higher time-updated heart rate adjusted for baseline was associated with an 11% ($p<0.001$) increase in risk.

None of the studies of ACS patients identified in the review of Chapter 2 evaluated risk of long-term HF hospitalisation. However, Bohm et al. further illustrated that a 5bpm higher baseline heart rate was associated with a similar 16% increase in the risk of hospital admission for HF in patients with chronic HF and LVSD[182].

It is not clear why OPTIMAAL was an outlier in the pooled analysis. The main differences between it and the other studies were that it followed patients up for around three years, while each of the others followed patients up for around one or two years, and only recruited patients aged 50 years or older. Further examination of OPTIMAAL would be required to understand if and how these differences affect the relationship between heart rate and outcome.

No association between an elevated baseline heart rate and the risk of fatal or non-fatal stroke was observed in the pooled analysis. Although discrimination of the model improved slightly with the addition of baseline heart rate (from 0.675 to 0.679 and 0.676 for categorical and continuous heart rate, respectively), there were no improvements in model calibration. However, the number of stroke events that occurred was less than 1000 ($n = 937$), whereas at least 3000 of each of the other endpoints occurred. In addition, a 5bpm higher baseline heart rate was borderline significantly associated with an increase in risk (HR 1.02, 95% CI 1.00 to 1.05), so there may have been an insufficient number of events for the association to reach significance. Similarly, no association between any of the heart rate variables and the risk of sudden death was observed in the CAPRICORN placebo population analysis. Again, discrimination of the models was improved with the addition of resting heart

rate, but there were no improvements in model calibration. However, the number of sudden deaths was also relatively small (n = 68). Moreover, both a 5bpm higher time-updated heart rate unadjusted and adjusted for baseline were borderline significantly associated with an increase in risk of sudden death (unadjusted for baseline: HR 1.08, 95% CI 0.99 to 1.19, p = 0.087; adjusted for baseline: HR 1.09, 95% CI 0.99 to 1.20, p = 0.094), so again there may have been an insufficient number of events for the association to reach significance. None of the studies of subjects with ACS identified in Chapter 2, or those that included subjects all of whom had LVSD, investigated the relationship between heart rate and stroke or sudden death. Thus, further analyses of the relationship between resting heart rate and risk of these endpoints including a greater number of events could be insightful.

None of the time-updated heart rate variables were able to predict risk of death due to HF, or non-fatal MI in the CAPRICORN placebo population analysis. This is likely due to there being only 30 deaths due to HF, and 57 non-fatal MI events. A 5bpm higher time-updated heart rate was borderline significantly associated with an increase in risk of both death due to HF (HR 1.12, 95% CI 1.00 to 1.25, p = 0.060) and non-fatal MI (HR 1.09, 95% CI 0.99 to 1.20, p = 0.089). Future studies of the relationship between time-updated heart rate and risk of HF death and non-fatal MI could be illuminating.

4.4.1 Chapter Summary and Conclusions

This chapter examined the associations between baseline and time-updated resting heart rate, and long-term adverse CV events, in post-MI patients with HF, LVSD, or both. Firstly, using the High Risk MI Database, a pooled individual patient meta-analysis of the CAPRICORN, EPHESUS, OPTIMAAL and VALIANT trials, assessing the predictive value of baseline resting heart rate, was carried out. Secondly, the prognostic value of both baseline and time-updated heart rate measurements in the CAPRICORN placebo population was evaluated.

An elevated baseline resting heart rate was shown to be a risk marker for all-cause death, CV death, CV hospital admission, HF hospital admission, subsequent MI and HF death in the population of post-MI patients with LVSD, HF or both who were included in the High Risk MI Database. In the CAPRICORN population of post-MI patients with LVSD, time-updated resting heart rate also carried additional prognostic information for all-cause death, CV death and hospitalisation for HF, regardless of whether baseline resting heart rate or the previous heart rate measurement were known.

Chapter 5 further assesses the predictive value of baseline and time-updated resting heart rate for adverse CV outcomes and mortality in the EUROPA population of patients, who had stable CHD without HF.

Chapter 5

Heart Rate and Risk in the EUROPA Population

5.1 Introduction

The prognostic value of baseline resting heart rate for death and adverse CV outcomes has previously been assessed in patients with stable CHD, some of whom had a history of HF[148-151,184,208]. An elevated baseline resting heart rate has been associated with an increase in the risk of all-cause death[148,149], CV death[148,184], and hospital admission for HF[148,149,184] in different populations of CHD patients. However, from the review of Chapter 2 it seems that associations between heart rate and risk of MI and coronary revascularisation have only been observed in CHD patients specifically with LVSD[184]. Furthermore, a relationship between heart rate and risk of stroke or angina has yet to be established, and risk of cardiac arrest has not yet been evaluated.

Using data from the EUROPA trial[240], this analysis examined the prognostic value of baseline and time-updated resting heart rate for death and adverse CV outcomes, including stroke, angina and cardiac arrest, in patients with stable CHD with no apparent HF. The systematic review of Chapter 2 did not identify any studies of time-updated heart rate in patients with CHD.

5.2 Methods and Results

Data of patients from both treatment arms of EUROPA (perindopril or placebo) were pooled for this analysis since perindopril does not directly affect heart rate. Baseline heart rate is defined as the heart rate the subjects had measured at their randomisation visit, Visit 3. 12,208 of the patients (99.9% of the 12,218 patients included in the trial) had a baseline heart rate measurement available and were included in the present analysis.

The following outcomes were assessed: the composite of CV mortality, non-fatal MI or cardiac arrest with successful resuscitation (the primary endpoint of EUROPA); its individual components (CV mortality, fatal or non-fatal MI, and cardiac arrest); the composite of total mortality, non-fatal MI, unstable angina or cardiac arrest with successful resuscitation (the first secondary endpoint of EUROPA); total mortality; unstable angina; stroke; revascularisation; and HF requiring hospital admission.

The heart rate cut-off of 70bpm was selected since prior published research has suggested that the risk associated with heart rate rises greatly above this value[148,156,208]. The baseline characteristics of the EUROPA population, overall and categorised into groups depending on whether their baseline resting heart rate was less than, or greater than or equal to, 70bpm are shown in Table 5-1. There were significant differences between the two groups of patients in terms of age, sex, history of PCI and CABG, PAD, diabetes, hypercholesterolemia, SBP, DBP, and treatment with platelet inhibitors, lipid-lowering agents, beta-blockers, CCBs, and diuretics. Patients with a heart rate of 70bpm or greater at baseline were younger, with a higher SBP and DBP than those with a baseline heart rate of less than 70bpm. They were also more likely to be female, have previously had a CABG procedure, PAD, and diabetes, and less likely to have had a PCI and have hypercholesterolemia. Patients in the higher heart rate group were also more likely to be treated with CCBs and diuretics, and less likely to be treated with platelet inhibitors, lipid-lowering agents, and beta-blockers.

The total number of events that occurred in the EUROPA population is presented in Table 5-2, along with the number that occurred in each of the baseline heart rate groups of patients. The percentage of patients with a baseline heart rate of 70bpm or greater who experienced an event was higher for every event compared to the patients with a baseline heart rate less than 70bpm.

Table 5-1: Baseline characteristics of the EUROPA study population.

	Baseline Heart Rate			
	All Subjects n = 12208	**<70bpm n = 7631**	**≥70bpm n = 4577**	**p-value**
Demographic Characteristics				
Age (years)	60.7 (9.3)	60.9 (9.2)	60.2 (9.5)	<0.001
Sex (female)	1779 (15%)	1019 (13%)	760 (17%)	<0.001
History of Coronary Heart Disease				
History of MI	7913 (65%)	4909 (64%)	3004 (66%)	0.14
History of PCI	3568 (29%)	2322 (30%)	1246 (27%)	<0.001
History of CABG	3582 (29%)	2104 (28%)	1478 (32%)	<0.001
Other Medical History				
Previous stroke or TIA	407 (3%)	245 (3%)	162 (4%)	0.33
Peripheral artery disease	882 (7%)	519 (7%)	363 (8%)	0.020
Hypertension	3312 (27%)	2086 (27%)	1226 (27%)	0.51
Diabetes mellitus	1502 (12%)	843 (11%)	659 (14%)	<0.001
Hypercholesterolemia	7730 (63%)	4891 (64%)	2839 (62%)	0.022
Medication at Randomisation (Visit 3)				
Platelet inhibitors	11266 (92%)	7126 (93%)	4140 (90%)	<0.001
Lipid-lowering therapy	7026 (58%)	4462 (58%)	2564 (56%)	0.0080
Beta-blockers	7530 (62%)	5392 (71%)	2138 (47%)	<0.001
Calcium-channel blockers	3822 (31%)	2319 (30%)	1503 (33%)	0.0047
Nitrates	5241 (43%)	3328 (44%)	1913 (42%)	0.050
Diuretics (potassium-sparing and other)	1028 (8%)	557 (7%)	471 (10%)	<0.001
Cardiac Parameters at Randomisation (Visit 3)				
Mean Heart Rate (bpm)	66.4 (10.4)	59.9 (5.9)	77.1 (7.0)	-
Mean SBP (mm Hg)	129.5 (16.2)	129.1 (16.4)	130.2 (16.0)	<0.001
Mean DBP (mm Hg)	78.1 (8.9)	77.6 (8.9)	78.9 (8.8)	<0.001

This table shows the clinical and demographic characteristics of the EUROPA patient population. Values are given for the overall population, as well as separately for patients who had a baseline resting heart rate <70bpm, and patients who had a baseline resting heart rate ≥70bpm. Data are the number of patients with the corresponding percentage, or the mean with the standard deviation, depending on whether the variable was categorical or continuous, respectively. Not all patients had every baseline measurement available. Therefore, percentages and means were calculated using the number of subjects with non-missing data as the denominator. The values of each characteristic were compared between the two different baseline resting heart rate groups using unpaired two-sample t-tests and chi-squared tests, for continuous and categorical variables, respectively.

Hypertension was defined as a blood pressure >160/95 mm Hg or receiving antihypertensive treatment. Hypercholesterolemia was defined as a total cholesterol >6.5 mmol/L or receiving lipid-lowering treatment.

Subjects had their blood pressure measured twice at baseline and the mean of both SBP and DBP values was taken as their overall baseline value. The overall mean for each heart rate group was then calculated using the mean baseline SBP and DBP values of each patient.

CABG = Coronary Artery Bypass Graft; DBP = Diastolic Blood Pressure; MI = Myocardial Infarction; PCI = Percutaneous Coronary Intervention; SBP = Systolic Blood Pressure; TIA = Transient Ischemic Attack.

Table 5-2: The number of first events that occurred in the EUROPA population.

		Baseline Heart Rate	
	Total Population n = 12208	**<70bpm n = 7631**	**≥70bpm n = 4577**
Primary Composite Endpoint			
Cardiovascular mortality, MI, or cardiac arrest	1091 (9%)	422 (6%)	669 (15%)
Individual Components of the Primary Composite Endpoint			
Cardiovascular mortality	464 (4%)	193 (3%)	271 (6%)
Fatal or non-fatal MI	738 (6%)	268 (4%)	470 (10%)
Cardiac arrest	17 (0.1%)	7 (0.1%)	10 (0.2%)
Other Composite Endpoints			
Total mortality, MI, unstable angina or cardiac arrest	1946 (16%)	748 (10%)	1198 (26%)
Other Mortality Endpoints			
Total mortality	795 (7%)	338 (4%)	457 (10%)
Other Individual Endpoints			
Unstable Angina	708 (6%)	251 (3%)	457 (10%)
Stroke	199 (2%)	73 (1%)	126 (3%)
Revascularisation	1177 (10%)	392 (5%)	785 (17%)
Heart failure requiring hospital admission	166 (1%)	78 (1%)	88 (2%)

This table shows the total number of EUROPA patients with available baseline resting heart rate data who experienced any pre-specified events of interest, as well as the number in relation to baseline heart rate, partitioned at 70bpm. Data are number of patients who experienced the event as a first event and the corresponding percentage of the particular group. Note that first event refers to the first event of each type: for example, a patient may have experienced a stroke, and then subsequently been admitted to hospital for HF at a later date.

MI = Myocardial Infarction.

The Cox regression models were adjusted for the variables which were significantly different between the two baseline heart rate groups ($p<0.05$): age; sex; history of PCI; history of CABG; PAD; diabetes mellitus; hypercholesterolemia; treatment with platelet inhibitors; lipid-lowering therapies; beta-blockers; CCBs; and diuretics (potassium-sparing and other); and SBP and DBP.

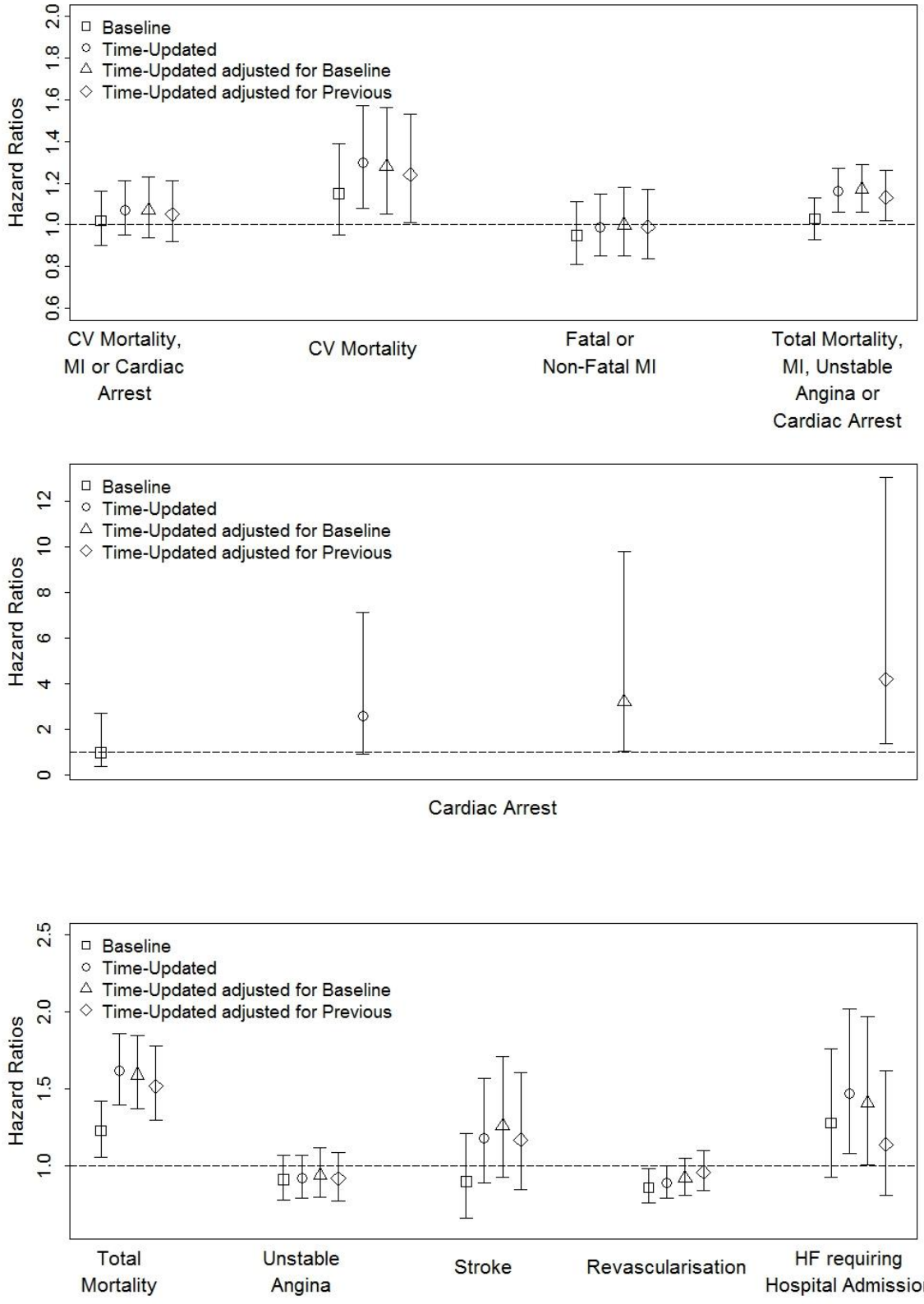
The linearity of effect for each continuous heart rate variable was evaluated by plotting the Martingale residuals (a linear transformation of Cox-Snell residuals)[252,253] of each model against the heart rate values. No violations of the linearity assumption were observed.

Comparing the risk of each of the outcomes between patients with a baseline or time-updated heart rate greater than or equal to 70bpm versus patients with a heart rate less than 70bpm produced the HRs and CIs shown by Figure 5-1 and in Table A3-1 provided in

Appendix 3. The CIs of the HRs for cardiac arrest were much wider than the others due to the small number of events which is why they are plotted individually.

A heart rate ≥70bpm was associated with an increase in risk of total mortality in all models fitted. A baseline resting heart rate ≥70bpm was not associated with an increase in risk of CV mortality, the combined endpoint of total mortality, MI, unstable angina or cardiac arrest, or HF requiring hospital admission. However, time-updated resting heart rate ≥70bpm predicted a 30% ($p = 0.0059$) increase in risk of CV mortality, and a 16% ($p = 0.0017$) increase in risk of the combined endpoint of total mortality, MI, unstable angina or cardiac arrest, with the association remaining even after adjustment for baseline or the previous heart rate category. Similarly, time-updated heart rate ≥70bpm predicted a 47% ($p = 0.015$) increase in risk of HF requiring hospital admission, with the association remaining after adjustment for baseline ($p = 0.042$) but being attenuated after adjustment for the previous heart rate category ($p = 0.46$). Despite there being only 17 cardiac arrest events over the length of follow-up, a time-updated heart rate ≥70bpm adjusted for baseline, and adjusted for the most previous measurement, was found to be associated with a 220% ($p = 0.041$) and 219% ($p = 0.013$) increase in risk of cardiac arrest, respectively. A baseline heart rate ≥70bpm was associated with a 14% ($p = 0.020$) decrease in risk of revascularisation, while none of the time-updated heart rate variables were associated with an increase or decrease in risk. There was no significant increase in risk observed with elevated heart rate for the combined endpoint of CV mortality, MI or cardiac arrest, or the individual endpoints fatal or non-fatal MI, unstable angina, or stroke.

Figure 5-1: Results of fitting Cox proportional hazards models. Hazard ratios with corresponding 95% confidence intervals for a heart rate ≥70bpm compared to a heart rate <70bpm in the EUROPA population.

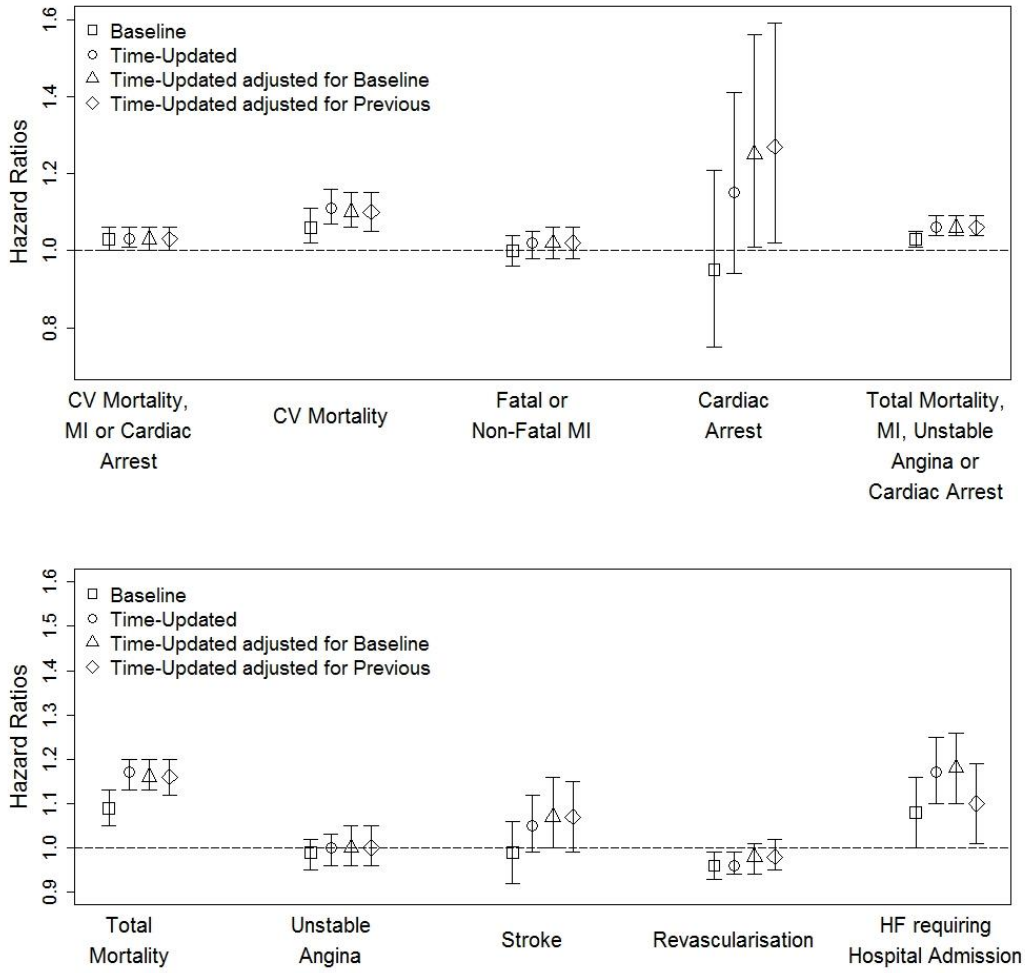


The confidence intervals of the hazard ratios for cardiac arrest were much wider than the others due to the small number of events which is why they are plotted individually. CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction.

Models were additionally adjusted for: age; sex; history of percutaneous coronary intervention (PCI); history of coronary artery bypass graft (CABG); peripheral artery disease (PAD); diabetes mellitus; hypercholesterolemia; treatment with platelet inhibitors; lipid-lowering therapies; beta-blockers; calcium channel blockers (CCBs); and diuretics (potassium sparing and other); and systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Analysing continuous heart rate measurements produced the HRs and CIs shown by Figure 5-2 and in Table A3-2 provided in Appendix 3. A 5bpm higher heart rate was associated with higher risk of CV mortality, the combined endpoint of total mortality, MI, unstable angina or cardiac arrest, and the individual endpoints of total mortality and HF requiring hospital admission in all models (baseline heart rate was borderline significant for HF requiring hospital admission (p = 0.052)).

Figure 5-2: Results of fitting Cox proportional hazards models. Hazard ratios with corresponding 95% confidence intervals for a 5bpm higher heart rate in the EUROPA population.



CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction.

Models were additionally adjusted for: age; sex; history of percutaneous coronary intervention (PCI); history of coronary artery bypass graft (CABG); peripheral artery disease (PAD); diabetes mellitus; hypercholesterolemia; treatment with platelet inhibitors; lipid-lowering therapies; beta-blockers; calcium channel blockers (CCBs); and diuretics (potassium sparing and other); and systolic blood pressure (SBP) and diastolic blood pressure (DBP).

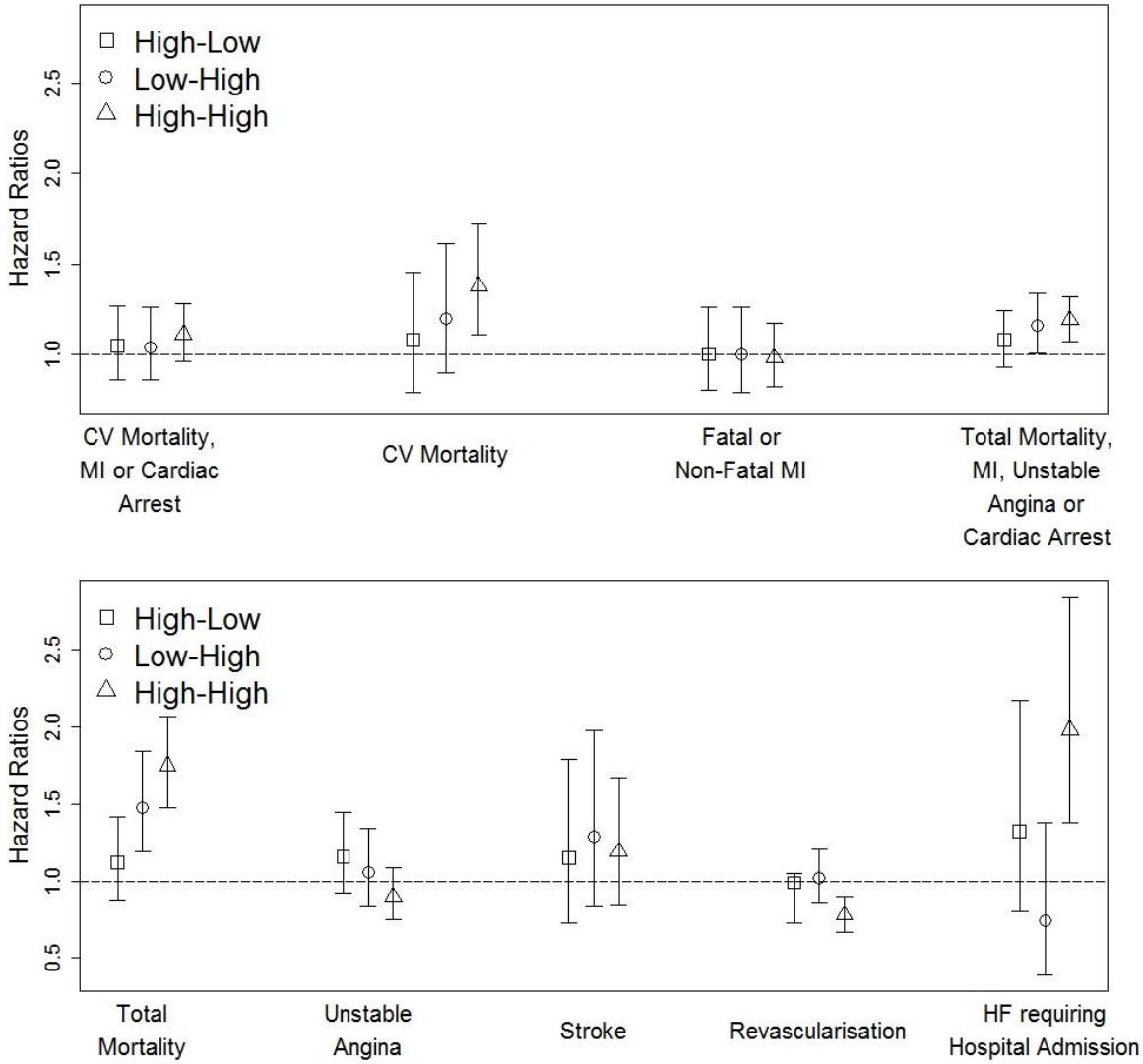
An elevated continuous baseline heart rate was not associated with an increase in risk of the combined endpoint of CV mortality, MI or cardiac arrest, and cardiac arrest analysed individually. However, a 5bpm higher time-updated heart rate was associated with a 3% (p = 0.019) increase in risk of CV mortality, MI or cardiac arrest; the association was attenuated when time-updated heart rate was adjusted for baseline or the previous measurement. On the other hand, a 5bpm higher time-updated heart rate was not associated with an increase in risk of cardiac arrest, but time-updated heart rate adjusted for baseline and the previous measurement was associated with a 25% (p = 0.045) and a 27% (p = 0.035) increase in risk of cardiac arrest, respectively. Both a 5pm higher baseline resting heart rate, and a 5bpm higher time-updated heart were found to be associated with a 4% (p = 0.0070 for baseline and p = 0.011 for time-updated) lower risk of revascularisation. There were no significant associations between elevated continuous heart rate and risk of fatal or non-fatal MI, unstable angina, or stroke (although time-updated heart rate adjusted for baseline was borderline significant for stroke (p = 0.051)).

Figure 5-3 and Table A3-3 provided in Appendix 3 show the adjusted HRs and 95% CIs estimated using the time-updated categorical heart rate patterns models. Comparing the current heart rate measurement at each visit to the previous heart rate measurement, patients who had a heart rate ≥70bpm at both visits (high-high) were found to be at a higher risk of CV mortality (38% increase in risk, 95% CI 11 to 72%, p = 0.0040) and HF requiring hospitalisation (98%, 38 to 184%, p<0.001), compared to patients who had a heart rate <70bpm at both visits (low-low). In contrast, subjects with a persistently high heart rate were shown to be at a lower risk of revascularisation (22% decrease in risk, 95% CI 10 to 33%, p = 0.0010), compared to patients who had a heart rate <70bpm at both visits (low-low). Patients with a high heart rate at both visits (high-high), and an increase in heart rate from below 70bpm at the previous visit, to ≥70bpm at the current visit (low-high), were at a higher risk of the combined endpoint of total mortality, MI, unstable angina or cardiac arrest (low-high: 16%, 95% CI

1 to 34%, p = 0.035; high-high: 19% 95% CI 7 to 32%, p = 0.0020), as well as total mortality analysed individually (low-high: 48%, 95% CI 19 to 84%, p<0.001; high-high: 75%, 95% CI 48 to 107%, p<0.001), compared to those patents who had a heart rate <70bpm at both visits (low-low). No significant associations between time-updated heart rate pattern and risk were observed for the combined endpoint CV mortality, MI or cardiac arrest, or the individual endpoints fatal or non-fatal MI, unstable angina, and stroke. There were not enough cardiac arrest events to allow HRs to be calculated using the time-updated categorical heart rate patterns models.

The discrimination and calibration of the models were evaluated using Harrell's C-statistic and likelihood ratio tests, respectively. Table A3-4 provided in Appendix 3 shows Harrell's C-statistics for the model excluding resting heart rate, and the models including the heart rate variables that categorised subjects according to whether they had a heart rate less than, or greater than or equal to 70bpm, for each outcome. Regardless of whether any resting heart rate category variables were included, the models had the greatest predictive ability for cardiac arrest and HF requiring hospital admission: the C-statistics of the models both excluding and including resting heart rate ranged from 0.808 to 0.850, and 0.754 to 0.768 for each of these outcomes, respectively. The models had the least predictive ability for unstable angina, with C-statistics ranging from 0.587 to 0.585. The C-statistics of the models for the other outcomes ranged from 0.602 to 0.721. The addition of baseline or time-updated resting heart rate category improved discrimination for CV mortality, total mortality, and HF requiring hospital admission, compared to the model excluding heart rate. The same was true for unstable angina and revascularisation, although the C-statistics increased by only 0.001 or 0.002 with the addition of one of the heart rate category variables. The model including time-updated heart rate category additionally adjusted for the previous heart rate category had the best discrimination for the former three endpoints. Only the addition of the time-updated heart rate category variable, with or without

Figure 5-3: Results of fitting Cox proportional hazards models. Hazard ratios with corresponding 95% confidence intervals for the time-updated categorical heart rate patterns 'high-low', 'low-high' and 'high-high' relative to the category 'low-low' in the EUROPA population.



Patients were classified as being in the low-low category if their heart rate measurement at both the current and previous visit was below 70bpm. Similarly, patients were classified as being in the high-high category if their heart rate measurement at both the current and previous visit was greater than or equal to 70bpm, and so on. There were not enough cardiac arrest events to allow HRs to be calculated using these models, hence why it is not included here.

CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction.

Models were additionally adjusted for: age; sex; history of percutaneous coronary intervention (PCI); history of coronary artery bypass graft (CABG); peripheral artery disease (PAD); diabetes mellitus; hypercholesterolemia; treatment with platelet inhibitors; lipid-lowering therapies; beta-blockers; calcium channel blockers (CCBs); and diuretics (potassium sparing and other); and systolic blood pressure (SBP) and diastolic blood pressure (DBP).

adjustment for baseline or the previous heart rate category, improved the discrimination of the models for stroke, cardiac arrest, and the combined endpoints of CV mortality, MI or cardiac arrest, and total mortality, MI, unstable angina or cardiac arrest. While discrimination was substantially improved for cardiac arrest, the C-statistics for stroke and the two composite outcomes increased by only 0.001 or 0.002 with the addition of time-updated heart rate category. Again, the model including time-updated heart rate category additionally adjusted for the previous heart rate category had the best discrimination for cardiac arrest. There was no improvement in discrimination for fatal or non-fatal MI with the addition of any of the heart rate category variables. The likelihood ratio test statistics and corresponding p-values for the addition of the heart rate category variables to the models are also presented in Table A3-4. The addition of any of the heart rate category variables resulted in statistically significant improvements in the calibration of the model for total mortality. Similarly, the addition of baseline or time-updated heart rate category, but only when additionally adjusted for baseline or the previous heart rate category, improved the calibration of the model for revascularisation. Only the addition of the time-updated heart rate category variable, with or without adjustment for baseline or the previous heart rate category, improved the calibration of the models for CV mortality, HF requiring hospital admission, and the combined endpoint of total mortality, MI, unstable angina or cardiac arrest. Furthermore, only the time-updated heart rate model adjusted for previous heart rate category had a significantly better calibration compared to the model not including heart rate for cardiac arrest. There were no significant improvements in model calibration for the combined endpoint of CV mortality, MI, or cardiac arrest, or the individual endpoints of fatal or non-fatal MI, unstable angina, and stroke with the addition of any of the heart rate category variables.

Harrell's C-statistics for the model excluding resting heart rate, and the models including the continuous heart rate variables, for each outcome, are shown in Table A3-

5 provided in Appendix 3, along with the likelihood ratio test statistics and corresponding p-values for the addition of the different continuous heart rate variables. The results were very similar to those observed for the heart rate categories according to whether subjects had a heart rate less than, or greater than or equal to 70bpm, although the addition of the time-updated heart rate category variable, with or without adjustment for baseline or the previous heart rate category, improved the discrimination of the model for fatal or non-fatal MI, whereas previously there was no improvement with the addition of any of the heart rate category variables.

Table A3-6 provided in Appendix 3 shows Harrell's C-statistics for the model excluding resting heart rate, and the models including the time-updated categorical heart rate patterns variable for each outcome. Again, irrespective of whether resting heart rate was included, the models had the greatest and least predictive ability for HF requiring hospital admission and unstable angina, respectively (there were not enough cardiac arrest events to allow HRs to be calculated using the time-updated categorical heart rate patterns models). The addition of time-updated categorical heart rate pattern improved discrimination for all of the outcomes excluding fatal or non-fatal MI. However, the C-statistics for unstable angina, stroke, revascularisation, and the two composite endpoints, increased by only 0.001 or 0.002 with the addition of time-updated heart rate pattern. The likelihood ratio test statistics and corresponding p-values for the addition of the heart rate patterns variable to the models are also presented in Table A3-6. The addition of heart rate pattern resulted in statistically significant improvements in the calibration of the models for CV mortality, total mortality, revascularisation, HF requiring hospital admission, and the composite of total mortality, MI, unstable angina or cardiac arrest; there were no significant improvements in model calibration for any of the other outcomes.

None of the models exhibited evidence of non-proportionality of hazards associated with heart rate over time (see Table A3-7, Table A3-8 and Table A3-9 in Appendix 3 for the p-values of the Grambsch and Therneau 1994 test for non-proportionality).

5.3 Discussion

In this large population of patients with stable CHD and no evidence of HF, an elevated resting heart rate was associated with an increase in risk of the majority of the endpoints evaluated, including all-cause death, CV death, HF requiring hospital admission, and cardiac arrest. Unexpectedly, an elevated baseline heart rate was associated with a decrease in the risk of coronary revascularisation. No significant associations between heart rate and the risk of fatal or non-fatal MI, stroke, or unstable angina were observed.

Both an elevated baseline and time-updated heart rate, analysed categorically or continuously, unadjusted and adjusted for the baseline or previous heart rate measurement, were associated with an increase in the risk of all-cause death. Incorporating time-updated heart rate strengthened the association. The same was true for CV death when heart rate was analysed continuously (a baseline heart rate ≥70bpm did not predict risk of CV death). For example, a 5bpm higher baseline heart rate, and time-updated heart rate adjusted for baseline, was associated with a 9% ($p<0.001$) and 16% ($p<0.001$) increase in the risk of all-cause death, and a 6% ($p=0.058$) and a 10% ($p<0.001$) increase in the risk of CV death, respectively. Thus, even if the baseline or previous heart rate measurement is known, the updated heart rate measurement offers significant additional information in regards to the risk of death from all causes and CV causes in CHD patients without HF. The addition of baseline or time-updated resting heart rate improved discrimination for all-cause and CV mortality, compared to the model excluding heart rate, although the time-updated heart rate models were the best at differentiating between subjects who experienced such deaths from those that that did not. While the addition of baseline heart rate category did not improve calibration

of the model for CV death, the addition of any of the continuous heart rate variables resulted in statistically significant improvements in model calibration for both outcomes, as did the addition of any of the categorical heart rate variables for all-cause death.

While no associations between baseline heart rate and risk of hospital admission for HF were observed, an elevated time-updated heart rate, analysed categorically or continuously, was associated with an increase in risk. An elevated continuous time-updated heart rate retained its prognostic value even after adjustment for baseline heart rate or the previous heart rate measurement. A time-updated heart rate ≥70bpm was similarly predictive after adjustment for baseline heart rate group, but was no longer predictive after adjustment for the previous heart rate group. These results further imply that, if heart rate is analysed as a continuous measurement, the current measurement adds prognostic value to the prediction of hospital admission for HF, even if the baseline and previous measurement are known, although note that the confidence intervals did overlap substantially across the models. The discrimination of the model for hospital admission for HF improved with the addition of any of the resting heart rate variables; on the other hand, only the addition of the time-updated heart rate variables, with or without adjustment for baseline or the previous heart rate measurement, significantly improved calibration. The time-updated heart rate model adjusted for previous heart rate measurements was found to have the greatest discriminative ability for hospital admission for HF regardless of whether heart rate was treated as a categorical or continuous variable.

Despite only 17 cardiac arrest events occurring during follow-up, a time-updated heart rate adjusted for baseline, or the previous heart rate measurement, was associated with an increase in the risk of cardiac arrest, whether analysed as a categorical or a continuous variable. No associations between time-updated heart rate and risk were observed when it was not additionally adjusted for either of the other heart rate

variables. Only the addition of the time-updated heart rate variables, with or without adjustment for baseline or the previous heart rate, improved the discrimination of the models; the time-updated model adjusted for previous heart rate yielded the highest C-statistic. The categorical time-updated heart rate model adjusted for previous heart rate category was the only model found to have a significantly better calibration compared to the model not including heart rate for cardiac arrest.

The present findings for all-cause death are similar to those previously found by Diaz et al. 2005[148](heart rate ≥83bpm: HR 1.32, 95% CI 1.19 to 1.47), Ho et al. 2010[149] (in which a small percentage of the patients had HF, some of whom may have had LVSD) (heart rate ≥70bpm: HR 1.40, 95% CI 1.14 to 1.71), and Anselmino et al. 2010 (in the subgroup of CHD patients with diabetes) (10bpm higher heart rate: HR 1.34, 95% CI 1.06 to 1.69)[150]. The results in relation to CV death and hospital admission for HF are also similar to those previously found by Diaz et al. 2005[148] (heart rate ≥83bpm: HR 1.31, 95% CI 1.15 to 1.48 for CV death; HR 1.32, 95% CI 1.01 to 1.75 for HF), as well as those found by Fox et al. 2008[184] (heart rate ≥70bpm: HR 1.34, 95% CI 1.10 to 1.63 for CV death; HR 1.53, 95% CI 1.25 to 1.88 for HF) where all patients had LVSD, many of whom also had HF. Ho et al. 2010 contrastingly found that patients with a baseline heart rate ≥70bpm were at a much higher risk of HF hospitalisation (HR 2.30, 95% CI 1.80 to 2.95)[149]. However, the present analysis did find that patients whose heart rates were ≥70bpm at two or more consecutive visits over time were at a 98% (95% CI 1.38 to 2.84, $p<0.001$) higher risk of HF hospital admission compared to those whose heart rates were <70bpm at two or more consecutive visits.

The current analysis found that patients with a baseline heart rate ≥70bpm were at a 14% ($p = 0.020$) lower risk of revascularisation compared to those with a heart rate <70bpm. Additionally, a 5bpm higher baseline heart rate, and time-updated heart rate, were associated with a 4% ($p = 0.0070$ for baseline and $p = 0.011$ for time-updated) decrease in risk. Although discrimination was improved when the resting heart rate

variables were added to the model, the C-statistic increased by a maximum of only 0.003. However, the addition of any of the heart rate variables resulted in statistically significant improvements in the calibration of the model (borderline significant for the time-updated categorical heart rate model not adjusted for baseline or the previous heart rate measurement (p = 0.051)).

In contrast to the current findings, Fox et al. 2008 demonstrated that CHD patients with LVSD, many of whom had HF, with a baseline heart rate ≥70bpm, were at a 38% (p = 0.037) higher risk of revascularisation compared to those with a heart rate <70bpm[184]. In addition, a 5bpm higher baseline heart rate was shown to be associated with an 8% (p = 0.034) increase in risk[184]. It is not clear why an elevated resting heart rate was associated with a decrease in risk of revascularisation in this analysis and an increase in risk in the BEAUTIFUL analysis. EUROPA recruited patients from 1997 to 2000, whereas BEAUTIFUL recruited patients from 2004 to 2006. In the 1990s, revascularisation was mainly used to treat angina, whereas from 2000 onwards it began to be used more frequently as a treatment for acute MI[276]. It could therefore be that revascularisation was a marker of different conditions in EUROPA and BEAUTIFUL. However further exploration would need to be carried out to better understand the reasons for the differences in findings.

No associations between any of the heart rate variables and the risk of fatal or non-fatal MI, stroke, or unstable angina were observed. Moreover, there were no significant improvements in model calibration, and only very small improvements in model discrimination (a maximum increase in the C-statistic of 0.002) for these endpoints with the addition of resting heart rate. The number of fatal or non-fatal MI and unstable angina events were relatively large (n = 738 and n = 708, respectively). Moreover, none of the results relating to these two outcomes showed any evidence of significant differences. The studies by Diaz et al. 2005[148] and Ho et al. 2010[149] similarly observed no associations between baseline heart rate and risk of MI, despite there being high

numbers of subjects included in the analyses. Additionally, Diaz et al. 2005 observed no significant association between heart rate and risk of hospital admission due to angina, although a heart rate ≥83bpm was borderline significantly associated with an increase in risk (HR 1.12, 95% CI 0.99 to 1.27)[148]. In contrast, in patients with CHD and LVSD, many of whom had HF, Fox et al. 2008 showed that a heart rate ≥70bpm was associated with a 46% (95% CI 11 to 91%, p = 0.0066) increase in the risk of admission to hospital for fatal or non-fatal MI, and a 5bpm increase was also borderline significantly associated with a 7% increase in risk (95% CI 0 to 14%, p = 0.052), despite only 226 MI events occurring[184]. These results suggest that heart rate is not associated with risk of MI or unstable angina in CHD patients without HF or a reduced LVEF, but further studies are required to confirm this.

Diaz et al. 2005[148] and Ho et al. 2010[149] also examined the relationship between baseline heart rate and stroke, and neither observed any association. Only 199 stroke events occurred in the EUROPA population. A 5bpm higher time-updated heart rate, unadjusted and adjusted for baseline, and adjusted for the previous measurement, was borderline significantly associated with an increase in the risk of stroke (time-updated: HR 1.05, 95% CI 0.99 to 1.12, p = 0.12; time-updated adjusted for baseline: HR 1.07, 95% CI 1.00 to 1.16, p = 0.051; time-updated adjusted for previous: HR 1.07, 95% CI 0.99 to 1.15, p = 0.10). Thus, there may have not have been enough events for the associations to reach significance. Further analyses of the relationship between resting heart rate and risk of stroke including a greater number of events could be informative.

5.3.1 Chapter Summary and Conclusions

This chapter evaluated both baseline and time-updated resting heart rate as risk markers for death and adverse CV outcomes in the EUROPA population.

Raised time-updated heart rate was found to be predictive of an elevated risk of all-cause death, CV death, hospital admission for HF, and cardiac arrest in the EUROPA

population of CHD patients without HF. Despite knowledge of the baseline or previous heart rate measurement, the most recent heart rate measurement provided significant additional information about the risk of each of these endpoints. On the contrary, an elevated time-updated heart rate was associated with a decrease in risk of revascularisation in this population of patients.

Chapter 6 further explored the associations between baseline and time-updated resting heart rate and risk of adverse outcomes in the PROSPER population of elderly individuals with, or at an increased risk of, vascular disease.

Chapter 6

Heart Rate and Risk in the PROSPER Population

6.1 Introduction

A higher baseline resting heart rate has been associated with an increase in the risk of all-cause death[188,189,216], CV death[138,188,216] and hospitalisation for HF[138,216] among mixed populations of subjects with, or at an increased risk of, vascular disease. Nanchen et al. 2013, for example, demonstrated that participants of the PROSPER trial with a baseline heart rate in the highest third of the distribution were at a 73% and 80% higher risk of CV death and HF hospitalisation, respectively, compared to those with a heart rate in the lowest third[138]. An elevated baseline heart rate has also been associated with an increase in the risk of all-cause death[141,147] and CV death[141] in older individuals with diabetes and hypertension.

On the other hand, studies of such populations have yet to establish an association between baseline heart rate and the risk of stroke or MI[188,216]. Lonn et al. 2014, for example, observed no association between baseline heart rate and the risk of MI or stroke within a model that adjusted for conventional baseline variables ($p = 0.090$ for MI; $p = 0.57$ for stroke)[216]. However, a 10bpm higher mean follow-up heart rate was associated with a 12% ($p = 0.0006$) increase in the risk of stroke.

The mean of multiple heart rate measurements gathered over time, however, is calculated using different numbers of heart rate measurements at different points during follow-up, and so interpreting the estimated association in practice can be difficult. Furthermore, it does not necessarily reflect localised increases or decreases in heart rate, whereas time-updated individual heart rate measurements do. Ho et al. 2014 demonstrated that an 11bpm (one standard deviation) increase in time-updated heart rate was associated with a 19% ($p<0.001$) increase in risk of CHD in a population of subjects from the general population with no evidence of prior MI, HF or AF, whereas no

associations between baseline or mean follow-up heart rate and risk of CHD were observed[204].

Using data from the PROSPER trial, which enrolled elderly individuals with, or at an increased risk of, vascular disease, the first objective of this analysis was to examine the association between baseline heart rate and risk of each of the other 15 endpoints that were assessed in the original PROSPER trial publication[243], such as stroke and non-fatal MI, that were not previously studied by Nanchen et al. 2013[138]. The second objective was to determine whether or not time-updated heart rate would strengthen the associations for each of these outcomes, as well as CV death and HF hospitalisation, which were previously studied by Nanchen et al. 2013 in relation to baseline heart rate only[138]. The systematic review of Chapter 2 did not identify any studies of time-updated heart rate in patients with, or at an increased risk of, vascular disease. Differences between participants who were and were not taking anti-arrhythmic medications and/or beta-blockers at baseline in relation to the effect of heart rate, were also assessed.

6.2 Methods and Results

The following 17 outcomes were thus assessed: (1) the composite of CHD death, non-fatal MI or any stroke (the primary endpoint of PROSPER); (2) the composite of CHD death or non-fatal MI; (3) fatal or non-fatal stroke; (4) non-fatal MI; (5) non-fatal stroke; (6); TIA; (7) PTCA or CABG; (8) peripheral arterial surgery/angioplasty; (9) any CV event; (10) fatal or non-fatal stroke or TIA; (11); HF hospitalisation; (12); CHD death; (13) stroke death; (14) vascular death; (15) non-vascular death; (16) cancer death; and (17) all-cause death.

Data of patients from both treatment arms of PROSPER (pravastatin or placebo), were pooled for this analysis since pravastatin does not directly affect heart rate. 5,684 of the patients (97.9% of the 5,804 patients included in the original trial) had baseline

heart rate measurements available. The original baseline heart rate analysis[138] excluded four participants with baseline AF, 149 taking anti-arrhythmic drugs and 1,447 taking beta-blockers, because of the effects of anti-arrhythmic drugs and beta-blockers on heart rate. The participants with baseline AF were similarly excluded in the current analysis, but those on anti-arrhythmic drugs or beta-blockers were not, so that differences between participants who were and were not taking anti-arrhythmic medications and/or beta-blockers at baseline in relation to the effect of heart rate could be explored. Hence 5,680 subjects were included in the present analysis.

To make the current results as comparable as possible to the previously published results by Nanchen et al. 2013[138], the study population was divided into three groups according to the tertiles of the distribution of baseline heart rate values, since this was the method employed in their analysis of baseline heart rate in the PROSPER population. This was done separately for women and men because women have a higher resting heart rate than men[250]. The male participants were divided into 'low', 'medium' and 'high' baseline heart rate groups according to the tertiles of their distribution of baseline heart rate, and the female participants were divided in the same way. The participants in the 'low', 'medium', and 'high' groups were then combined to produce three groups of subjects both male and female.

The tertiles of the distribution of male and female baseline heart rate values were 59bpm and 68bpm, and 62bpm and 72bpm, respectively. Male participants with a baseline heart rate less than or equal to 59bpm, between 60 and 68bpm, and greater than 68bpm, were classed as being in the 'low', 'medium' and 'high' heart rate thirds, respectively. Similarly, female participants with a baseline heart rate less than or equal to 62bpm, between 63 and 72bpm, and greater than 72bpm were classed as being in the 'low', 'medium' and 'high' heart rate thirds. The baseline characteristics of the PROSPER patients, overall and categorised into 'low', 'middle' and 'high' heart rate groups depending on their baseline resting heart rate are shown in Table 6-1.

There were significant differences between the groups of patients in terms of age, sex, smoking status, alcohol consumption, history of hypertension and diabetes, history of vascular disease, CHD and angina, Mini Mental State Examination score, SBP, DBP, height, BMI, low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol, fasting glucose, creatinine, eGFR, thyroid stimulating hormone and treatment with beta-blockers, aspirin, nitrates and ACE inhibitors. Patients in the 'high' heart rate group were older, more likely to be current smokers, and drank more alcohol each week than those in the 'low' heart rate group. Those with a 'high' baseline heart rate were more likely to have a history of diabetes and a lower Mini Mental State Examination score, but less likely to have a history of hypertension, vascular disease, CHD and angina, compared with the 'low' heart rate group subjects. Patients in the 'high' group were also more likely to be treated with ACE inhibitors, and less likely to be treated with beta-blockers, aspirin and nitrates. Compared to patients in the 'low' baseline group, they had a higher SBP, DBP, BMI, HDL cholesterol, fasting glucose and eGFR, but a lower LDL cholesterol, creatinine and thyroid stimulating hormone.

The total number of events that occurred in the PROSPER population is presented in Table 6-2, along with the number that occurred in each of the baseline heart rate groups.

Table 6-1: Baseline characteristics of the PROSPER study population.

		Baseline Heart Rate			
	All Subjects n = 5680	**Low Heart Rate Third n = 1976**	**Middle Heart Rate Third n = 1877**	**High Heart Rate Third n = 1827**	**p-value**
Demographics					
Age, years	75.3 (3.4)	75.2 (3.3)	75.4 (3.4)	75.4 (3.4)	0.013
Female	2929 (52%)	987 (50%)	1030 (45%)	912 (50%)	0.0021
Smoking status					**<0.001**
Never	1930 (34%)	698 (35%)	652 (35%)	580 (32%)	
Former	2228 (39%)	860 (44%)	685 (36%)	683 (37%)	
Current	1522 (27%)	418 (21%)	540 (29%)	564 (31%)	
Alcohol consumption, drinks/week	5.2 (9.3)	5.1 (9.1)	4.9 (8.8)	5.6 (9.9)	0.046
Co-morbidities					
Hypertension	3509 (62%)	1288 (65%)	1137 (61%)	1084 (59%)	<0.001
Diabetes	611 (11%)	149 (8%)	205 (11%)	257 (14%)	<0.001
History of vascular disease	**2496 (44%)**	**967 (49%)**	**773 (41%)**	**756 (41%)**	**<0.001**
History of coronary heart disease	875 (15%)	346 (18%)	252 (13%)	277 (15%)	0.0020
History of angina	1530 (27%)	656 (33%)	450 (24%)	424 (23%)	<0.001
History of cerebrovascular disease	628 (11%)	218 (11%)	201 (11%)	209 (11%)	0.78
History of peripheral artery disease	437 (8%)	131 (7%)	149 (8%)	157 (9%)	0.068
Lower MMSE score	1813 (32%)	573 (29%)	603 (32%)	637 (35%)	<0.001
Objective Measures					
Heart rate, bpm	66.3 (11.7)	54.6 (5.0)	65.8 (3.2)	79.5 (8.0)	-
SBP, mmHg	154.7 (21.9)	153.0 (22.0)	154.6 (21.9)	156.7 (21.6)	<0.001
DBP, mmHg	83.8 (11.5)	82.4 (11.5)	83.9 (11.3)	85.2 (11.5)	<0.001
Weight, kg	73.4 (13.4)	73.7 (12.7)	72.9 (13.2)	73.6 (14.2)	0.48
Height, cm	1.7 (0.09)	1.7 (0.09)	1.7 (0.10)	1.6 (0.09)	<0.001
BMI, kg/m^2	26.8 (4.2)	26.8 (3.9)	26.7 (4.1)	27.0 (4.5)	0.0018
Total cholesterol, mmol/L	**5.7 (0.9)**	**5.7 (0.9)**	**5.7 (0.9)**	**5.7 (0.9)**	**0.42**
LDL-cholesterol, mmol/L	3.8 (0.8)	3.8 (0.8)	3.8 (0.8)	3.7 (0.8)	<0.001
HDL-cholesterol, mmol/L	1.3 (0.3)	1.2 (0.3)	1.3 (0.4)	1.3 (0.4)	<0.001
Triglycerides, mmol/L	1.5 (0.7)	1.6 (0.7)	1.5 (0.7)	1.5 (0.7)	0.52
Fasting glucose, mmol/L	5.4 (1.4)	5.3 (1.2)	5.3 (1.3)	5.5 (1.6)	<0.001
Creatinine, µmol/L	101.3 (22.4)	103.0 (22.6)	99.8 (22.3)	101.1 (22.1)	<0.001
eGFR, mL/min	60.1 (14.6)	59.2 (14.2)	60.6 (14.9)	60.5 (14.6)	<0.001
TSH, mIU/L	2.3 (2.1)	2.3 (1.9)	2.4 (2.4)	2.2 (2.1)	<0.001
Randomised Treatment					
Pravastatin	2833 (50%)	1,004 (51%)	935 (50%)	894 (49%)	0.51

Table continued and footnote provided on following page.

Table 6-1 (Cont.): Baseline characteristics of the PROSPER study population.

		Baseline Heart Rate			
	All Subjects n = 5680	**Low Heart Rate Third n = 1976**	**Middle Heart Rate Third n = 1877**	**High Heart Rate Third n = 1827**	**p-value**
Medication use					
Anti-arrhythmic drugs	152 (3%)	57 (3%)	43 (2%)	52 (3%)	0.45
Beta-blockers	1,472 (26%)	905 (46%)	381 (20%)	186 (10%)	<0.001
Aspirin	2,066 (36%)	825 (42%)	636 (34%)	605 (33%)	<0.001
Nitrates	1,073 (19%)	477 (24%)	318 (17%)	278 (15%)	<0.001
Diuretics	2,301 (41%)	779 (39%)	753 (40%)	769 (42%)	0.23
CCBs	1,428 (25%)	503 (25%)	468 (25%)	457 (25%)	0.92
ACE inhibitors	929 (16%)	309 (16%)	274 (15%)	346 (19%)	<0.001
ARBs	113 (2%)	35 (2%)	42 (2%)	36 (2%)	0.58
Other antihypertensive drugs	233 (4%)	70 (4%)	82 (4%)	81 (4%)	0.30

This table shows that clinical and demographic characteristics of the PROSPER patients who had baseline resting heart rate measurements available, and who were in sinus rhythm. Values are given for the total population, as well as according to gender-specific heart rate thirds. Data are the number of patients with the corresponding percentage, or the mean with the standard deviation, depending on whether the variable was categorical or continuous. Not all patients had every baseline measurement available. Therefore, percentages and means were calculated using the number of subjects with non-missing data as the denominator. The values of each characteristic were compared between the three different baseline resting heart rate groups using one-way ANOVA and chi-squared tests, for continuous and categorical variables, respectively.

Vascular disease is defined as a history of coronary heart disease, angina, cerebrovascular disease, or peripheral artery disease.

Coronary heart disease is defined as a history of myocardial infarction, percutaneous coronary intervention, or coronary artery bypass surgery.

Cerebrovascular disease is defined as a history of stroke or transient ischemic attack.

Peripheral artery disease is defined as a history of claudication or peripheral vascular surgery.

ACE = Angiotensin-Converting Enzyme; ARB = Angiotensin II Receptor Block; BMI = Body Mass Index; CCB = Calcium Channel Blocker; DBP = Diastolic Blood Pressure; eGFR = estimated Glomerular Filtration Rate; HDL = High Density Lipoprotein; LDL = Low Density Lipoprotein; MMSE = Mini Mental State Examination; SBP = Systolic Blood Pressure; TSH = Thyroid-Stimulating Hormone.

Table 6-2: The number of first events that occurred in the PROSPER population.

		Subjects Separated by Gender-Specific Baseline Heart Rate Thirds		
	Total Population n = 5680	**Low Heart Rate Third n = 1976**	**Middle Heart Rate Third n = 1877**	**High Heart Rate Third n = 1827**
Primary Endpoint				
CHD death or non-fatal MI or fatal or non-fatal stroke	868 (15%)	308 (16%)	262 (14%)	298 (16%)
Secondary Endpoints				
CHD death or non-fatal MI	639 (11%)	227 (11%)	194 (10%)	218 (12%)
Fatal or non-fatal stroke	261 (5%)	96 (5%)	73 (4%)	92 (5%)
Other Outcomes				
Non-fatal MI	471 (8%)	172 (9%)	143 (8%)	156 (9%)
Non-fatal stroke	231 (4%)	86 (4%)	65 (3%)	80 (4%)
TIA	177 (3%)	74 (4%)	48 (3%)	55 (3%)
PTCA or CABG	87 (2%)	42 (2%)	29 (2%)	16 (1%)
Peripheral arterial surgery/angioplasty	79 (1%)	30 (2%)	23 (1%)	26 (1%)
All cardiovascular events	963 (17%)	350 (18%)	292 (16%)	321 (18%)
Fatal or non-fatal stroke or TIA	409 (7%)	159 (8%)	112 (6%)	138 (8%)
HF hospitalisation	232 (4%)	61 (3%)	79 (4%)	92 (5%)
Deaths				
CHD	212 (4%)	66 (3%)	65 (3%)	81 (4%)
Stroke	35 (1%)	12 (1%)	9 (0.5%)	14 (1%)
Vascular	287 (5%)	89 (5%)	83 (4%)	115 (6%)
Non-vascular	303 (5%)	87 (4%)	85 (5%)	131 (7%)
Cancer	199 (4%)	60 (3%)	63 (3%)	76 (4%)
All-causes	590 (10%)	176 (9%)	168 (9%)	246 (13%)

This table shows the total number of PROSPER patients with available baseline resting heart rate data who experienced any pre-specified events of interest, as well as the number according to gender-specific heart rate thirds. Data are number of patients who experienced the event as a first event, with the corresponding percentage. Note that first event refers to the first event of each type: for example, a patient may have experienced a non-fatal MI, and then subsequently been hospitalised for HF at a later date.

All cardiovascular events is defined as the primary endpoint, CABG, PTCA, peripheral arterial surgery, or angioplasty.

Vascular death is defined as CHD death, fatal stroke, or other vascular death, and is equivalent to the cardiovascular death endpoint analysed in the original baseline heart rate paper[138].

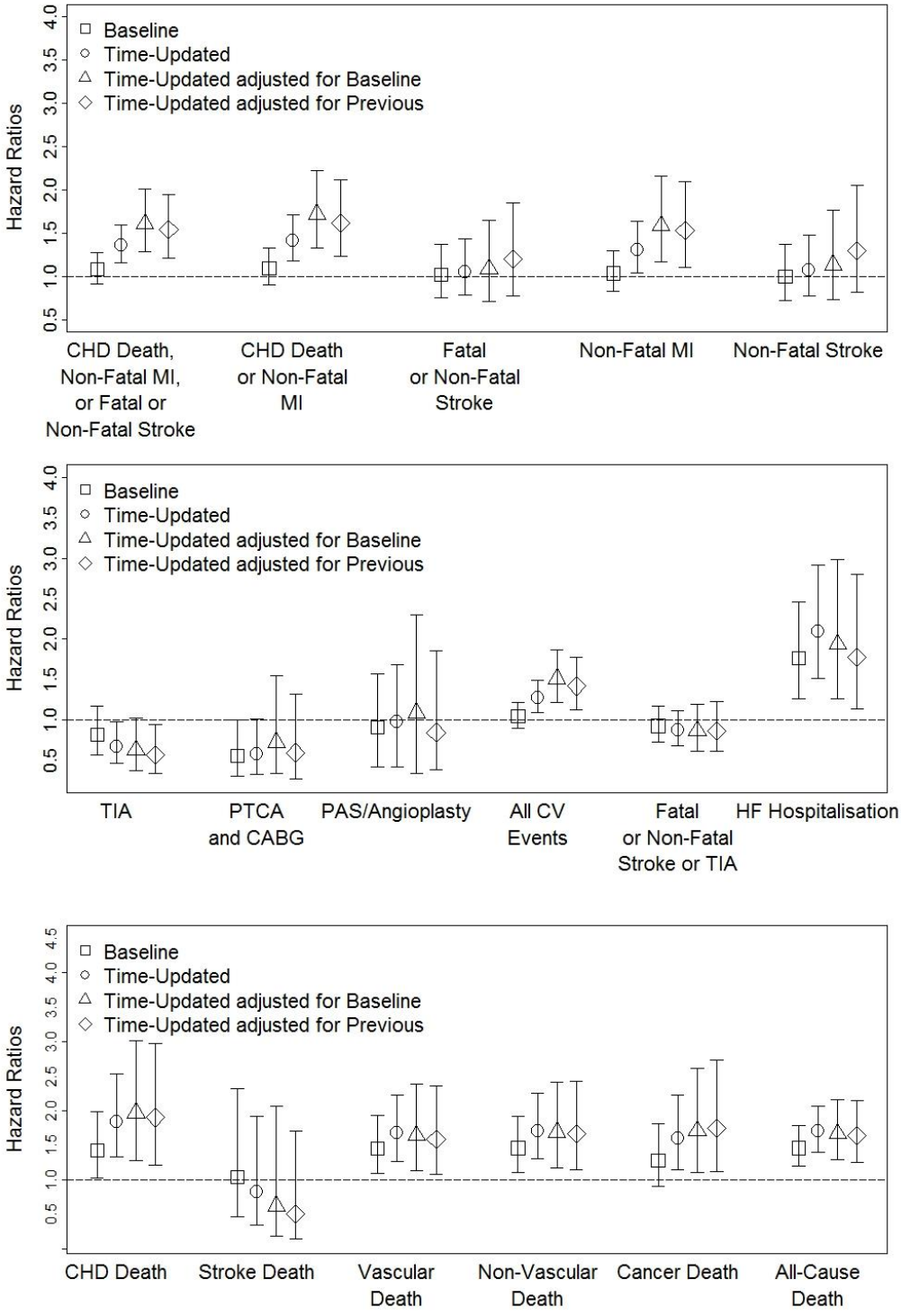
CABG = Coronary Artery Bypass Graft; CHD = Coronary Heart Disease; HF = Heart Failure; MI = Myocardial Infarction; PTCA = Percutaneous Transluminal Coronary Angioplasty; TIA = Transient Ischemic Attack.

The previous study by Nanchen et al. 2013[138], which examined the associations between baseline heart rate and risk of CV death and HF hospitalisation in the PROSPER population, fitted a "basic" multivariate adjusted model, as well as this "basic" multivariate adjusted model additionally adjusted for drug use at baseline and treatment group in the trial, referred to in the publication as the "multivariate-adjusted model additionally adjusted for treatment". To make the current results as comparable as possible to the previously published results by Nanchen et al. 2013[138], the Cox regression models adjusted for the same variables adjusted for in the "multivariate-adjusted model additionally adjusted for treatment", excluding history of angina: age; smoking status; diabetes; history of vascular disease; hypertension; BMI; HDL-cholesterol; thyroid stimulating hormones; eGFR; treatment group (pravastatin or placebo); and intake of aspirin, nitrates, diuretics, ACE inhibitors and ARBs. History of angina was not adjusted for individually as it was included in history of vascular disease in the current analysis.

The linearity of effect for each continuous heart rate variable was evaluated by plotting the Martingale residuals (a linear transformation of Cox-Snell residuals)[252,253] of each model against the heart rate values. No violations of the linearity assumption were observed.

Comparing the risk of each of the outcomes between patients with a baseline or time-updated heart rate in the 'high' category and the 'low' category produced the HRs and 95% CIs shown by Figure 6-1 and in Table A4-1 provided in Appendix 4. The HRs, 95% CIs and p-values comparing patients with a heart rate in the 'middle' category and the 'low' category are also given in Table A4-1, but were omitted from Table 6-1 because the majority of them were not significant.

Figure 6-1: Results of fitting Cox proportional hazards models. Hazard ratios with corresponding 95% confidence intervals for a 'high' heart rate relative to a 'low' heart rate in the PROSPER population.



Male participants with a baseline heart rate less than or equal to 59bpm, between 60 and 68bpm, and greater than 68bpm, were classed as being in the 'low', 'medium' and 'high' heart rate thirds, respectively. Similarly, female participants with a baseline heart rate less than or equal to 62bpm, between 63 and 72bpm, and greater than 72bpm were classed as being in the 'low', 'medium' and 'high' heart rate thirds.

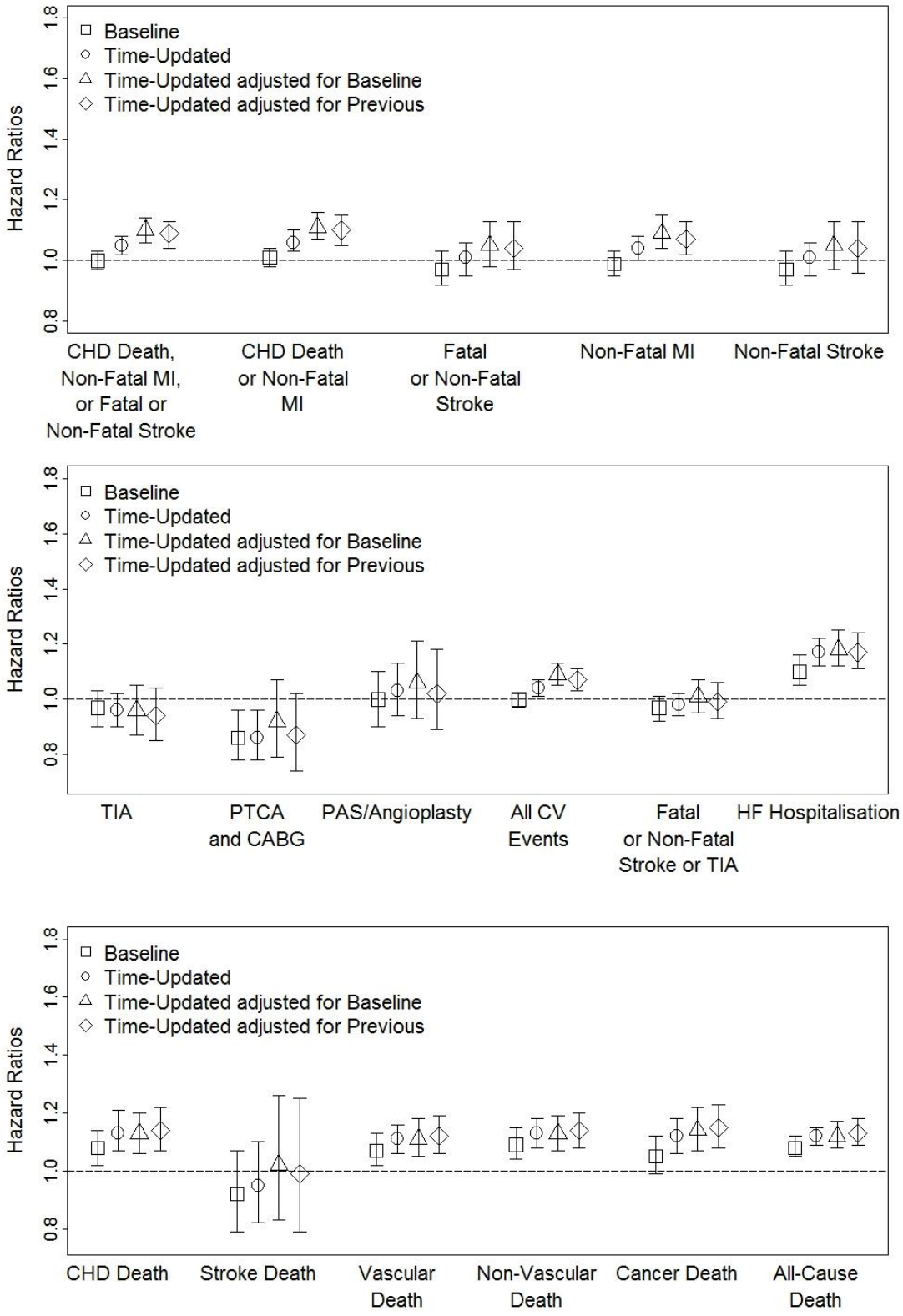
CABG = Coronary Artery Bypass Graft; CHD = Coronary Heart Disease; CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction; PAS = Peripheral Artery Surgery; PTCA = Percutaneous Transluminal Coronary Angiography; TIA = Transient Ischemic Attack.

Models were additionally adjusted for: age; smoking status; diabetes; history of vascular disease; hypertension; body mass index (BMI); high-density lipoprotein (HDL) cholesterol; thyroid stimulating hormones; estimated Glomerular Filtration Rate (eGFR); treatment group (pravastatin or placebo); and intake of aspirin, nitrates, diuretics, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs).

A ‘high’ heart rate was associated with an increase in risk of HF hospitalisation, CHD death, vascular death, non-vascular death, and all-cause death in all models fitted. Patients with a ‘high’ baseline heart rate were not found to be at a higher risk of the combined endpoints of CHD death, non-fatal MI or fatal or non-fatal stroke, and CHD death or non-fatal MI, or the individual endpoints non-fatal MI, all CV events, and cancer death. However, a ‘high’ time-updated resting heart rate predicted an increase in risk of each of these endpoints, even after adjustment for baseline or the previous heart rate category. In contrast, a ‘high’ baseline heart rate was also not associated with an increase in risk of TIA, but a ‘high’ time-updated heart rate, and time-updated heart rate adjusted for the previous category, was associated with a 32% ($p = 0.038$) and a 43% ($p = 0.031$) lower risk of TIA. No significant differences in risk of fatal or non-fatal stroke, non-fatal stroke, PTCA or CABG, peripheral arterial surgery/angioplasty, fatal or non-fatal stroke or TIA, and stroke death between patients with a ‘high’ heart rate compared to a ‘low’ heart rate were observed using any of the models.

Analysing continuous heart rate measurements produced the HRs and CIs shown by Figure 6-2 and in Table A4-2 provided in Appendix 4. In regards to the individual endpoints, 5bpm higher heart rate was associated with an increase in risk of HF hospitalisation, CHD death, vascular death, non-vascular death and all-cause death in all models. An elevated continuous baseline heart rate was not associated with an increase in risk of non-fatal MI, all CV events, or cancer death. However, a 5bpm higher time-updated heart rate was associated with a 4% ($p = 0.0024$) increase in risk of all CV events, and a 12% ($p<0.001$) increase in risk of cancer death. These associations remained significant even after adjustment for baseline or previous heart rate.

Figure 6-2: Results of fitting Cox proportional hazards models. Hazard ratios with corresponding 95% confidence intervals for a 5bpm higher heart rate in the PROSPER population.



CABG = Coronary Artery Bypass Graft; CHD = Coronary Heart Disease; CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction; PAS = Peripheral Artery Surgery; PTCA = Percutaneous Transluminal Coronary Angiography; TIA = Transient Ischemic Attack.

Models were additionally adjusted for: age; smoking status; diabetes; history of vascular disease; hypertension; body mass index (BMI); high-density lipoprotein (HDL) cholesterol; thyroid stimulating hormones; estimated Glomerular Filtration Rate (eGFR); treatment group (pravastatin or placebo); and intake of aspirin, nitrates, diuretics, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs).

A 5bpm higher time-updated heart rate was borderline significantly associated with an increase in risk of non-fatal MI (p = 0.050), but time-updated heart rate adjusted for baseline heart rate was associated with a 9% (p<0.001) increase in risk, and time-updated heart rate adjusted for previous heart rate was associated with a 7% increase in risk (p = 0.0097). A 5bpm higher baseline resting heart rate, and time-updated heart rate, were associated with a 14% lower risk of PTCA or CABG.

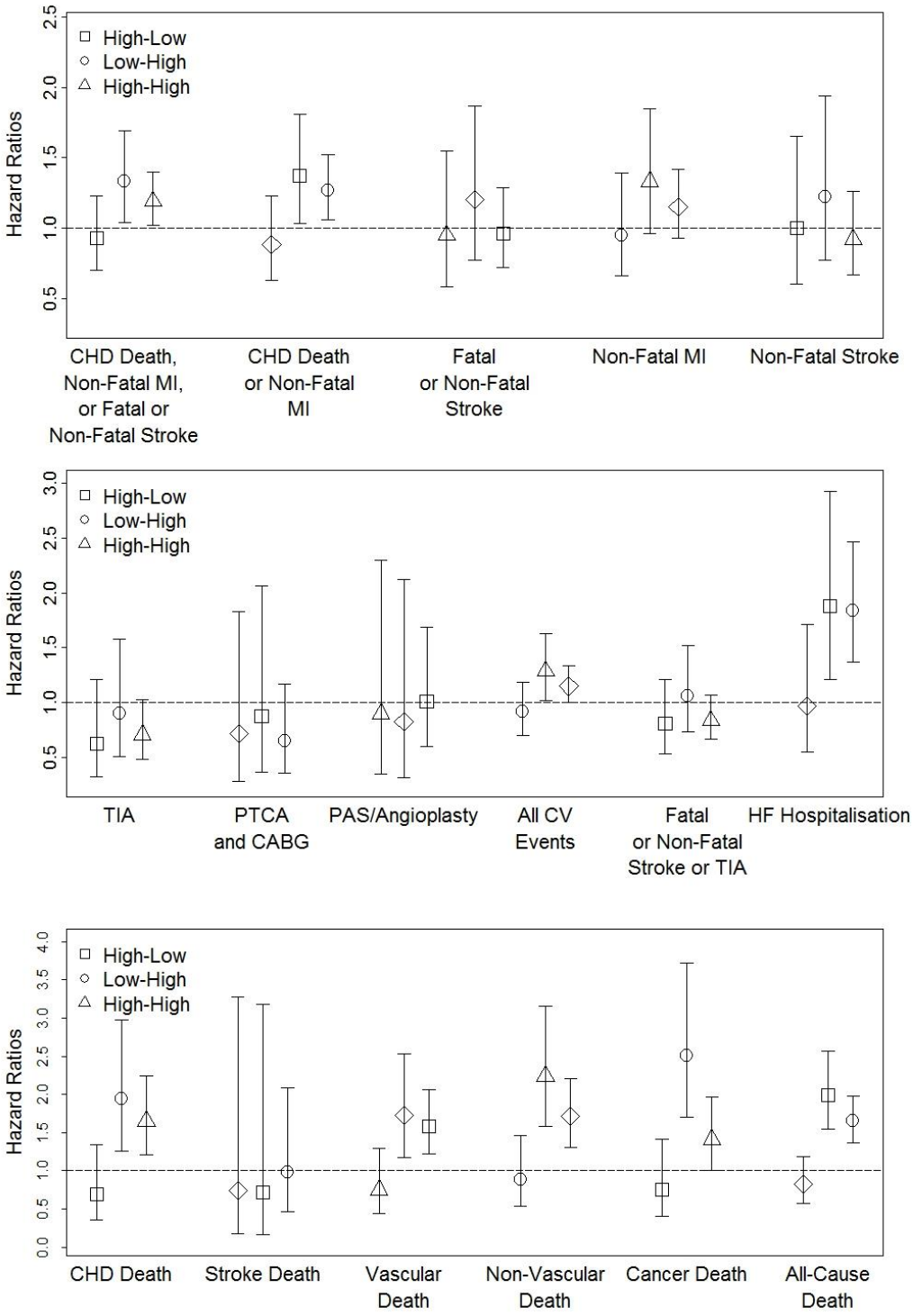
In regards to the composite endpoints, an elevated continuous baseline heart rate was not associated with an increase in risk of the combined endpoint of CHD death, non-fatal MI or fatal or non-fatal stroke, the combined endpoint of CHD death or non-fatal MI. However, a 5bpm higher time-updated heart rate was associated with a 5% (p<0.001) increase in risk of CHD death, non-fatal MI or fatal and non-fatal stroke, a 6% (p<0.001) increase in risk of CHD or non-fatal MI. These associations also remained significant even after adjustment for baseline or previous heart rate.

No significant associations between continuous heart rate and risk were observed for fatal or non-fatal stroke, non-fatal stroke, TIA, peripheral artery surgery/angioplasty, the combination of fatal or non-fatal stroke or TIA, or stroke death.

Figure 6-3 and Table A4-3 provided in Appendix 4 show the adjusted HRs and 95% CIs estimated using the time-updated categorical heart rate patterns models. The heart rate cut-off of 70bpm was selected since prior published research has suggested that the risk associated with heart rate rises greatly above this value[148,208,156].

Comparing the current heart rate measurement at each visit to the previous heart rate measurement, patients who had a heart rate ≥70bpm at both visits (high-high), and an increase in heart rate from below 70bpm at the previous visit, to ≥70bpm at the current visit (low-high), were at a higher risk of the combined endpoint of CHD death, non-fatal MI or fatal or non-fatal stroke, the combined endpoint of CHD death or non-fatal MI, all CV events (high-high borderline significant (p = 0.057)), HF hospitalisation, CHD death,

Figure 6-3: Results of fitting Cox proportional hazards models. Hazard ratios with corresponding 95% confidence intervals for the time-updated categorical heart rate patterns 'high-low', 'low-high' and 'high-high' relative to the category 'low-low' in the PROSPER population.



Patients were classified as being in the low-low category if their heart rate measurement at both the current and previous visit was below 70bpm. Similarly, patients were classified as being in the high-high category if their heart rate measurement at both the current and previous visit was greater than or equal to 70bpm, and so on.

CABG = Coronary Artery Bypass Graft; CHD = Coronary Heart Disease; CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction; PAS = Peripheral Artery Surgery; PTCA = Percutaneous Transluminal Coronary Angiography; TIA = Transient Ischemic Attack.

Models were additionally adjusted for: age; smoking status; diabetes; history of vascular disease; hypertension; body mass index (BMI); high-density lipoprotein (HDL) cholesterol; thyroid stimulating hormones; estimated Glomerular Filtration Rate (eGFR); treatment group (pravastatin or placebo); and intake of aspirin, nitrates, diuretics, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs).

vascular death, non-vascular death, cancer death and all-cause death, compared to patients who had a heart rate <70bpm at both visits (low-low). No significant associations between any of the time-updated categorical heart rate patterns were observed for fatal or non-fatal stroke, non-fatal MI, non-fatal stroke, TIA, PTCA or CABG, peripheral arterial surgery/angioplasty, the combined endpoint of fatal or non-fatal stroke or TIA, and stroke death.

The discrimination and calibration of the models were evaluated using Harrell's C-statistic and likelihood ratio tests, respectively. Table A4-4 provided in Appendix 4 shows Harrell's C-statistics for the model excluding resting heart rate, and the models including the gender-specific heart rate thirds variables, for each outcome. Regardless of whether any resting heart rate third variables were included, the models had the greatest predictive ability for PTCA or CABG, and stroke death: the C-statistics of the models both excluding and including resting heart rate ranged from 0.769 to 0.774, and 0.794 to 0.799 for each of these outcomes, respectively. The models had the last predictive ability for non-fatal stroke, with the C-statistics ranging from 0.595 to 0.603. The C-statistics of the models for the other outcomes ranged from 0.614 to 0.757. The addition of baseline or time-updated resting heart rate third improved discrimination for all of the outcomes, compared to the model excluding heart rate, except for non-fatal MI, peripheral artery surgery/angioplasty, and CHD death: only the addition of the time-updated heart rate thirds variable, with or without adjustment for baseline or the previous heart rate group, improved the discrimination of these latter three outcomes. The greatest improvements in discrimination were observed for CHD death, vascular death, and all-cause death: the models not including resting heart rate had a C-statistic of 0.702, 0.701 and 0.673, whereas the models including time-updated resting heart rate had a C-statistic of 0.721 (increase of 0.019), 0.720 (increase of 0.019), and 0.679 (increase of 0.016), for each of these outcomes, respectively. The smallest improvements in discrimination were observed for PTCA or CABG, peripheral arterial surgery/angioplasty, and fatal or non-fatal stroke or TIA: the models not including

resting heart rate had a C-statistic of 0.769, 0.755, and 0.620, whereas the models including time-updated heart rate (adjusted for the previous heart rate third for first two endpoints and baseline heart rate third for the last) had a C-statistic of 0.774 (increase of 0.005), 0.757 (increase of 0.002) and 0.625 (increase of 0.005). The likelihood ratio test statistics and corresponding p-values for the addition of the heart rate thirds variables to the models are also presented in Table A4-4. The addition of any of the heart rate thirds variables to the models resulted in statistically significant improvements in the calibration of the models for HF hospitalisation, vascular death, non-vascular death and all-cause death. Only the addition of the time-updated heart rate thirds variable, with or without adjustment for baseline or the previous heart rate third, improved the calibration of the models for the combined endpoints of CHD death, non-fatal MI or fatal or non-fatal stroke, and CHD death or non-fatal MI, and the individual endpoints of non-fatal MI, all CV events, CHD death and cancer death. On the other hand, only the addition of baseline heart rate third improved the calibration of the models for fatal or non-fatal stroke, and fatal or non-fatal stroke or TIA. There were no significant improvements in model calibration for non-fatal stroke, TIA, PTCA or CABG, peripheral arterial surgery/angioplasty, or stroke death with the addition of any of the heart rate thirds variables.

Harrell's C-statistics for the model excluding resting heart rate, and the models including the continuous heart rate variables, for each outcome, are shown in Table A4-5 provided in Appendix 4, along with the likelihood ratio test statistics and corresponding p-values for the addition of the different continuous heart rate variables. The results were very similar to those observed for the heart rate thirds, with the exception that addition of any of the continuous heart rate variables resulted in statistically significant improvements in the calibration of the model for PTCA or CABG, whereas previously there was no improvement with the addition the heart rate thirds variables.

Table A4-6 provided in Appendix 4 shows Harrell's C-statistics for the model excluding resting heart rate, and the models including the time-updated categorical heart rate patterns variable for each outcome. Again, irrespective of whether resting heart rate was included, the models had the greatest predictive ability for PTCA or CABG and stroke death, and the least for non-fatal stroke. The addition of time-updated categorical heart rate pattern improved discrimination for all of the outcomes except fatal or non-fatal stroke, peripheral arterial surgery/angioplasty, and stroke death. However, the C-statistics for non-fatal MI, non-fatal stroke, PTCA or CABG, and fatal or non-fatal stroke or TIA only increased by 0.001 or 0.002 with the addition of time-updated heart rate pattern. The likelihood ratio test statistics and corresponding p-values for the addition of the heart rate patterns variable to the models are also presented in Table A4-6. The addition of heart rate pattern resulted in statistically significant improvements in the calibration of the models for HF hospitalisation, CHD death, vascular death, non-vascular death, cancer death, all-cause death, and the combined endpoints of CHD death, non-fatal MI, or fatal or non-fatal stroke, and CHD death or non-fatal MI; there were no significant improvements in model calibration for any of the other outcomes.

Table A4-7, Table A4-8 and Table A4-9 in Appendix 4 show the p-values for the Grambsch and Therneau 1994 test for non-proportionality for all of the models and outcomes. Neither a 'high' heart rate, an elevated continuous heart rate, nor any of the time-updated categorical heart rate patterns exhibited evidence of non-proportionality of hazards over time for any of the outcomes.

Table A4-10 provided in Appendix 4 shows the HRs, 95% CIs, and p-values for a 5bpm higher time-updated heart rate adjusted for baseline heart rate calculated separately for subjects who were or were not taking anti-arrhythmics and/or beta-blockers at randomisation, along with the p-values for the interactions calculated using likelihood ratio tests. Significant interactions between continuous time-updated heart rate and

intake of beta-blockers or anti-arrhythmics at randomisation were observed for fatal or non-fatal stroke (p = 0.042), non-fatal stroke (p = 0.041) and fatal or non-fatal stroke or TIA (p = 0.0078).

In each case, no significant associations were observed between an elevated continuous time-updated heart rate and risk in those not taking beta-blockers or anti-arrhythmics at baseline (p = 0.99, p = 0.93 and p = 0.23, respectively). On the other hand, in patients who were taking either or both drugs at randomisation, a 5bpm higher time-updated heart rate adjusted for baseline heart rate was associated with a 13% increase (95% CI 3 to 25%, p = 0.013) in risk of fatal or non-fatal stroke, a 13% increase (95% CI 2 to 25%, p = 0.022) in risk of non-fatal stroke, and an 11% increase (95% CI 2 to 20%, p = 0.0017) in risk of fatal or non-fatal stroke or TIA. In each case the number of events that occurred in the group of patients who were taking beta-blockers or anti-arrhythmics at randomisation was smaller than the number of events that occurred in the group of patients who were not.

6.3 Discussion

In this population of elderly individuals with vascular disease (coronary disease, cerebral disease or PAD), or who were at an increased risk of vascular disease (because they smoked, or had diabetes or hypertension), an elevated resting heart rate was associated with a higher risk of the majority of endpoints studied, including all-cause, cancer, non-vascular, vascular and CHD death, as well as HF hospitalisation, and non-fatal MI. An elevated heart rate was associated with a decrease in the risk of TIA and PTCA or CABG. While an elevated heart rate was not found to be associated with risk of any of the stroke-related endpoints in the overall study population, an elevated time-updated heart rate adjusted for baseline was associated with an increase in each of the stroke related endpoints, excluding stroke death, in the subgroup of participants taking anti-arrhythmic medications and/or beta-blockers at randomisation, despite fewer events occurring in this subgroup. No significant associations between heart rate and stroke

death or peripheral arterial surgery/angioplasty were observed, although the numbers of these events were low.

Both an elevated baseline and time-updated resting heart rate, analysed categorically or continuously, were associated with an increase in the risk of all-cause death, vascular death (equivalent to CV death), non-vascular death, CHD death and HF hospitalisation. Time-updated heart rate remained a significant predictor for each of these outcomes after adjustment for baseline heart rate or the previous heart rate measurement. This indicates that updated measurements of heart rate contribute additional information about the risk of each of these endpoints in individuals with, or at an increased risk of, vascular disease, regardless of whether the baseline or previous heart rate measurement is known. Using time-updated heart rate strengthened the associations found for all of these outcomes. The addition of the baseline or time-updated resting heart rate variables also improved discrimination for each of these outcomes. In general, the time-updated heart rate models, unadjusted or adjusted for baseline or the previous heart rate measurement, yielded the highest and similar C-statistics, and thus had the best discriminative ability for each of these endpoints. Moreover, the addition of any of the heart rate variables to the models resulted in statistically significant improvements in their calibration, although when heart rate was analysed as a categorical variable, only the addition of the time-updated heart rate tertiles variable, with or without adjustment for baseline or the previous heart rate third, improved the calibration of the model for CHD death.

While no associations between baseline heart rate and risk of non-fatal MI or cancer death were observed, patients with a time-updated heart rate ≥70bpm were at a higher risk of both endpoints compared to those with a time-updated heart rate <70bpm. An elevated continuous time-updated heart rate was also associated with an increase in the risk of cancer death, and was borderline significantly associated with an increase in risk of non-fatal MI ($p = 0.05$). However, time-updated heart rate, adjusted for baseline or

the previous heart rate measurement, was a significant predictor of both endpoints, whether analysed categorically or continuously. For example, a 5bpm higher time-updated heart rate adjusted for baseline was associated with a 9% ($p<0.001$) and a 14% ($p<0.001$) increase in the risk of non-fatal MI and cancer death, respectively.

The addition of any of the resting heart rate variables improved the discrimination of the model for cancer death, and resulted in significantly better calibration when heart rate was analysed as a continuous variable: in regards to the heart rate tertiles variables, only the addition of the time-updated variable, with or without adjustment for baseline or the previous heart rate third, significantly improved calibration. Each of the time-updated models performed similarly well at discriminating between subjects who experienced cancer death from those that did not, and did so better than the baseline heart rate model. For non-fatal MI, only the addition of time-updated resting heart rate, analysed categorically or continuously, with or without adjustment for baseline or the previous heart rate, improved the discrimination of the model. Each of the three time-updated heart rate tertiles models were also found to have a significantly better calibration than the model excluding resting heart rate. When heart rate was analysed as a continuous variable, however, only the time-updated heart rate model additionally adjusted for baseline heart rate had significantly improved calibration. The model including time-updated heart rate alongside baseline heart rate was found to have the greatest predictive ability for MI, for both categorical and continuous resting heart rate.

The current findings for all-cause death correspond to those previously found by: Hillis et al. 2012[141] and Palatini et al. 2002[147], studies which included older subjects all of whom had diabetes and hypertension, respectively; Bemelmans et al. 2013[188], which included subjects all of whom had vascular disease; and Lonn et al. 2014[216], which included subjects who had vascular disease or diabetes with end-organ damage. The results for CV death and HF hospitalisation are also similar to those previously found by

Hillis et al. 2012[141], Bemelmans et al. 2013[188], and Lonn et al. 2014[216]. Excluding those taking anti-arrhythmic medications and/or beta-blockers at baseline, Nanchen et al. 2013 previously found that the PROSPER participants with a 'high' baseline heart rate were at a 73% (95% CI 22 to 145%) and 80% (95% CI 22 to 165%) higher risk of CV death and HF hospitalisation, respectively, compared to those with a 'low' baseline heart rate, after adjustment for conventional baseline risk factors and medications[138]. Including subjects taking anti-arrhythmic medications and/or beta-blockers at baseline, the current analysis exhibited that those with a 'high' baseline heart rate were at a 45% ($p = 0.0099$) and a 77% ($p<0.001$) higher risk of CV death and HF hospitalisation, respectively, compared to those with a 'low' baseline heart rate. Those with a high time-updated heart rate, adjusted for baseline heart rate group, were at a 64% ($p = 0.0095$) and a 94% ($p = 0.0024$) higher risk, respectively, compared to those with a 'low' time-updated heart rate.

Neither Bemelmans et al. 2013[188] or Lonn et al. 2014[216] found a significant association between heart rate and MI after adjustment for baseline risk factors. Moreover, van Kruijsdijk et al. 2014[189] found no association between an elevated baseline heart rate and risk of cancer death using the Fine and Gray model[143], adjusting for competing mortality, in the same population of patients as Bemelmans et al. 2013[188].

While Bemelmans et al. 2013[188] and Lonn et al. 2014[216] previously observed no associations between baseline heart rate and risk of stroke, Lonn et al. 2014 demonstrated that a 5bpm higher mean follow-up heart rate was associated with a 6% ($p = 0.0006$) increase in the risk of stroke in the total study population, 57% of whom were taking beta-blockers. In the present analysis, a higher time-updated heart rate adjusted for baseline was associated with a 13% increase in the risk of both fatal and non-fatal stroke, and non-fatal stroke ($p = 0.013$ and $p = 0.022$, respectively), and an 11% ($p = 0.017$) increase in the risk of the combined endpoint of fatal or non-fatal stroke or TIA, in the subgroup of participants taking anti-arrhythmic medications and/or beta-

blockers at randomisation, but not in the overall study population, or those not taking such drugs at baseline. In the study population as a whole, only small increases in the C-statistic were observed when the resting heart rate variables were added to the models for these outcomes. In addition, only the model including baseline resting heart rate tertiles had a significantly improved calibration compared to the model not including the heart rate thirds variables for each of the three stroke-related endpoints. Similarly, only the model including continuous baseline heart rate had a significantly improved calibration for fatal or non-fatal stroke, and no improvements in calibration were observed for non-fatal stroke, or fatal or non-fatal stroke or TIA, with the addition of any of the continuous heart rate variables. Only 26%, and 3% of the PROSPER subjects were taking beta-blockers and anti-arrhythmic drugs at baseline, respectively. Further exploration into the relationship between heart rate, stroke-related endpoints, and anti-arrhythmic medications and/or beta-blockers could assist in explaining such findings.

In the current analysis, an elevated heart rate was associated with a decrease in the risk of TIA and PTCA or CABG. The addition of baseline or time-updated heart rate improved discrimination of the models for both endpoints. All of models including heart rate yielded similar C-statistics for PTCA or CABG, and the same was true for the continuous heart rate models for TIA: the time-updated heart rate model adjusted for baseline heart rate yielded the highest C-statistic for TIA when heart rate was treated as a categorical variable. However, there were no improvements in calibration when any of the heart rate tertiles variables were added to the models for both outcomes, or when the continuous heart rate variables were added to the model for TIA. On the other hand, the addition of any of the continuous heart rate variables resulted in significantly improved calibration for PTCA or CABG.

No prior studies of subjects with vascular disease, or of older subjects with diabetes or hypertension, were identified in the systematic review of Chapter 2 that examined

associations between heart rate and the risk of TIA or revascularisation. However, the analysis of the relationship between heart rate and risk in the EUROPA population of patients who had stable CHD with no HF, described in Chapter 5, also found that an elevated baseline and time-updated heart rate were associated with a decrease in the risk of revascularisation. On the other hand, elevated baseline heart rate was associated with an increase in the risk of revascularisation in the BEAUTFIUL population of patients who had CHD and LVSD, many of whom also had HF[184]. In Chapter 5, it was suggested that this may have been because revascularisation was a marker for different conditions in these studies, since in the 1990s revascularisation was mainly used to treat angina, whereas from 2000 onwards it began to be used more frequently as a treatment for acute MI[276]. EUROPA recruited patients from 1997 to 2000, and PROSPER recruited patients from 1997 to 1999, whereas BEAUTIFUL recruited patients from 2004 to 2006. However, further exploration would need to be carried out to better understand the reasons for the differences in findings, and to understand why elevated heart rate would be associated with a decrease in risk of TIA.

No associations between any of the heart rate variables and the risk of peripheral arterial surgery/angioplasty or stroke death were observed. Furthermore, there were no significant improvements in model calibration for either endpoint with the addition of any of the heart rate variables, and only very small improvements in model discrimination were observed. However, only 79 peripheral arterial surgery/angioplasty events and 35 stroke deaths occurred, whereas over 170 of each of the other endpoints occurred (ranging from 177 TIA events to 963 all CV events) with the exception of PTCA or CABG (of which there were only 87). Thus, there may have been an insufficient number of events for the associations to reach significance. None of the studies identified in Chapter 2 of subjects with vascular disease, or of older subjects with diabetes or hypertension, evaluated the risk of stroke death or peripheral arterial surgery/angioplasty, so further analysis including a greater number of events could be illuminating.

6.3.1 Chapter Summary and Conclusions

This chapter investigated the prognostic value of baseline and time-updated resting heart rate for adverse outcomes in the PROSPER population.

An elevated time-updated heart rate was associated with an increase in the risk of all-cause, cancer, non-vascular, vascular and CHD death, as well as HF hospitalisation, and non-fatal MI, in this population of elderly individuals with, or at an increased risk of, vascular disease, irrespective of whether or not they were taking anti-arrhythmic drugs or beta-blockers. Updated measurements of heart rate over time contributed significant prognostic information about the risk of each of these endpoints, regardless of whether the baseline or previous heart rate measurements were known. Conversely, raised time-updated heart rate was predictive of a decrease in risk of TIA and PTCA or CABG. Furthermore, time-updated heart rate was predictive of risk of stroke-related outcomes in the subgroup of individuals taking anti-arrhythmic drugs and/or beta-blockers.

Chapter 7 similarly examined the predictive value of baseline and time-updated resting heart rate for adverse outcomes in the PERFORM population of patients who had recently experienced an ischemic stroke or TIA.

Chapter 7

Heart Rate and Risk in the PERFORM Population

7.1 Introduction

An elevated baseline resting heart rate has been associated with an increase in the risk of all-cause death[190,191], vascular death[190,191], recurrent stroke[191,192] and MI[191] in subjects who had previously had a stroke or TIA. Associations are less consistent in regards to recurrent stroke and MI, compared to all-cause and vascular death, however. In the PERFORM population, for example, Fox et al. 2013 found that an elevated continuous baseline heart rate was associated with an increase in the risk of fatal or non-fatal MI, and non-fatal MI[191]. In addition, patients with a baseline heart rate ≥70bpm were found to be at a higher risk of fatal or non-fatal MI (but not non-fatal MI individually), and fatal or non-fatal stroke. However, neither an elevated continuous baseline heart rate, nor a baseline heart rate ≥70bpm, were associated with an increase in the risk of specifically ischemic stroke.

Using data from the PERFORM trial[245], which enrolled individuals who had recently experienced an ischemic stroke or TIA, the first objective was to assess the association between baseline heart rate and risk of cardiac death, and hospitalisation due to cardiac causes – endpoints not previously evaluated by Fox et al. 2013[191], and not assessed before in post-stroke subjects. The second objective was to establish whether or not time-updated heart rate would have stronger associations with these outcomes, in addition to the outcomes previously evaluated by Fox et al. 2013 for baseline heart rate[191]. It was of particular interest to see whether time-updated heart rate would be associated with risk of ischemic stroke. The systematic review of Chapter 2 did not identify any studies of time-updated heart rate in post-stroke or -TIA patients.

7.2 Methods and Results

Ten outcomes were examined: the composite of fatal or non-fatal MI, fatal or non-fatal ischemic stroke, or other vascular death (the primary endpoint of PERFORM); fatal or non-fatal MI; non-fatal MI; fatal or non-fatal ischemic stroke; non-fatal ischemic stroke; all fatal or non-fatal stroke; vascular death; all-cause death; cardiac death; and hospitalisation due to cardiac causes. Note that vascular death did not include haemorrhagic death of any origin, as defined in the original trial publication[245].

Data of patients from both treatment arms of PERFORM (terutroban or aspirin) were pooled for this analysis since neither treatment directly affects heart rate. 18,993 of the patients (99.4% of the 19,100 patients included in the original trial) had a baseline heart rate measurement available and were included in the present analysis.

The baseline heart rate cut-off of 70bpm was selected on the basis that it was the cut-off used in the previous analysis by Fox et al. 2013[191], and was also close to the median heart rate of 72bpm. The baseline characteristics of the population, overall and split by baseline resting heart rate less than, or greater than or equal to, 70bpm, are shown in Table 7-1.

Table 7-1: Baseline characteristics of the PERFORM study population.

	Baseline Heart Rate			
	All Subjects n = 18993	**<70bpm n = 7907**	**≥70bpm n = 11086**	**p-value**
Demographic characteristics				
Sex (male)	11888 (63%)	5209 (66%)	6679 (60%)	<0.001
Age (years)	67.2 (7.9)	67.7 (7.9)	66.9 (7.9)	<0.001
Ethnic origin				**<0.001**
Caucasian	15928 (84%)	6849 (87%)	9079 (82%)	
Asian	2239 (18%)	735 (9%)	1504 (14%)	
Black	317 (2%)	136 (2%)	181 (2%)	
Other	509 (3%)	187 (2%)	322 (2%)	
Physical examination				
BMI (kg/m^2)	27.1 (4.3)	27.0 (4.2)	27.1 (4.4)	0.003
SBP (mm Hg)	138.3 (16.8)	138.2 (17.3)	138.3 (16.4)	0.538
DBP (mm Hg)	80.1 (9.4)	79.0 (9.7)	80.9 (9.1)	<0.001
Heart rate (bpm)	71.6 (10.5)	62.1 (5.3)	78.4 (7.6)	-
Smoking habits				**<0.001**
Never smoked	9253 (49%)	3629 (46%)	5624 (51%)	
Current smoker	5061 (27%)	2171 (27%)	2890 (26%)	
Stopped smoking >6 months previously	4685 (25%)	2111 (27%)	2574 (23%)	
Medical history				
Hypertension	15877 (84%)	6488 (82%)	9389 (85%)	<0.001
Hypercholesterolaemia	9131 (48%)	3912 (49%)	5219 (47%)	0.001
Hypertriglyceridemia	1794 (9%)	689 (9%)	1105 (10%)	0.0036
Diabetes	5275 (28%)	1794 (23%)	3481 (31%)	<0.001
Prior ischemic stroke	2879 (15%)	1130 (14%)	1749 (16%)	0.005
Prior TIA	1433 (8%)	673 (9%)	760 (7%)	<0.001
Angina pectoris	1806 (10%)	800 (10%)	1006 (9%)	0.016
Myocardial infarction	1468 (8%)	703 (9%)	765 (7%)	<0.001
Peripheral artery disease	735 (4%)	305 (4%)	430 (4%)	0.940
Previous treatments				
Antiplatelet agents	17021 (90%)	7216 (91%)	9805 (88%)	<0.001
Statin	10992 (58%)	4804 (61%)	6188 (56%)	<0.001
ACE Inhibitor	10392 (55%)	4213 (53%)	6179 (56%)	<0.001
ARB	2642 (14%)	1157 (15%)	1485 (13%)	0.015
Diuretic	6820 (36%)	2828 (36%)	3992 (36%)	0.730
Calcium channel blocker	5267 (28%)	2138 (27%)	3138 (28%)	0.055
Beta-blocker	5159 (27%)	2658 (34%)	2501 (23%)	<0.001
Antidiabetic agent	4288 (23%)	1430 (18%)	2858 (26%)	<0.001
Modified Rankin Scale				**<0.001**
Class 0 (no symptoms)	4212 (22%)	1967 (25%)	2245 (20%)	
Class 1 (no significant disability)	7274 (38%)	3065 (39%)	4209 (38%)	
Class 2 (slight disability)	4284 (26%)	1730 (22%)	2554 (23%)	
Class 3 (moderate disability)	2043 (11%)	733 (9%)	1310 (12%)	
Class 4 (moderately severe disability)	1196 (6%)	420 (5%)	776 (7%)	

This table shows the clinical and demographic characteristics of the PERFORM patients who had baseline resting heart rate measurements available. Values are given for the total population, as well as separately for patients who had a baseline resting heart rate <70bpm, and patients who had a baseline resting heart rate ≥70bpm. Data are the number of patients with the corresponding percentage, or the mean with the standard deviation, depending on whether the variable was categorical or continuous. Not all patients had every baseline measurement available. Therefore, percentages and means were calculated using the number of subjects with non-missing data as the denominator. The values of each characteristic were compared between the two different baseline resting heart rate groups using unpaired two-sample t-tests and chi-squared tests, for continuous and categorical variables, respectively.

The variable 'antiplatelet agents' includes aspirin, dipyridamole, clopidogrel and ticlopidine.

ACE = Angiotensin-Converting Enzyme; ARB = Angiotensin II Receptor Block; BMI = Body Mass Index; DBP = Diastolic Blood Pressure; SBP = Systolic Blood Pressure; TIA = Transient Ischemic Attack.

There were significant differences between the two groups of patients in terms of almost all of the baseline characteristics excluding SBP, the presence of PAD, and the intake of CCBs and diuretics. Patients in the ≥70bpm baseline heart rate group were more likely to be female and younger; they were also more likely to be Asian and less likely to be Caucasian. Those in the higher heart rate group were also more likely to have a higher BMI and DBP, and have never smoked. Hypertension, hypertriglyceridemia and diabetes were more prevalent in the higher heart rate group, while hypercholesterolaemia was less prevalent. It was also less likely that those in the higher heart rate group had experienced a prior TIA, angina or an MI, but more likely that they had experienced a prior ischemic stroke. The use of antiplatelet agents, statins, ARBs, and beta-blockers was lower in the higher heart rate group, while the use of ACE inhibitors and antidiabetic agents was higher. Finally, patients with a baseline heart rate ≥70bpm were more likely to be assessed as Class 2, 3 or 4 by the Modified Rankin Scale.

The total number of events is presented in Table 7-2, along with the number that occurred in each of the baseline heart rate groups. The percentage of patients in the greater than or equal to 70bpm heart rate group was higher for: the primary endpoint; all fatal and non-fatal MI; vascular death; all-cause death; and cardiac death, compared to the less than 70bpm baseline group. For all other events, the percentage of patients in each group who experienced the event was similar.

The Cox regression models adjusted for the same variables adjusted for in the baseline heart rate publication[191] with the exception of Country: age; gender; smoking; BMI; prior ischemic stroke; prior MI; prior TIA; hypertension; diabetes; and the intake of beta-blockers, statins and antiplatelet agents after the qualifying event.

Table 7-2: The number of first events that occurred in the PERFORM population.

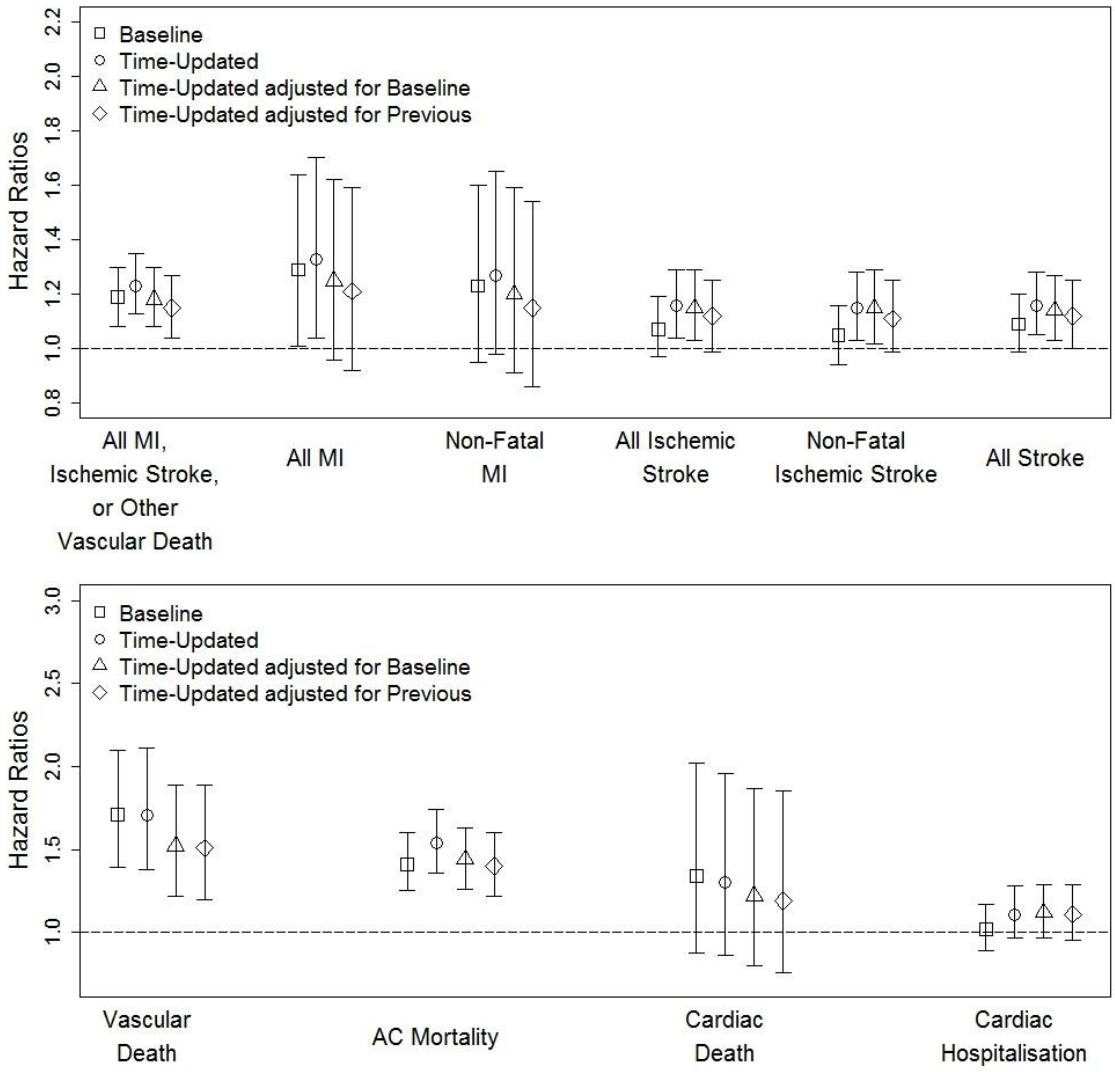
		Subjects Separated by Baseline Heart Rate	
	Total Population n = 18993	**<70bpm n = 7907**	**>=70bpm n = 11086**
Primary Composite Endpoint			
Fatal or non-fatal MI, fatal or non-fatal ischemic stroke, or other vascular death	2141 (11%)	835 (11%)	1306 (12%)
MI-Related Endpoints			
All fatal or non-fatal MI	285 (2%)	108 (1%)	177 (2%)
Non-fatal MI	251 (1%)	98 (1%)	153 (1%)
Stroke-Related Endpoints			
All fatal or non-fatal ischemic stroke	1,541 (8%)	631 (8%)	910 (8%)
Non-fatal ischemic stroke	1,446 (8%)	643 (8%)	843 (8%)
All fatal or non-fatal stroke	1,667 (9%)	676 (9%)	991 (9%)
Mortality-Related Endpoints			
Vascular death	436 (2%)	136 (2%)	300 (3%)
All-cause mortality	1174 (6%)	414 (5%)	760 (7%)
Cardiac Endpoints			
Cardiac death	103 (1%)	39 (<1%)	64 (1%)
Hospitalisation due to a cardiac cause	887 (5%)	384 (5%)	503 (5%)

This table shows the total number of PERFORM patients with available baseline resting heart rate data who experienced any pre-specified events of interest, as well as the number in relation to baseline heart rate, partitioned at 70bpm. Data are number of patients who experienced the event as a first event, with the corresponding percentage. MI = Myocardial Infarction. Note that first event refers to the first event of each type: for example, a patient may have experienced a non-fatal MI, and then have subsequently experienced a non-fatal ischemic stroke at a later date.

The linearity of effect for each continuous heart rate variable was evaluated by plotting the Martingale residuals (a linear transformation of Cox-Snell residuals)[252,253] of each model against the heart rate values. No violations of the linearity assumption were observed.

Comparing the risk of each of the outcomes between patients with a baseline or time-updated heart rate ≥70bpm, or <70bpm, produced the HRs and CIs shown by Figure 7-1 and in Table A5-1 provided in Appendix 5.

Figure 7-1: Results of fitting Cox proportional hazards models. Hazard ratios with corresponding 95% confidence intervals for a heart rate ≥70bpm compared to a heart rate <70bpm in the PERFORM population.



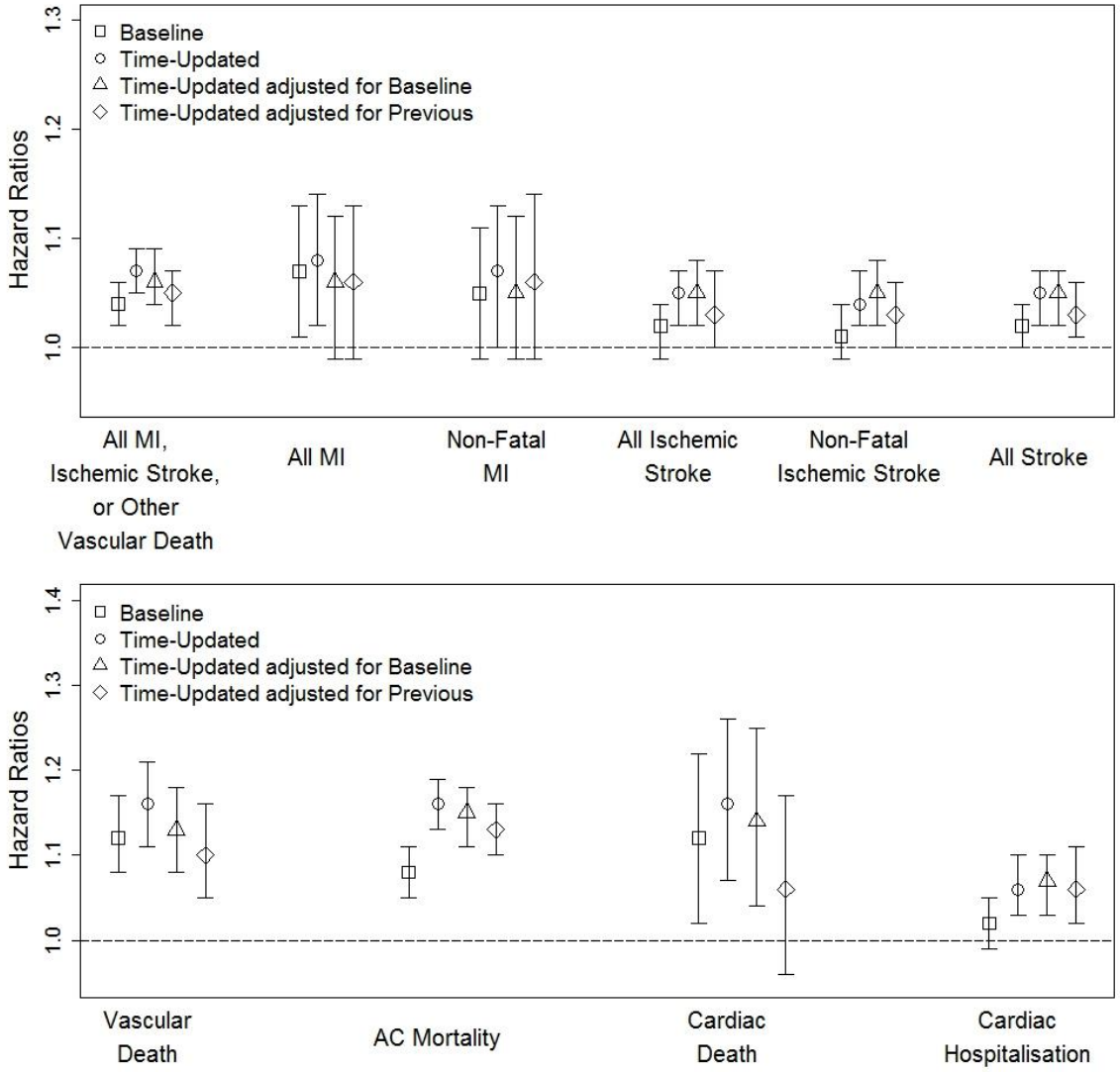
AC = All-Cause; MI = Myocardial Infarction.

Models were additionally adjusted for: age; gender; smoking; body mass index (BMI); prior ischemic stroke; prior myocardial infarction (MI); prior transient ischemic attack (TIA); hypertension; diabetes; and the intake of beta-blockers, statins and antiplatelet agents after the qualifying event.

A heart rate ≥70bpm was associated with a higher risk of the combined endpoint of fatal or non-fatal MI, fatal or non-fatal ischemic stroke, or other vascular death, and the individual endpoints of vascular death and all-cause death in all models fitted. A baseline resting heart rate ≥70bpm was not associated with a higher risk of all fatal or non-fatal ischemic stroke, non-fatal ischemic stroke, or all fatal or non-fatal stroke. However, time-updated resting heart rate ≥70bpm was associated with a 16% ($p = 0.0057$) increase in risk of all fatal or non-fatal ischemic stroke, a 15% ($p = 0.013$) increase in risk of non-fatal ischemic stroke, and a 16% ($p = 0.0044$) increase in risk of all fatal or non-fatal stroke. The associations for each of these three outcomes also remained after adjustment for baseline heart rate group, but were attenuated when the previous time-updated heart rate group was adjusted for ($p = 0.069$ for fatal or non-fatal ischemic stroke; $p = 0.085$ for non-fatal ischemic stroke; and $p = 0.054$ for all fatal or non-fatal stroke). In regards to all fatal or non-fatal MI, a baseline and a time-updated heart rate ≥70bpm were associated with a 29% ($p = 0.044$) and 33% ($p = 0.025$) increase in risk, respectively. The association between time-updated heart rate and risk lost its association when baseline and previous heart rate were adjusted for ($p = 0.094$ and $p = 0.18$, adjusted for baseline and the previous heart rate, respectively). No associations between a heart rate ≥70bpm and risk of non-fatal MI, cardiac death, or hospitalisation due to cardiac cause were observed.

Analysing continuous heart rate measurements produced the HRs and CIs shown by Figure 7-2 and in Table A5-2 provided in Appendix 5.

Figure 7-2: Results of fitting Cox proportional hazards models. Hazard ratios with corresponding 95% confidence intervals for a 5bpm higher heart rate in the PERFORM population.



AC = All-Cause; MI = Myocardial Infarction.

Models were additionally adjusted for: age; gender; smoking; body mass index (BMI); prior ischemic stroke; prior myocardial infarction (MI); prior transient ischemic attack (TIA); hypertension; diabetes; and the intake of beta-blockers, statins and antiplatelet agents after the qualifying event.

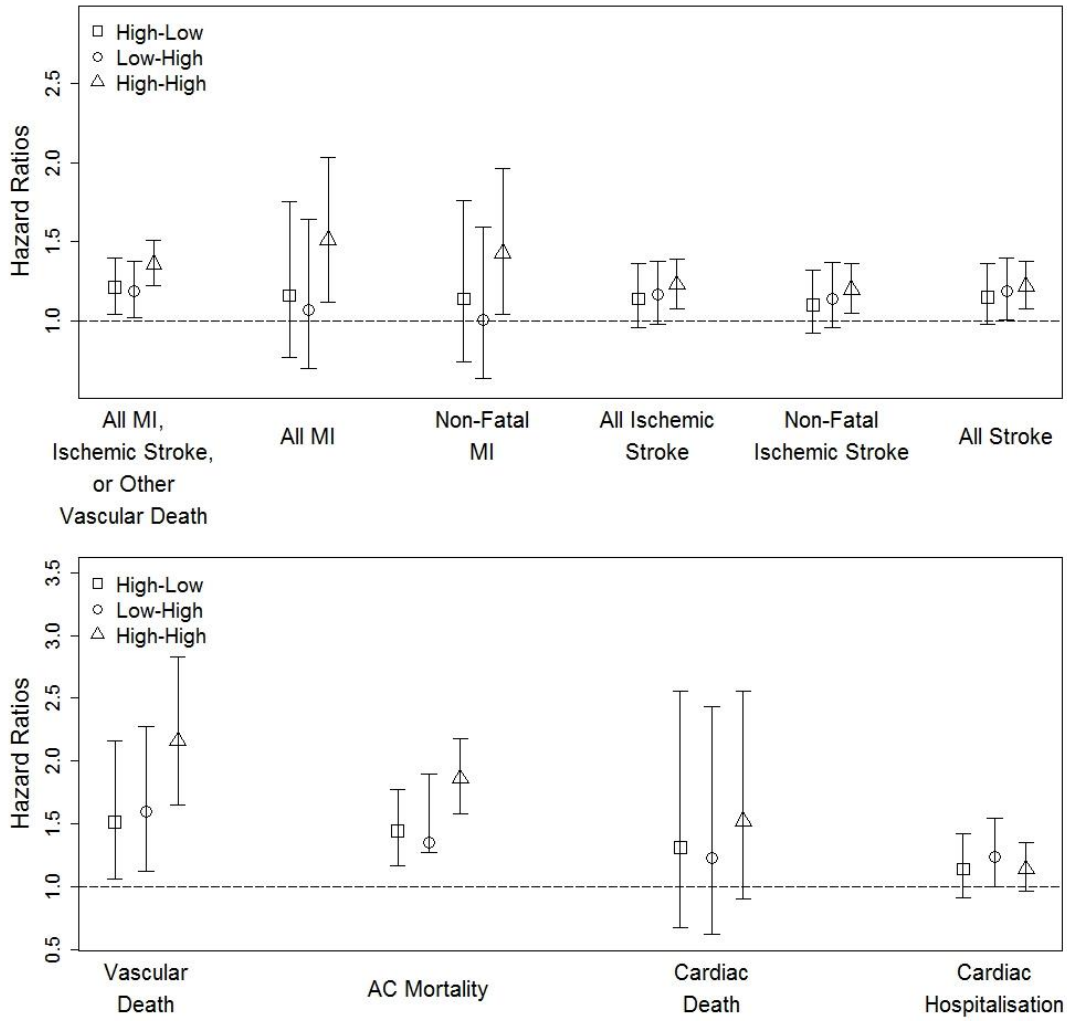
A 5bpm higher heart rate was associated with higher risk of the combined endpoint of fatal or non-fatal MI, fatal or non-fatal ischemic stroke, or other vascular death, and the individual endpoints of vascular death and all-cause mortality, in all models. Elevated baseline, time-updated and time-updated heart rate adjusted for baseline were associated with an increase in risk of cardiac death, but the association was attenuated when the previous heart rate measurement was adjusted for ($p = 0.26$). A 5bpm higher baseline heart rate, and time-updated heart rate, were associated with a

7% (p = 0.013) and 8% (p = 0.0074) increase in risk of fatal or non-fatal MI, respectively, but the association was similarly attenuated after adjustment for baseline (p = 0.077) and the previous heart rate measurement (p = 0.10). An elevated continuous baseline heart rate was not associated with an increase in risk of non-fatal MI, fatal or non-fatal ischemic stroke, non-fatal ischemic stroke, all fatal or non-fatal stroke, or cardiac death. However, a 5bpm higher time-updated heart rate was associated with an 8% (p = 0.0074) increase in risk of non-fatal MI, a 5% (p<0.001) increase in risk of fatal or non-fatal ischemic stroke, a 4% (p = 0.011) increase in risk of non-fatal ischemic stroke, a 5% (p<0.001) increase in risk of all fatal or non-fatal stroke, and a 6% (p<0.001) increase in risk of hospitalisation due to cardiac cause. The association between elevated continuous time-updated heart rate and risk remained after adjustment for baseline and the previous heart rate measurement for fatal or non-fatal ischemic stroke, all fatal or non-fatal stroke, and hospitalisation due to cardiac cause. The association with risk of non-fatal ischemic stroke remained after adjustment for baseline (p = 0.012) but was attenuated slightly when previous heart rate was adjusted for (p = 0.057). Elevated continuous time-updated heart rate adjusted for baseline or previous heart rate did not remain predictive of risk of non-fatal MI (p = 0.13 and p = 0.090 adjusted for baseline and the previous heart rate, respectively).

Figure 7-3 and Table A5-3 provided in Appendix 5 show the adjusted HRs and 95% CIs estimated using the time-updated categorical heart rate patterns models. Comparing the current heart rate measurement at each visit to the previous heart rate measurement, all patients who did not have a heart rate below 70bpm at both the current and previous visit (low-low) were found to be at a higher risk of the combined endpoint of fatal or non-fatal MI, ischemic stroke, or other vascular death, and the individual endpoints vascular death and all-cause death. Patients with a heart rate ≥70bpm at both visits (high-high), and whose heart rate increased from below 70bpm at the previous visit to ≥70bpm at the current visit (low-high), were at a higher risk of all fatal or non-fatal stroke (low-high: 19%, 95% CI 1 to 40%, p = 0.038; high-high: 22%, 95%

CI 8 to 38%, p = 0.0012). Those with a high heart rate at both visits were at a 51% (p = 0.0074) higher risk of fatal or non-fatal MI, a 43% (p = 0.026) higher risk of non-fatal MI, a 23% (p = 0.0015) higher risk of fatal or non-fatal ischemic stroke, and a 20% higher risk of non-fatal ischemic stroke (p = 0.0066). No significant associations between risk and heart rate pattern were observed for either of the cardiac endpoints, although a low-high heart rate was borderline significantly associated with an increase in risk of hospitalisation due to a cardiac cause (p = 0.054).

Figure 7-3: Results of fitting Cox proportional hazards models. Hazard ratios with corresponding 95% confidence intervals for the time-updated categorical heart rate patterns 'high-low', 'low-high' and 'high-high' relative to the category 'low-low' in the PERFORM population.



Patients were classified as being in the low-low category if their heart rate measurement at both the current and previous visit was below 70bpm. Similarly, patients were classified as being in the high-high category if their heart rate measurement at both the current and previous visit was greater than or equal to 70bpm, and so on.

AC = All-Cause; MI = Myocardial Infarction.

Models were additionally adjusted for: age; gender; smoking; body mass index (BMI); prior ischemic stroke; prior myocardial infarction (MI); prior transient ischemic attack (TIA); hypertension; diabetes; and the intake of beta-blockers, statins and antiplatelet agents after the qualifying event.

The discrimination and calibration of the models were evaluated using Harrell's C-statistic and likelihood ratio tests, respectively. Table A5-4 provided in Appendix 5 shows Harrell's C-statistics for the model excluding resting heart rate, and the models including the heart rate variables that categorised subjects according to whether they had a heart rate less than, or greater than or equal to 70bpm, for each outcome. Regardless of whether any resting heart rate category variables were included, the models had the greatest predictive ability for vascular and cardiac death: the C-statistics of the models both excluding and including resting heart rate ranged from 0.711 to 0.731, and 0.748 to 0.753 for each of these outcomes, respectively. The models had the least predictive ability for the three stroke-related endpoints (all ischemic strokes, non-fatal ischemic strokes, and all strokes), with C-statistics ranging from 0.612 to 0.622. The C-statistics of the models for the other outcomes ranged from 0.630 to 0.694. The addition of baseline or time-updated resting heart rate category improved discrimination for all of the endpoints except non-fatal MI and cardiac hospitalisation compared to the model excluding heart rate. However, the C-statistics for each of the three stroke-related endpoints increased by up to 0.004 only with the addition of the heart rate category variables. The model including time-updated heart rate category additionally adjusted for baseline heart rate category had the best discrimination for vascular death and all-cause death; the model including time-updated heart rate category additionally adjusted for the previous heart rate category had the best discrimination for the combined endpoint of fatal or non-fatal MI, ischemic stroke, or other vascular death; and both time-updated heart rate models adjusted for either baseline or the previous heart rate category had the best discrimination for fatal or non-fatal MI and cardiac death. Only the addition of the time-updated heart rate category variable, with adjustment for baseline or the previous heart rate category, improved the discrimination of the model for non-fatal MI. There was no improvement in discrimination for cardiac hospitalisation with the addition of any of the heart rate category variables. The likelihood ratio test statistics and corresponding p-values for the addition of the heart rate category variables to the models are also presented in

Table A5-4. The addition of any of the heart rate category variables resulted in statistically significant improvements in the calibration of the models for the combined endpoint of fatal or non-fatal MI, ischemic stroke, or other vascular death, and the individual endpoints of fatal or non-fatal MI, vascular death, and all-cause death. Only the addition of the time-updated heart rate category variable, with or without adjustment for baseline or the previous heart rate category, improved the calibration of the models for non-fatal MI, each of the three stroke-related endpoints, and cardiac hospitalisation. There were no significant improvements in model calibration for cardiac death.

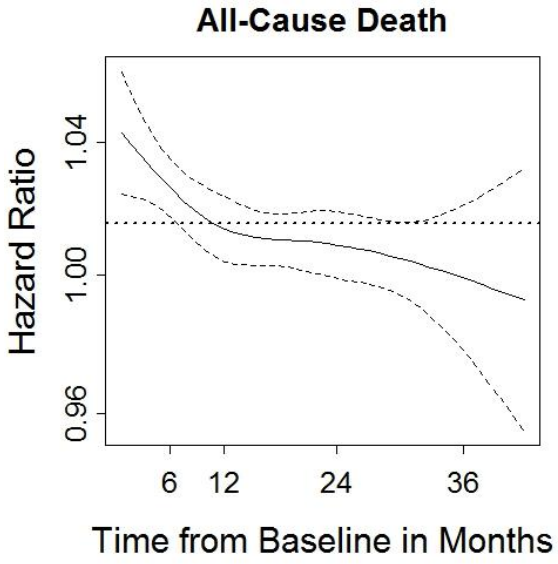
Harrell's C-statistics for the model excluding resting heart rate, and the models including the continuous heart rate variables, for each outcome, are shown in Table A5-5 provided in Appendix 5, along with the likelihood ratio test statistics and corresponding p-values for the addition of the different continuous heart rate variables. The results were very similar to those observed for the heart rate categories according to whether subjects had a heart rate less than, or greater than or equal to 70bpm, with a couple of exceptions. First, while there was no improvement in discrimination for cardiac hospitalisation with addition of any of the heart rate category variables, the addition of the continuous time-updated heart rate category variable, with or without adjustment for baseline or the previous heart rate category, improved the discrimination of the models, but only by 0.001, from 0.662 to 0.663. Second, the addition of any of the continuous heart rate variables resulted in statistically significant improvements in the calibration of the models for cardiac death.

Table A5-6 provided in Appendix 5 shows Harrell's C-statistics for the model excluding resting heart rate, and the models including the time-updated categorical heart rate patterns variable for each outcome. Again, irrespective of whether resting heart rate was included, the models had the greatest predictive ability for vascular and cardiac death, and the least for the three stroke-related endpoints. The addition of time-

updated categorical heart rate pattern improved discrimination for all of the outcomes, although the C-statistic increased by only 0.001 for hospitalisation due to a cardiac cause, and only 0.003 for each of the stroke-related endpoints. Other small improvements in discrimination were observed for fatal or non-fatal MI, non-fatal MI, and cardiac death, with the C-statistics increasing from 0.676 to 0.681, 0.673 to 0.677, and 0.748 to 0.753, respectively, when time-updated heart rate pattern was added to the models. The largest improvements were observed for vascular and all-cause death, with the C-statistics increasing from 0.711 to 0.727, and 0.678 to 0.693, respectively. The likelihood ratio test statistics and corresponding p-values for the addition of the heart rate patterns variable to the models are also presented in Table A5-6. The addition of heart rate pattern resulted in statistically significant improvements in the calibration of the models for all of the outcomes except cardiac death.

Table A5-7, Table A5-8 and Table A5-9 in Appendix 5 show the p-values of the Grambsch and Therneau 1994 test for non-proportionality for all the models and outcomes. Evidence of non-proportionality of the effect of an elevated continuous baseline heart rate on the hazard of all-cause death was found. Examination of the plot of the smoothed curve and corresponding 95% CIs of the Schoenfeld residuals for a 5bpm higher baseline heart rate and risk of all-cause death, shown by Figure 7-4, suggested that the effect of heart rate was highest at the beginning of follow-up, and then decreased over time. No violations of the proportional hazards assumption for any of the other heart rate variables that were associated with risk of outcome were observed.

Figure 7-4: The Schoenfeld residuals plot of the effect of a 5bpm higher baseline heart rate on the risk of all-cause death in the PERFORM population.



The horizontal dotted line represents the previously calculated 'average' hazard ratio of all-cause death.

7.3 Discussion

In this large population of patients aged 55 years or older who had recently experienced an ischemic stroke or TIA, an elevated resting heart rate was associated with an increase in the risk of all of the endpoints evaluated, including non-fatal MI, all fatal or non-fatal ischemic stroke, non-fatal ischemic stroke, cardiac death and hospitalisation due to cardiac causes.

An elevated baseline and time-updated heart rate, both unadjusted and adjusted for baseline heart rate or the previous heart rate measurement, analysed as a categorical or continuous variable, was associated with an increase in the risk of all-cause and vascular death. Moreover, the addition of any of the heart rate variables improved the discriminative ability, and resulted in statistically significant improvements in the calibration of the models: the time-updated models adjusted for baseline or the previous heart rate measurements yielded the highest C-statistics. Thus, even if the baseline or previous heart rate measurement are known, time-updated heart rate supplies significant additional information about the risk of death from all causes or CV causes in post-stroke or or-TIA patients.

While no associations between baseline heart rate and risk of any of the stroke-related endpoints were observed, an elevated time-updated heart rate was associated with an increase in risk of each of the stroke-related endpoints. A time-updated heart rate ≥70bpm remained a significant predictor of each of the outcomes after adjustment for baseline group, but associations were attenuated slightly when previous heart rate group was adjusted for. The same was true of elevated continuous time-updated heart rate in regards to non-fatal ischemic stroke. On the other hand, an elevated continuous time-updated heart rate was associated with an increase in risk of fatal or non-fatal ischemic stroke, and all fatal or non-fatal ischemic stroke, after adjustment for both baseline and the previous heart rate measurement. While only small improvements in discrimination were observed when each of the resting heart rate variables were added to the models, the greatest improvements resulted from the inclusion of the time-updated resting heart rate variables. Only the addition of the time-updated heart rate variables, with or without adjustment for baseline or the previous heart rate measurements, improved the calibration of the models for each of the three stroke-related endpoints.

Both an elevated baseline and time-updated heart rate were associated with a higher risk of all fatal or non-fatal MI. However, the association with time-updated heart rate was attenuated when either baseline heart rate or the previous heart rate measurement were adjusted for. Minor improvements in discrimination were observed when each of the resting heart rate variables were added to the models. The addition of any of the heart rate variables resulted in statistically significant improvements in the calibration of the models: the improvement appeared to be greatest with the inclusion of time-updated resting heart rate (all time-updated heart rate models $p<0.001$ compared to $p = 0.42$ and $p = 0.014$ for the models including only categorical and continuous baseline heart rate, respectively). No associations between any of the categorical heart rate variables and the risk of non-fatal MI were observed. Conversely, an elevated continuous time-updated heart rate was associated with an increase in the risk of non-

fatal MI, although again, results were attenuated when baseline or the previous heart rate measurement were adjusted for. Only very small improvements in discrimination were observed with the addition of some of the resting heart rate variables, and only the models including time-updated resting heart rate were found to be better calibrated than the model not including resting heart rate for non-fatal MI.

No associations between any of the categorical heart rate variables and the risk of either of the cardiac endpoints were observed. Although the addition of baseline or time-updated resting heart rate category improved discrimination for cardiac death, there was no improvement for cardiac hospitalisation with the addition of any of the heart rate category variables. Conversely, there were no significant improvements in model calibration for cardiac death, whereas the addition of the time-updated heart rate category variable, with or without adjustment for baseline or the previous heart rate category, improved the calibration of the models for cardiac hospitalisation. In contrast, an elevated continuous time-updated heart rate was associated with an increase in risk of both cardiac death and hospitalisation due to cardiac causes. An elevated continuous time-updated heart rate retained its prognostic value even after adjustment for baseline heart rate or the previous heart rate measurement for hospitalisation due to cardiac causes, but adjustment for the previous measurement attenuated the association with cardiac death. Again, the addition of baseline or time-updated resting heart rate improved discrimination of the model for cardiac death, however the addition of continuous time-updated heart rate, with or without adjustment for baseline or the previous heart rate measurement, also increased the C-statistic of the model for cardiac hospitalisation, but only by 0.001. Furthermore, the addition of any of the continuous heart rate variables resulted in statistically significant improvements in the calibration of the models for cardiac death, while again, the addition of the time-updated heart rate variable, with or without adjustment for baseline or the previous heart rate measurement, improved the calibration of the models for cardiac hospitalisation.

The current findings for all-cause death and CV death were generally similar to those previously found by Bohm 2012[190] and Fox 2013[191]. While Bohm et al. 2012 and Fox et al. 2013 found no associations between an elevated baseline heart rate and the risk of any type of recurrent stroke or MI[190], or ischemic stroke[191], respectively, this study demonstrated that an elevated time-updated resting heart rate was associated with a higher risk of both fatal and non-fatal MI and ischemic stroke. No prior studies of post-stroke or -TIA subjects were identified in the systematic review of Chapter 2 that examined associations between heart rate and the risk of cardiac death or hospitalisation due to cardiac causes.

7.3.1 Chapter Summary and Conclusions

This chapter assessed the associations between baseline and time-updated resting heart rate, and risk of death and adverse CV events, in the PERFORM population.

Raised time-updated heart rate was associated with an increase in risk of all of the adverse events that were studied, including all-cause death, non-fatal MI, cardiac death and hospitalisation due to cardiac causes in this population of patients who had recently experienced an ischemic stroke or TIA. While baseline resting heart rate was not found to be associated with risk of any of the stroke-related endpoints that were evaluated, an elevated time-updated heart rate was associated with an increase in risk of each of them.

Chapter 8 similarly explores baseline and time-updated resting heart rate as risk markers in the BEAUTIFUL and SHIFT placebo populations, both individually and pooled: each trial enrolled patients with LVSD who were in sinus rhythm.

Chapter 8

Heart Rate and Risk in Patients with Left-Ventricular Systolic Dysfunction

8.1 Introduction

In the placebo-randomised patients of the BEAUTIFUL trial, who had CHD and LVSD, with a baseline heart rate ≥60bpm (many of whom also had HF), Fox et al. 2008 established that an elevated baseline resting heart rate was associated with an increase in the risk of CV death, hospital admission for HF and MI, and coronary revascularisation[184]. Patients with a baseline heart rate ≥70bpm, for example, were found to be at a 46% (p = 0.0066) higher risk of hospital admission for MI. A 5bpm higher baseline heart rate, however, was only borderline significantly associated with a 7% (p = 0.052) increase in the risk of hospital admission for MI.

Similarly, in the placebo-randomised patients of the SHIFT trial, who had chronic HF and LVSD, with a baseline heart rate ≥70bpm, Bohm et al. 2010 demonstrated that a raised resting heart rate at baseline was associated with an increase in the risk of death from a number of different causes, and adverse CV outcomes such as hospital admission for HF and MI[182]. However, the predictive value of an elevated continuous resting heart rate was only evaluated in relation to the primary endpoint – CV death or hospital admission for HF – and its individual components.

Vazir et al. 2014 recently demonstrated that an elevated time-updated heart rate was associated with an increase in the risk of adverse events in a population of patients with chronic HF[215]. However, the systematic review of Chapter 2 did not identify any studies of time-updated heart rate in patients specifically with LVSD and either CHD or chronic HF.

In Section 8.2, data from the BEAUTIFUL trial was used to investigate the association between baseline heart rate and risk of the other five endpoints that were assessed in the original BEAUTIFUL trial publication[248] , such as all-cause and cardiac death, that were not previously studied by Fox et al. 2008[184]. The analysis also aimed to determine whether or not time-updated heart rate would strengthen the associations for each of these outcomes, as well as the four originally studied by Fox et al. 2008[184].

In Section 8.3, data from the SHIFT trial was used to explore the associations between baseline heart rate and hospital admission for non-fatal MI, and the composite of CV death or hospital admission for non-fatal MI - endpoints that were not previously studied by Bohm et al. 2010[182]. The analysis also aimed to establish whether or not time-updated heart rate would strengthen the associations for each of these outcomes, as well as those originally studied by Bohm et al. 2010[182].

Since both trials enrolled patients with LVSD in sinus rhythm, data from each were pooled, and an individual patient meta-analysis of the predictive value of baseline and time-updated resting heart rate for common outcomes across the trials was carried out in Section 8.4. Differences between the trials, in relation to the effect of heart rate, were also examined.

8.2 The Predictive Value of Baseline and Time-Updated Heart Rate Measurements in the BEAUTIFUL Placebo Patients

Only the placebo group of the BEAUTIFUL trial was included in this analysis since ivabradine lowers the heart rate. All of the patients assigned to the placebo group (n = 5,438) had baseline heart rate measurements available and were included.

Nine outcomes were assessed: the composite of CV death or admission to hospital for MI or new-onset or worsening HF (the primary endpoint of BEAUTIFUL); all-cause death; CV death; cardiac death; admission to hospital for HF; the composite of CV death or

admission to hospital for new-onset or worsening HF; admission to hospital for MI; the composite of admission to hospital for MI or unstable angina; and coronary revascularisation.

The baseline heart rate cut-off of 70bpm was selected on the basis that it was the cut-off used in the previous analysis[184] and was also very close to the median heart rate of 69bpm of the BEAUTIFUL placebo patients included in the current analysis. The baseline characteristics of the placebo-assigned BEAUTIFUL patients, overall and categorised into groups depending on whether their baseline resting heart rate was less than or greater than or equal to 70bpm are shown in Table 8-1. There were significant differences between the two groups of patients in terms of age, smoking status, BMI, history of diabetes, previous MI, previous PCI or CABG, PAD, SBP, DBP, LVEF, NYHA class, and treatment with aspirin, beta-blockers, statins, diuretics (excluding anti-aldosterone), organic nitrates, and anti-aldosterone agents at randomisation. Patients with a heart rate of 70bpm or greater were younger, had a higher BMI, SBP and DBP, and had a lower LVEF than those with a heart rate of less than 70bpm. They were also more likely to smoke, have diabetes and PAD, and be in NYHA class III, and less likely to have had an MI or revascularisation. Patients in the higher heart rate group were also more likely to be treated with diuretics, organic nitrates, and anti-aldosterone agents, and less likely to be treated with aspirin, beta-blockers, and statins.

The total number of events that occurred in the placebo group is presented in Table 8-2, along with the numbers that occurred in each of the baseline heart rate groups of patients. The percentage of patients with a baseline heart rate of 70bpm or higher who experienced an event was higher for every event compared to the patients with a baseline heart rate lower than 70bpm.

Table 8-1: Baseline characteristics of the BEAUTIFUL placebo study population.

		Baseline Heart Rate		
	All Subjects n = 5438	**<70bpm n = 2745**	**≥70bpm n = 2693**	**p-value**
Demographic Characteristics				
Age (years)	65.0 (8.4)	65.6 (8.2)	64.4 (8.6)	<0.001
Sex (male)	4507 (83%)	2298 (84%)	2209 (82%)	0.098
Smoking (current)	835 (15%)	353 (13%)	482 (18%)	<0.001
BMI (kg/m^2)	28.5 (4.4)	28.3 (4.1)	28.7 (4.7)	0.002
Medical History				
Hypertension	3838 (71%)	1911 (70%)	1927 (72%)	0.117
Diabetes	2019 (37%)	864 (31%)	1155 (43%)	<0.001
Dyslipidaemia	4278 (79%)	2155 (79%)	2123 (79%)	0.768
Prior MI	4817 (89%)	2648 (90%)	2349 (87%)	0.002
Prior PCI or CABG	2824 (52%)	1464 (53%)	1360 (51%)	0.037
Prior stroke	971 (18%)	468 (17%)	503 (19%)	0.117
Peripheral artery disease	748 (14%)	346 (13%)	402 (15%)	0.013
Cardiac Parameters				
Heart rate (bpm)	71.6 (9.9)	64.1 (2.8)	79.2 (8.7)	-
SBP (mm Hg)	127.9 (15.5)	127.2 (15.2)	128.5 (15.7)	0.002
DBP (mm Hg)	77.5 (9.2)	76.7 (9.2)	78.3 (9.2)	<0.001
LVEF (%)	32.3 (5.5)	32.7 (5.3)	31.9 (5.7)	<0.001
NYHA Class				**<0.001**
Class I heart failure	840 (15%)	467 (17%)	373 (14%)	
Class II heart failure	3359 (62%)	1744 (64%)	1615 (60%)	
Class III heart failure	1239 (23%)	534 (19%)	705 (26%)	
Medication at Randomisation				
Aspirin	4588 (84%)	2438 (86%)	2240 (83%)	0.017
ACE inhibitor, ARB or both	4873 (90%)	2452 (89%)	2421 (90%)	0.488
Beta-blocker	4738 (87%)	2465 (90%)	2273 (84%)	<0.001
Statin	4032 (74%)	2087 (76%)	1945 (72%)	0.001
Diuretics (excluding anti-aldosterone)	3194 (59%)	1490 (54%)	1704 (63%)	<0.001
Organic nitrates	2335 (43%)	1133 (41%)	1202 (45%)	0.012
Anti-aldosterone agents	1466 (27%)	666 (24%)	800 (30%)	<0.001

This table shows the clinical and demographic characteristics of the BEAUTIFUL placebo patients. Values are given for the total placebo population, as well as separately for patients who had a baseline resting heart rate <70bpm, and patients who had a baseline resting heart rate ≥70bpm. Data are the number of patients with the corresponding percentage, or the mean with the standard deviation, depending on whether the variable was categorical or continuous. Not all patients had every baseline measurement available. Therefore, percentages and means were calculated using the number of subjects with non-missing data as the denominator. The values of each characteristic were compared between the two different baseline resting heart rate groups using unpaired two-sample t-tests and chi-squared tests, for continuous and categorical variables, respectively.

Aspirin did not include other antithrombotic agents (which it did in the original baseline heart rate paper).

ACE = Angiotensin-Converting Enzyme; ARB = Angiotensin II Receptor Blocker; BMI = Body Mass Index; CABG = Coronary Artery Bypass Graft; DBP = Diastolic Blood Pressure; LVEF = Left-Ventricular Ejection Fraction; MI = Myocardial

Infarction; NYHA = New York Heart Association; PCI = Percutaneous Coronary Intervention; SBP = Systolic Blood Pressure.

Table 8-2: The number of first events that occurred in the BEAUTIFUL placebo population.

		Subjects Separated by Baseline Heart Rate	
	Total Placebo Population n = 5438	**<70bpm n = 2745**	**≥70bpm n = 2693**
Primary Composite Endpoint			
Cardiovascular death or admission to hospital for myocardial infarction or new-onset or worsening heart failure	832 (15%)	334 (12%)	498 (18%)
Mortality Endpoints			
All-cause death	547 (10%)	223 (8%)	324 (12%)
Cardiovascular death	435 (8%)	172 (6%)	263 (10%)
Cardiac death	151 (8%)	54 (2%)	97 (4%)
Heart Failure Endpoints			
Admission to hospital for heart failure	427 (8%)	156 (6%)	271 (10%)
Cardiovascular death or admission to hospital for new-onset or worsening heart failure	723 (13%)	281 (10%)	442 (16%)
Coronary Endpoints			
Admission to hospital for myocardial infarction	226 (4%)	95 (3%)	131 (5%)
Admission to hospital for myocardial infarction or unstable angina	317 (6%)	135 (5%)	182 (7%)
Coronary revascularisation	186 (3%)	78 (3%)	108 (4%)

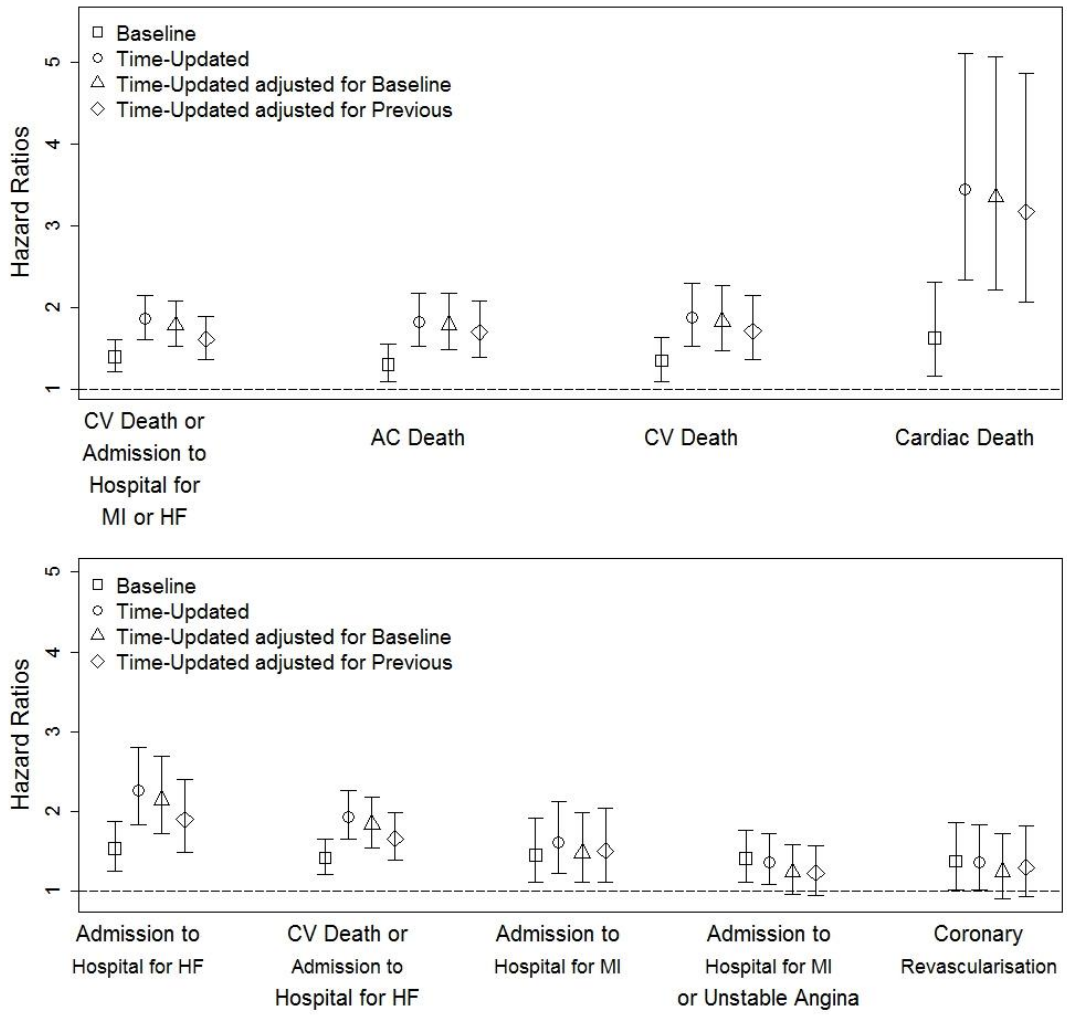
This table shows the total number of BEAUTIFUL placebo patients with available baseline resting heart rate data who experienced any pre-specified events of interest, as well as the number in relation to baseline heart rate, partitioned at 70bpm. Data are number of patients who experienced the event as a first event, with the corresponding percentage. Note that first event refers to the first event of each type: for example, a patient may have been admitted to hospital for an MI, and then subsequently been admitted to hospital for HF at a later date.

The Cox regression models adjusted for the same variables adjusted for in the baseline heart rate analysis[184] (all variables with nominal differences at baseline): age, smoking, BMI, history of diabetes, previous MI, previous PCI or CABG, PAD, SBP, DBP, LVEF, NYHA class, and treatment with aspirin (not including other antithrombotic agents as it was not available in the dataset used for the current analysis), beta-blockers, statins, diuretics (excluding anti-aldosterone), organic nitrates, and anti-aldosterone agents at randomisation.

The linearity of effect for each continuous heart rate variable was evaluated by plotting the Martingale residuals (a linear transformation of Cox-Snell residuals)[252,253] of each model against the heart rate values. No violations of the linearity assumption were observed.

Comparing the risk of each of the outcomes between patients with a baseline or time-updated heart rate greater than or equal to 70bpm, or less than 70bpm, produced the HRs and 95% CIs shown by Figure 8-1 and in Table A6-1 provided in Appendix 6. A heart rate ≥70bpm was associated with a higher risk of all of the endpoints in all models fitted, with the exceptions of admission to hospital for MI or unstable angina, and coronary revascularisation. Baseline and time-updated heart rates ≥70bpm were associated with a 41% ($p = 0.0032$) and 37% ($p = 0.0065$) higher risk of admission to hospital for MI or unstable angina, respectively, but the association between risk and time-updated heart rate was attenuated slightly when adjusted for baseline ($p = 0.084$) and the previous heart rate group ($p = 0.12$). Similarly, baseline and time-updated heart rate ≥70bpm were associated with a 38% ($p = 0.036$) and 37% ($p = 0.038$) increase in risk of coronary revascularisation, respectively, but again the association was attenuated after adjustment ($p = 0.17$ and $p = 0.13$ adjusted for baseline and the previous heart rate group, respectively).

Figure 8-1: Results of fitting Cox proportional hazards models. Hazard ratios with corresponding 95% confidence intervals for a heart rate ≥70bpm compared to a heart rate <70bpm in the BEAUTIFUL placebo population.



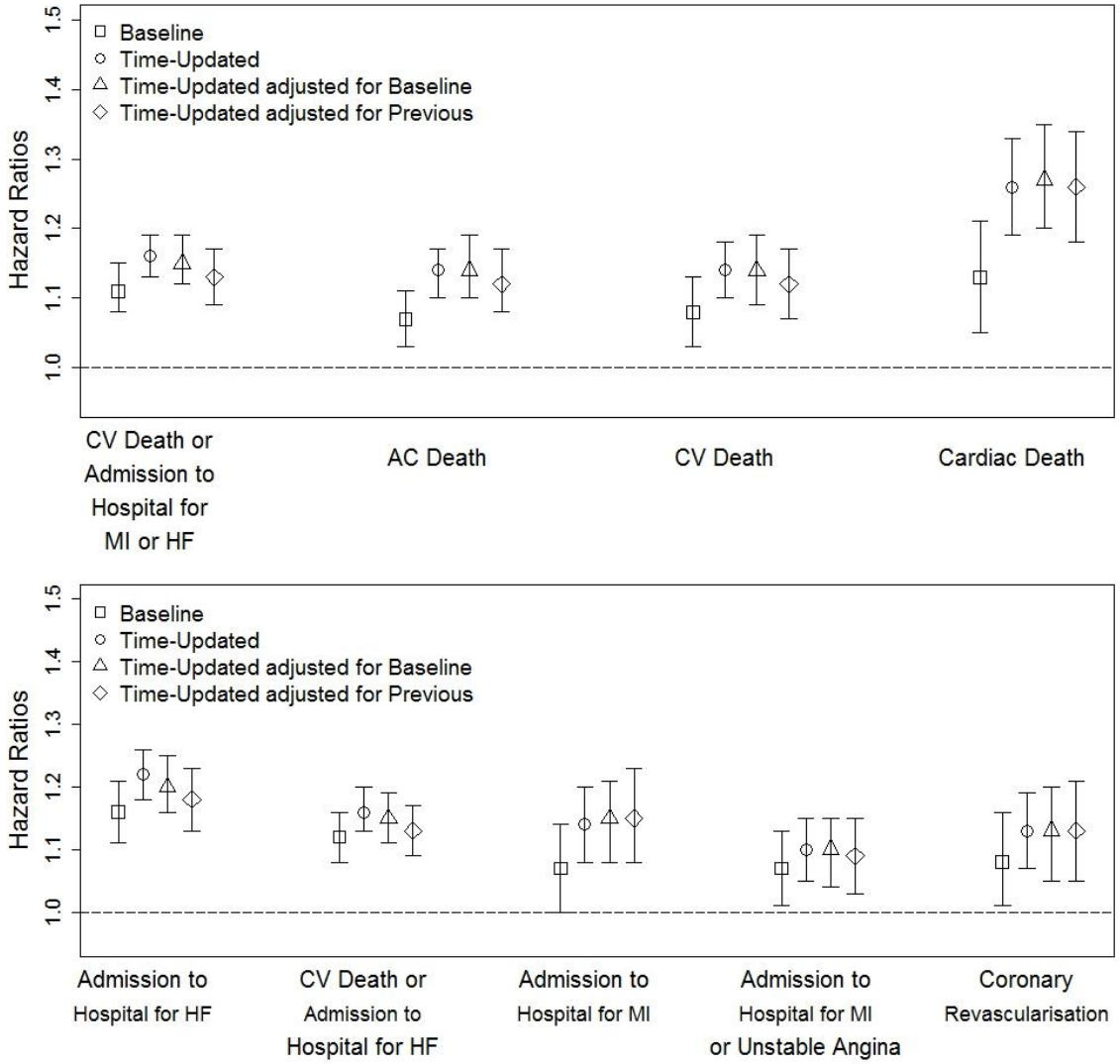
AC = All-Cause; CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction.

Models were additionally adjusted for: age; smoking; body mass index (BMI); history of diabetes; previous myocardial infarction (MI); previous percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG); peripheral artery disease (PAD); systolic blood pressure (SBP); diastolic blood pressure (DBP); left-ventricular ejection fraction (LVEF); New York Heart Association (NYHA) class; and treatment with aspirin (not including other antithrombotic agents), beta-blockers, statins, diuretics (excluding anti-aldosterone), organic nitrates and anti-aldosterone agents at randomisation.

Analysing continuous heart rate measurements produced the HRs and CIs shown by Figure 8-2 and in Table A6-2 provided in Appendix 6. An elevated continuous heart rate was associated with an increase in risk of all of the endpoints, with the exceptions of admission to hospital for MI, and the combination of admission to hospital for MI or unstable angina. An elevated continuous baseline heart rate was not associated with an increase in risk of admission to hospital for MI or admission to hospital for MI or unstable angina. However, a 5bpm higher time-updated heart rate was associated with a 14% ($p<0.001$) increase in risk of admission to hospital for MI, and a 10% ($p<0.001$) increase in risk of admission to hospital for MI or unstable angina. The association between time-updated heart rate and risk of each of the endpoints remained significant even after adjustment for baseline and the previous heart rate measurement.

Figure 8-3 and Table A6-3 provided in Appendix 6 show the adjusted HRs and 95% CIs estimated using the time-updated categorical heart rate patterns models. Comparing the current heart rate measurement at each visit to the previous heart rate measurement, all patients who did not have a heart rate below 70bpm at both the current and previous visit (low-low) were found to be at a higher risk of the combined endpoint of CV death or admission to hospital for MI or new-onset or worsening HF, and the combined endpoint of CV death or admission to hospital for new-onset or worsening HF. Patients with a heart rate ≥70bpm at both visits (high-high), and whose heart rate increased from below 70bpm at the previous visit to ≥70bpm at the current visit (low-high), were at a significantly higher risk of all-cause death, CV death, cardiac death, and admission to hospital for new-onset or worsening HF, compared to those patients who had a heart rate <70bpm at both visits (low-low). Subjects with a persistently high heart rate (high-high) were at an elevated risk of admission to hospital for MI (HR 1.73, 95% CI 1.27 to 2.37, $p<0.001$), admission to hospital for MI or unstable angina (HR 1.54, 95% CI 1.19 to 2.00, $p<0.001$) and coronary revascularisation (HR 1.44, 95% CI 1.03 to 2.02, $p = 0.032$).

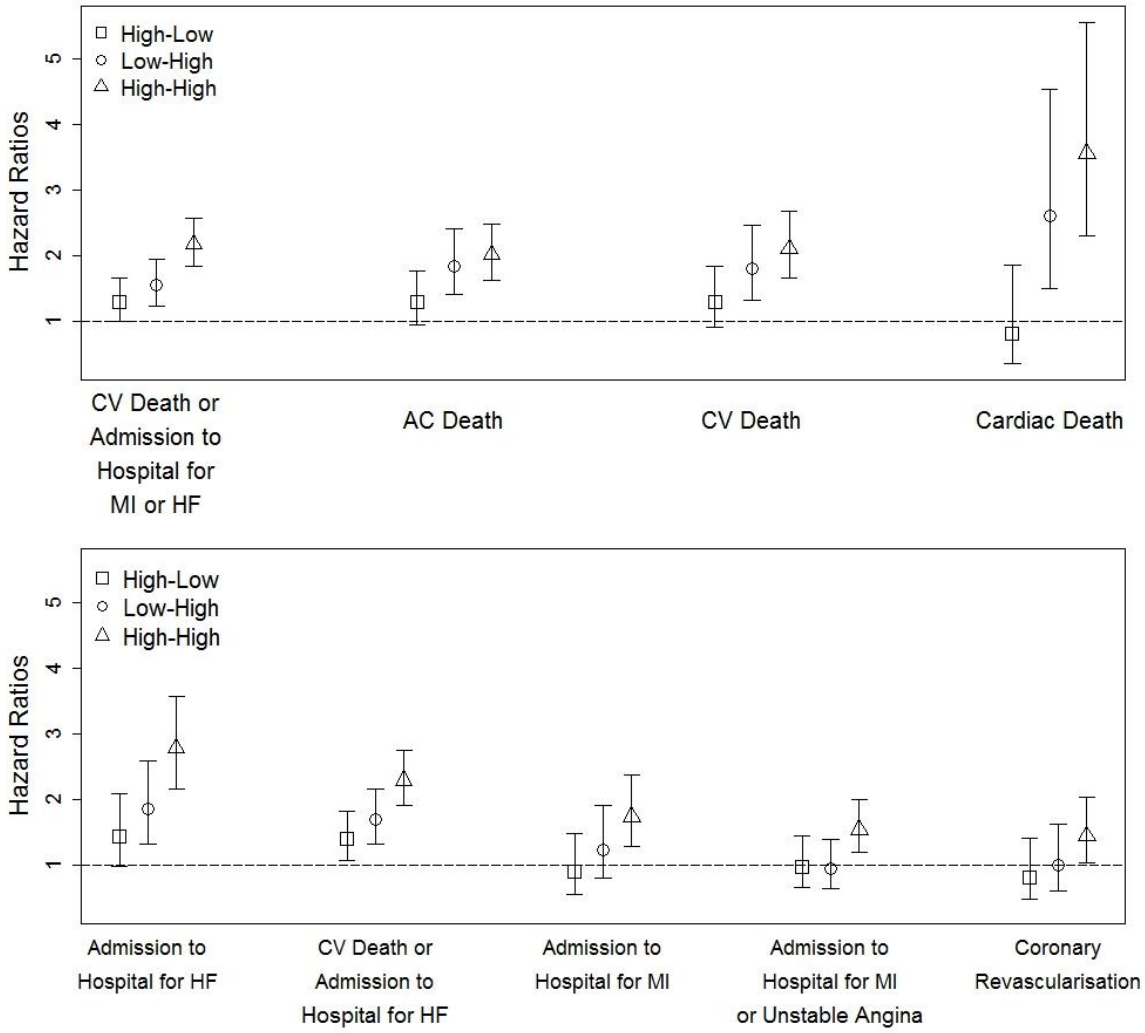
Figure 8-2: Results of fitting Cox proportional hazards models. Hazard ratios with corresponding 95% confidence intervals for a 5bpm higher heart rate in the BEAUTIFUL placebo population.



AC = All-Cause; CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction.

Models were additionally adjusted for: age; smoking; body mass index (BMI); history of diabetes; previous myocardial infarction (MI); previous percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG); peripheral artery disease (PAD); systolic blood pressure (SBP); diastolic blood pressure (DBP); left-ventricular ejection fraction (LVEF); New York Heart Association (NYHA) class; and treatment with aspirin (not including other antithrombotic agents), beta-blockers, statins, diuretics (excluding anti-aldosterone), organic nitrates and anti-aldosterone agents at randomisation.

Figure 8-3: Results of fitting Cox proportional hazards models. Hazard ratios with corresponding 95% confidence intervals for the time-updated categorical heart rate patterns 'high-low', 'low-high' and 'high-high' relative to the category 'low-low' in the BEAUTIFUL placebo population.



Patients were classified as being in the low-low category if their heart rate measurement at both the current and previous visit was below 70bpm. Similarly, patients were classified as being in the high-high category if their heart rate measurement at both the current and previous visit was greater than or equal to 70bpm, and so on.

AC = All-Cause; CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction.

Models were additionally adjusted for: age; smoking; body mass index (BMI); history of diabetes; previous myocardial infarction (MI); previous percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG); peripheral artery disease (PAD); systolic blood pressure (SBP); diastolic blood pressure (DBP); left-ventricular ejection fraction (LVEF); New York Heart Association (NYHA) class; and treatment with aspirin (not including other antithrombotic agents), beta-blockers, statins, diuretics (excluding anti-aldosterone), organic nitrates and anti-aldosterone agents at randomisation.

The discrimination and calibration of the models were evaluated using Harrell's C-statistic and likelihood ratio tests, respectively. Table A6-4 provided in Appendix 6 shows Harrell's C-statistics for the model excluding resting heart rate, and the models including the heart rate variables that categorised subjects according to whether they had a heart rate less than, or greater than or equal to 70bpm, for each outcome. Regardless of whether any resting heart rate category variables were included, the models had the greatest predictive ability for cardiac death and admission to hospital for HF: the C-statistics of the models both excluding and including resting heart rate ranged from 0.759 to 0.795, and 0.753 to 0.773 for each of these outcomes, respectively. The C-statistics of the models for the other outcomes ranged from 0.648 to 0.731. The addition of resting heart rate category improved discrimination for all of the outcomes compared to the model excluding heart rate. For cardiac death, admission to hospital for MI, coronary revascularisation, and the combined endpoint of admission to hospital for MI or unstable angina, the models including time-updated resting heart rate category adjusted for either baseline or the previous heart rate category had the best discrimination. Similarly, for the combined endpoints of CV death or admission to hospital for MI or HF, and CV death or admission to hospital for HF and the individual endpoint admission to hospital for HF, the model including time-updated heart rate additionally adjusted for the previous category had the best discrimination. All three of the time-updated heart rate models had the same and the best predictive ability for all-cause and CV death, compared to the model not including resting heart rate and the model including baseline heart rate only (C-statistic of each time-updated heart rate model: 0.710 and 0.716 for all-cause and CV death, respectively). The greatest improvement in discrimination was observed for cardiac death, with the C-statistic increasing from 0.759 to 0.795, and the smallest was observed for revascularisation, with the C-statistic increasing from 0.651 to only 0.656. The likelihood ratio test statistics and corresponding p-values for the addition of the heart rate category variables to the models are also presented in Table A6-4. The addition of any of the heart rate category variables resulted in statistically significant

improvements in the calibration of the models for all of the outcomes excluding revascularisation. For revascularisation, each of the models including a heart rate variable had a significantly better calibration than that of the model excluding heart rate, except that which included time-updated heart rate category additionally adjusted for the previous heart rate category.

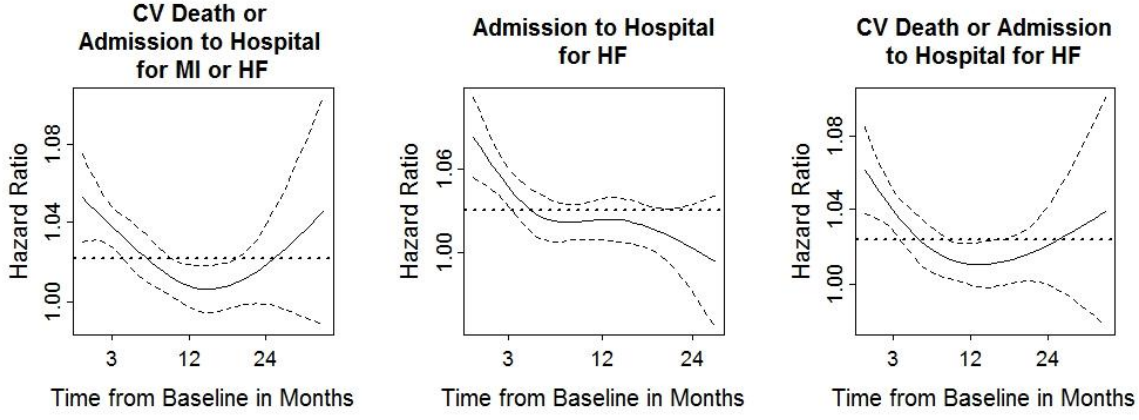
Harrell's C-statistics for the model excluding resting heart rate, and the models including the continuous heart rate variables, for each outcome, are shown in Table A6-5 provided in Appendix 6, along with the likelihood ratio test statistics and corresponding p-values for the addition of the different continuous heart rate variables. The results were very similar to those observed for the heart rate categories according to whether subjects had a heart rate less than, or greater than or equal to 70bpm, although the smallest improvement in discrimination was observed for admission to hospital for MI or unstable angina as opposed to revascularisation. Moreover, the addition of any of the continuous heart rate variables resulted in statistically significant improvements in the calibration of the model for revascularisation, while only the addition the addition of the continuous time-updated heart rate variable, with or without adjustment for baseline or the previous heart rate measurement, improved the calibration of the model for admission to hospital for MI.

Table A6-6 provided in Appendix 6 shows Harrell's C-statistics for the model excluding resting heart rate, and the models including the time-updated categorical heart rate patterns variable for each outcome. Again, irrespective of whether resting heart rate was included, the models had the greatest predictive ability for cardiac death and admission to hospital for HF, and the least for admission to hospital for MI or unstable angina, and revascularisation. The addition of time-updated categorical heart rate pattern improved discrimination for all of the outcomes. Similar to the results for categorical and continuous heart rate, the greatest and least improvements in discrimination were observed for cardiac death, and hospital admission for MI or

unstable angina, respectively. The likelihood ratio test statistics and corresponding p-values for the addition of the heart rate patterns variable to the models are also presented in Table A6-6. The addition of heart rate pattern resulted in statistically significant improvements in the calibration of the models for all of the outcomes except coronary revascularisation.

Table A6-7, Table A6-8 and Table A6-9 in Appendix 6 show the p-values of the Grambsch and Therneau 1994 test for non-proportionality for all the models and outcomes. Evidence of non-proportionality of the effect of heart rate over time was observed using a number of the different models for the combined endpoint of CV death or admission to hospital for MI or HF, hospital admission for HF individually, and the combination of CV death or HF hospital admission. Examination of the plots of the smoothed curve and corresponding 95% CIs of the Schoenfeld residuals for each model and outcome showed that the effect of elevated heart rate was highest at the beginning of follow-up, and then decreased over time. Figure 8-4 shows the Schoenfeld residual plots for a 5bpm higher baseline heart rate, and provides an illustration of this finding.

Figure 8-4: The Schoenfeld residuals plots for a 5bpm higher baseline heart rate for each of the outcomes where evidence of non-proportionality of the effect of heart rate over time was observed in the BEAUTIFUL placebo population.



The horizontal dotted lines represent the previously calculated 'average' hazard ratio of each outcome. CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction.

8.3 The Predictive Value of Baseline and Time-Updated Heart Rate Measurements in the SHIFT Placebo Patients

Once again, only the placebo group of the trial was included. Three of the patients assigned to the placebo group received ivabradine in error and were excluded. The remaining 3,261 placebo group patients (99.9% of the 3,264 included in the original trial) had baseline heart rate measurements available and were included in the present analysis.

Ten outcomes were evaluated: the combination of CV death or hospital admission for worsening HF (the primary endpoint of SHIFT); all-cause mortality; CV mortality; death from HF; all-cause hospital admission; hospital admission for worsening HF; any CV hospital admission; hospital admission for non-fatal MI; the combination of CV death or hospital admission for non-fatal MI; and the combination of CV death, hospital admission for worsening HF, or hospital admission for non-fatal MI.

The baseline heart rate cut-off of 80bpm was selected on the basis that it was close to the median baseline heart rate of 77bpm of the SHIFT placebo patients included in the current analysis: 80bpm as opposed to 75bpm was chosen because the SHIFT patients with a heart rate greater than the median of 77bpm had previously been found to be at higher risk of an event[32]. The baseline characteristics of the placebo-assigned SHIFT patients included in the present analysis, overall and categorised into groups depending on whether their baseline resting heart rate was less than, or greater than or equal to, 80bpm, are shown in Table 8-3.

Table 8-3: Baseline characteristics of the SHIFT placebo study population.

		Baseline Heart Rate		
	All Subjects n = 3261	**<80bpm n = 1940**	**≥80bpm n = 1321**	**P-value**
Demographic Characteristics				
Age (years)	60.6 (11.5)	61.2 (11.3)	59.6 (11.7)	<0.001
Sex (male)	2506 (77%)	1492 (77%)	1014 (77%)	0.922
Ethnic Origin				**0.016**
Caucasian	2889 (86%)	1747 (90%)	1142 (86%)	
Asian	264 (8%)	135 (7%)	129 (10%)	
Black	43 (1%)	23 (1%)	20 (2%)	
Other	65 (2%)	35 (2%)	30 (2%)	
Current smoking	577 (18%)	308 (16%)	269 (20%)	<0.001
BMI (kg/m^2)	28.0 (5.0)	27.8 (4.8)	28.1 (5.3)	0.094
Cardiac Parameters				
Heart rate (bpm)	80.1 (9.8)	73.8 (2.7)	89.4 (9.0)	-
SBP (mm Hg)	121.4 (15.9)	121.7 (15.5)	121.0 (16.4)	0.231
DBP (mm Hg)	75.6 (9.4)	75.4 (9.1)	75.8 (9.7)	0.281
LVEF (%)	29.0 (5.2)	29.3 (5.1)	28.4 (5.2)	<0.001
eGFR (mL/min per $1.73m^2$)	74.7 (23.0)	74.0 (23.0)	75.6 (22.9)	0.051
NYHA Class				**<0.001**
II	1584 (49%)	1026 (53%)	558 (42%)	
III or IV	1676 (51%)	914 (47%)	763 (58%)	
Medical History				
Duration of Heart Failure (years)	3.5 (4.2)	3.6 (4.3)	3.3 (3.9)	0.078
Primary Cause of Heart Failure				**0.003**
Ischemic	2201 (67%)	1348 (69%)	853 (65%)	
Non-ischemic	1060 (33%)	592 (31%)	468 (35%)	
Myocardial infarction	1836 (56%)	1139 (59%)	697 (53%)	<0.001
Hypertension	2151 (66%)	1307 (67%)	844 (64%)	0.043
Diabetes	1006 (31%)	572 (29%)	434 (33%)	0.049
Previous stroke	293 (9%)	152 (8%)	141 (11%)	0.007
History of AF and/or flutter	259 (8%)	154 (8%)	105 (8%)	0.99

Table continued and footnote provided on following page.

Table 8-3 (Cont.): Baseline characteristics of the SHIFT placebo study population.

	Baseline Heart Rate			
	All Subjects n = 3261	**<80bpm n = 1940**	**≥80bpm n = 1321**	**P-Value**
Treatment at Randomisation				
Beta-blocker	2921 (90%)	1792 (92%)	1129 (85%)	<0.001
ACE inhibitors	2548 (78%)	1571 (81%)	977 (74%)	<0.001
ARBs	472 (14%)	253 (13%)	219 (17%)	0.006
Diuretic (excluding anti-aldosterone)	2693 (83%)	1587 (82%)	1106 (84%)	0.170
Anti-aldosterone agents	1939 (59%)	1114 (57%)	825 (62%)	0.005
Cardiac glycosides	708 (22%)	366 (19%)	342 (26%)	<0.001
Devices	**134 (4%)**	**73 (4%)**	**61 (5%)**	
CRT	44 (1%)	23 (1%)	21 (2%)	0.408
ICD	115 (4%)	61 (3%)	54 (4%)	0.181

This table shows the clinical and demographic characteristics of the SHIFT placebo patients. Values are given for the total placebo population, as well as separately for patients who had a baseline resting heart rate <80bpm, and patients who had a baseline resting heart rate ≥80bpm. Data are the number of patients with the corresponding percentage, or the mean with the standard deviation, depending on whether the variable was categorical or continuous. Not all patients had every baseline measurement available. The values of each characteristic were compared between the two different baseline resting heart rate groups using unpaired two-sample t-tests and chi-squared tests, for continuous and categorical variables, respectively.

One patient had an NYHA class that was "missing or Class I" and are not included in the table. Note that the counts for Devices do not necessarily equal the total of CRT plus ICD since certain patients may have both and therefore are only counted once in Devices.

ACE = Angiotensin-Converting Enzyme; AF = Atrial Fibrillation; ARB = Angiotensin II Receptor Blocker; BMI = Body Mass Index; CRT = Cardiac Resynchronisation Therapy; DBP = Diastolic Blood Pressure; eGFR = estimated Glomerular Filtration Rate; ICD = Implantable Cardioverter Defibrillator; LVEF = Left Ventricular Ejection Fraction; MI = Myocardial Infarction; NYHA = New York Heart Association; SBP = Systolic Blood Pressure.

There were significant differences between the two groups of patients in terms of age, ethnic origin, whether or not they were a current smoker, LVEF, NYHA class, primary cause of HF, previous MI, hypertension, diabetes, and stroke, and intake of beta-blockers, ACE inhibitors, ARBs, anti-aldosterone agents, and cardiac glycosides. Patients in the ≥80bpm baseline heart rate group were more likely to be younger, Asian or Black, and currently smoking. They were also more likely to have a lower LVEF, be in NYHA class III or IV, and have HF caused primarily by a non-ischemic cause as opposed to an ischemic cause. In terms of medical history, those in the higher heart rate group were less likely to have experienced an MI or hypertension in the past, but were more likely to have had a stroke, and have diabetes. The use of ARBs, anti-aldosterone agents, and cardiac glycosides was also higher in the ≥80bpm group, while the use of beta-blockers and ACE inhibitors was lower.

The total number of events that occurred in the placebo group is presented in Table 8-4 along with the number that occurred in each of the baseline heart rate groups of patients. The percentage of patients in the higher heart rate group who experienced an event was greater for all of the events, excluding hospital admission for non-fatal MI, for which it was smaller, compared to the patients with a baseline heart rate lower than 80bpm.

As Bohm et al. 2010[182] had previously explored the relationship between baseline resting heart rate and risk in the SHIFT placebo population, the Cox regression models adjusted for the same baseline variables that were adjusted for in their baseline rate analysis, to make the current results as comparable as possible to their previously published results: beta-blocker intake; NYHA class; LVEF; whether the primary cause of HF was ischemic or not; age; SBP; and eGFR.

Table 8-4: The number of first events that occurred in the SHIFT placebo population.

		Subjects Separated by Baseline Heart Rate	
	Total Placebo Population n = 3261	**<80bpm n = 1940**	**≥80bpm n = 1321**
Primary Endpoint			
Cardiovascular death or hospital admission for worsening heart failure	936 (29%)	446 (23%)	490 (37%)
Mortality Endpoints			
All-cause mortality	551 (17%)	251 (13%)	300 (23%)
Cardiovascular mortality	491 (15%)	221 (11%)	270 (20%)
Death from heart failure	151 (5%)	59 (3%)	92 (7%)
Individual Hospital Admission Endpoints			
All-cause hospital admission	1354 (42%)	739 (38%)	615 (47%)
Hospital admission for worsening heart failure	671 (21%)	323 (17%)	348 (26%)
Any cardiovascular hospital admission	1120 (34%)	604 (31%)	516 (39%)
Hospital admission for non-fatal myocardial infarction	86 (3%)	53 (3%)	33 (2%)
Other Composite Endpoints			
Cardiovascular death or hospital admission for non-fatal myocardial infarction	550 (17%)	257 (13%)	293 (22%)
Cardiovascular death, or hospital admission for worsening heart failure, or hospital admission for non-fatal myocardial infarction	977 (30%)	470 (24%)	507 (38%)

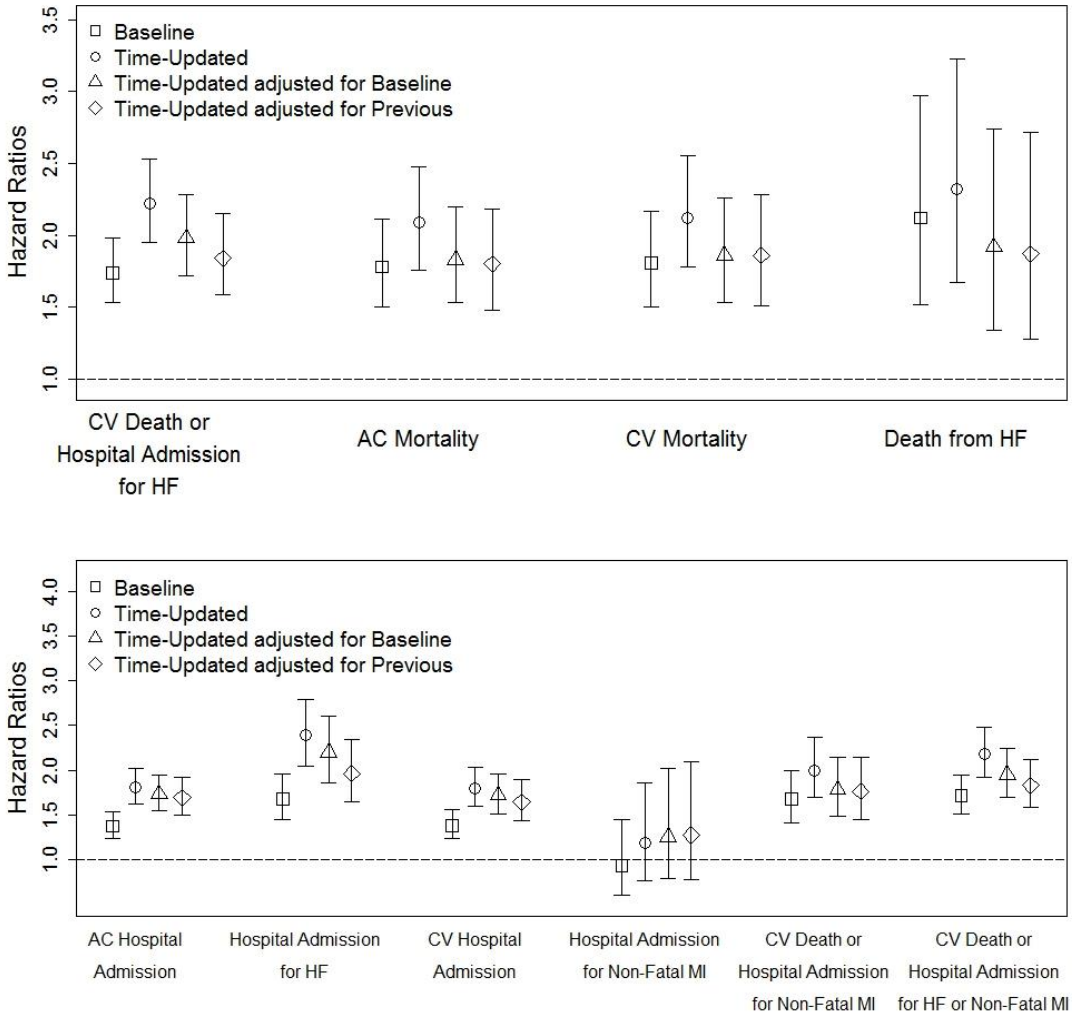
This table shows the total number of SHIFT placebo patients with available baseline resting heart rate data who experienced any pre-specified events of interest, as well as the number in relation to baseline heart rate, partitioned at 80bpm. Data are number of patients who experienced the event as a first event, with the corresponding percentage. Note that first event refers to the first event of each type: for example, a patient may have been admitted to hospital for a CV cause, and then subsequently been admitted to hospital for HF at a later date.

The linearity of effect for each continuous heart rate variable was evaluated by plotting the Martingale residuals (a linear transformation of Cox-Snell residuals)[252,253] of each model against the heart rate values. No violations of the linearity assumption were observed.

Comparing the risk of each of the outcomes between patients with a baseline or time-updated heart rate greater than or equal to 80bpm, or less than 80bpm, produced the HRs and CIs shown by Figure 8-5 and in Table A6-10 provided in Appendix 6. A heart rate ≥80bpm was associated with a higher risk of all of the endpoints, except hospital admission for non-fatal MI, in all models fitted. Using time-updated heart rate strengthened the association between heart rate and risk of each of these endpoints compared to using baseline heart rate. No association between heart rate and risk of hospital admission for MI was observed using any of the models. However, the association did appear to be strengthened by the addition of the time-updated heart rate measurements. For example, the HR for MI associated with a baseline heart rate ≥80bpm was 0.93 (95% CI 0.60 to 1.45, p = 0.750), while the HR associated with a time-updated heart rate ≥80bpm adjusted for baseline was 1.25 (95% CI 0.78 to 2.02, p = 0.354).

Analysing continuous heart rate measurements produced the HRs and 95% CIs given in Figure 8-6 and in Table A6-11 provided in Appendix 6. An elevated continuous heart rate was associated with higher risk of all of the endpoints, with the exception of hospital admission for non-fatal MI, in all models fitted. Again, time-updated heart rate strengthened the association between heart rate and risk of each of these endpoints compared to using baseline heart rate. An elevated continuous baseline heart rate was not associated with a higher risk of hospital admission for non-fatal MI, however, a 5bpm higher time-updated heart rate was associated with a 9% (p = 0.030) increase in risk. The association remained significant after adjustment for baseline heart rate (p = 0.010) and the previous heart rate measurement (p = 0.016).

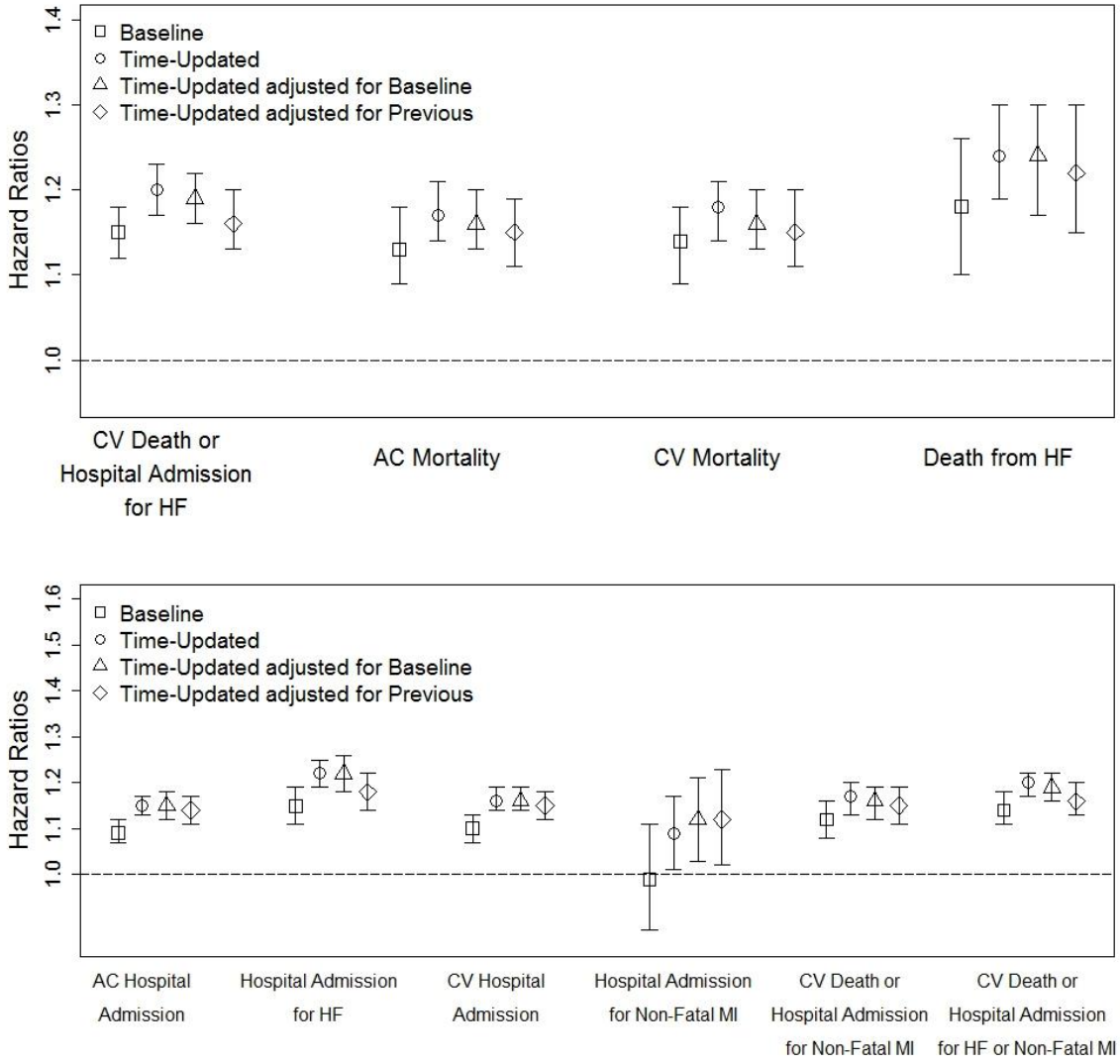
Figure 8-5: Results of fitting Cox proportional hazards models. Hazard ratios with corresponding 95% confidence intervals for a heart rate ≥80bpm compared to a heart rate <80bpm in the SHIFT placebo population.



AC = All-Cause; CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction.

Models were additionally adjusted for: beta-blocker intake; New York Heart Association (NYHA) class; left-ventricular ejection fraction (LVEF); whether the primary cause of heart failure (HF) was ischemic or not; age; systolic blood pressure (SBP); and estimated Glomerular Filtration Rate (eGFR).

Figure 8-6: Results of fitting Cox proportional hazards models. Hazard ratios with corresponding 95% confidence intervals for a 5bpm higher heart rate in the SHIFT placebo population.



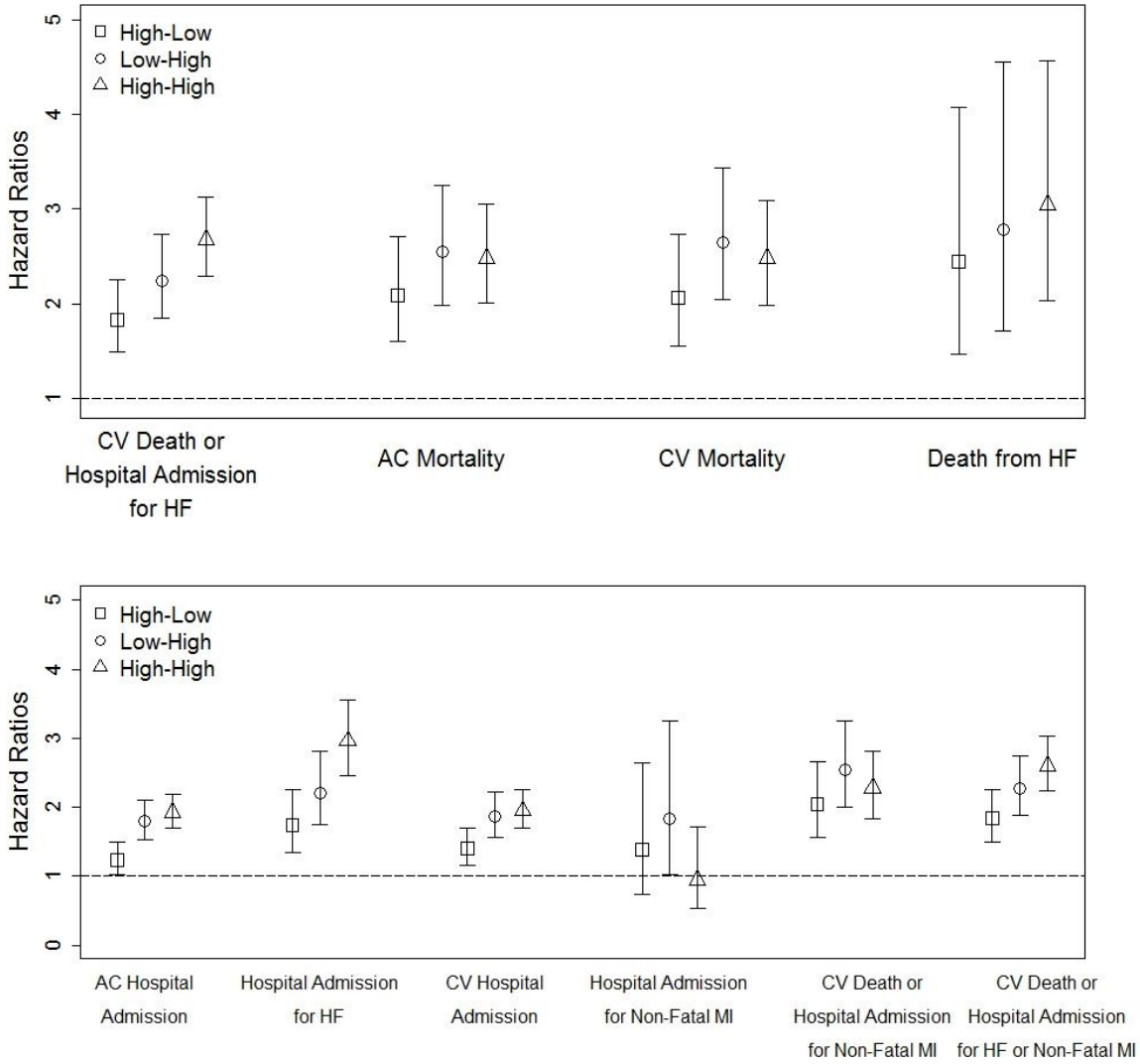
AC = All-Cause; CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction.

Models were additionally adjusted for: beta-blocker intake; New York Heart Association (NYHA) class; left-ventricular ejection fraction (LVEF); whether the primary cause of heart failure (HF) was ischemic or not; age; systolic blood pressure (SBP); and estimated Glomerular Filtration Rate (eGFR).

Figure 8-7 and Table A6-12 provided in Appendix 6 show the adjusted HRs and 95% CIs estimated using the time-updated categorical heart rate patterns models. Comparing the current heart rate measurement at each visit to the previous heart rate measurement, all patients who did not have a heart rate below 80bpm at both the current and previous visit (low-low) were found to be at a higher risk of all of the endpoints, excluding hospital admission for non-fatal MI, compared to those patients who did have a heart rate below 80bpm at both visits. Patients whose heart rate increased from below 80bpm at the previous visit to ≥80bpm at the current visit (low-high) were at an 83% higher risk (95% CI 2 to 225%, p = 0.041) of hospital admission for non-fatal MI, compared to those with a heart rate below 80bpm at both visits.

The discrimination and calibration of the models were evaluated using Harrell's C-statistic and likelihood ratio tests, respectively. Table A6-13 provided in Appendix 6 shows Harrell's C-statistics for the model excluding resting heart rate, and the models including the heart rate variables that categorised subjects according to whether they had a heart rate less than, or greater than or equal to 80bpm, for each outcome. Regardless of whether any resting heart rate category variables were included, the models had the greatest predictive ability for death from HF, with C-statistics ranging from 0.774 to 0.804. The C-statistics of the models for the other outcomes ranged from 0.601 to 0.713. The addition of resting heart rate category improved discrimination for all of the outcomes except hospital admission for non-fatal MI, compared to the model excluding heart rate. For all-cause death, death from HF, hospital admission for HF, CV hospital admission, and the combined endpoints of CV death or hospital admission for HF, and CV death or hospital admission for HF or non-fatal MI, the model including time-updated resting heart rate category additionally adjusted for the previous heart rate category had the best discrimination. For the other remaining outcomes – CV death, all-cause hospital admission, and the composite of CV death or hospital admission for non-fatal MI – both of the time-updated heart rate models adjusted for either baseline or the previous heart rate category had the same and the greatest predictive ability.

Figure 8-7: Results of fitting Cox proportional hazards models. Hazard ratios with corresponding 95% confidence intervals for the time-updated categorical heart rate patterns 'high-low', 'low-high' and 'high-high' relative to the category 'low-low' in the SHIFT placebo population.



Patients were classified as being in the low-low category if their heart rate measurement at both the current and previous visit was below 80bpm. Similarly, patients were classified as being in the high-high category if their heart rate measurement at both the current and previous visit was greater than or equal to 80bpm, and so on.

AC = All-Cause; CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction.

Models were additionally adjusted for: beta-blocker intake; New York Heart Association (NYHA) class; left-ventricular ejection fraction (LVEF); whether the primary cause of heart failure (HF) was ischemic or not; age; systolic blood pressure (SBP); and estimated Glomerular Filtration Rate (eGFR).

The greatest improvement in discrimination was observed for hospital admission for HF, with the C-statistic increasing from 0.646 to 0.698. Disregarding hospital admission or MI, even the smallest improvement in discrimination, which was observed for CV hospital admission, was relatively substantial, with the C-statistic increasing from 0.611 to 0.639. There was no improvement in discrimination for hospital admission for non-fatal MI with the addition of any of the heart rate category variables. The likelihood ratio test statistics and corresponding p-values for the addition of the heart rate category variables to the models are also presented in Table A6-13. The addition of any of the heart rate category variables resulted in statistically significant improvements in the calibration of the models for all of the outcomes except hospital admission for non-fatal MI, for which there were no improvements with the addition of any of the heart rate variables.

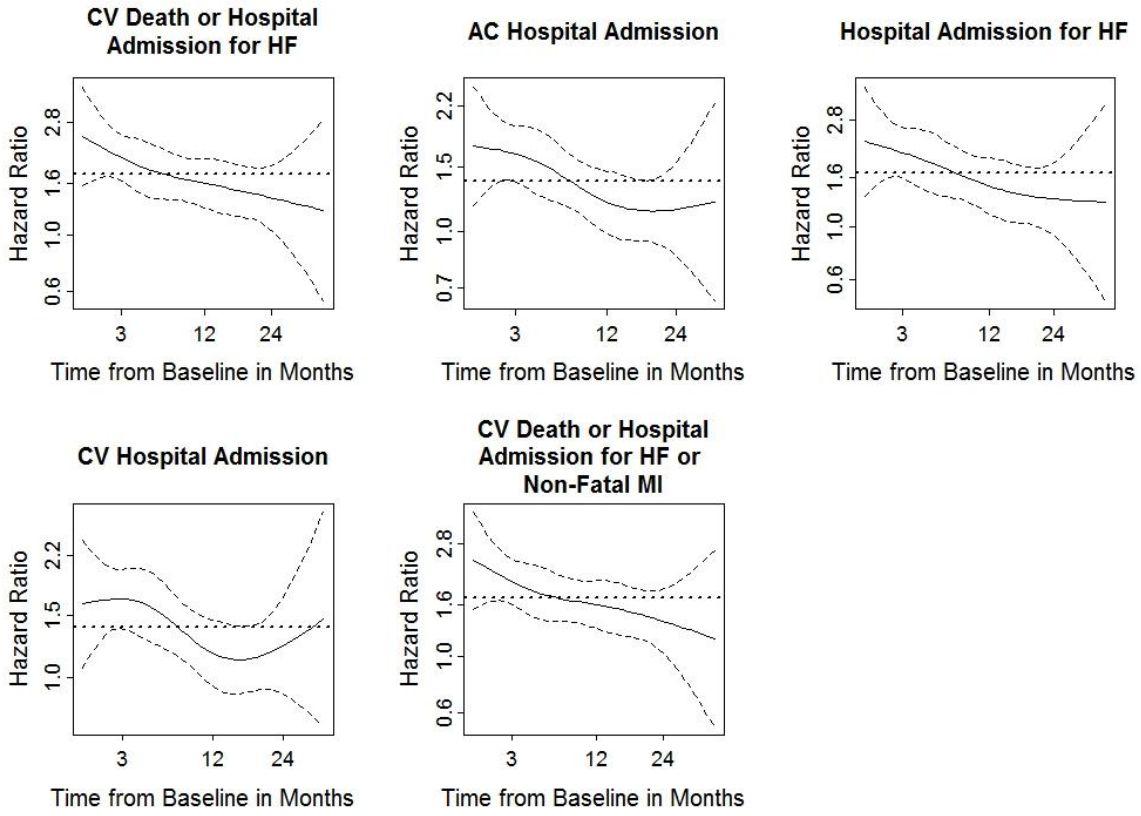
Harrell's C-statistics for the model excluding resting heart rate, and the models including the continuous heart rate variables, for each outcome, are shown in Table A6-14 provided in Appendix 6, along with the likelihood ratio test statistics and corresponding p-values for the addition of the different continuous heart rate variables. The results were very similar to those observed for the heart rate categories according to whether subjects had a heart rate less than, or greater than or equal to 80bpm. However, while there was no improvement in discrimination or calibration for hospital admission for non-fatal MI with the addition of any of the heart rate category variables, the addition of continuous time-updated heart rate, with or without adjustment for baseline or the previous heart rate measurement, improved discrimination for MI (although the C-statistic only increased from 0.713 to 0.716). Furthermore, the addition of continuous time-updated heart rate, with or without adjustment for baseline heart rate, but not previous heart rate measurements, significantly improved calibration.

Table A6-15 provided in Appendix 6 shows Harrell's C-statistics for the model excluding resting heart rate, and the models including the time-updated categorical heart rate patterns variable for each outcome. The addition of time-updated categorical heart rate pattern improved discrimination for all of the outcomes. The largest improvement in discrimination was again observed for hospital admission for HF, with the C-statistic increasing from 0.646 to 0.698; the smallest improvement was observed for hospital admission for non-fatal MI, with the C-statistic increasing by only 0.011, from 0.713 to 0.724. The likelihood ratio test statistics and corresponding p-values for the addition of the heart rate patterns variable to the models are also presented in Table A6-15. The addition of heart rate pattern resulted in statistically significant improvements in the calibration of the models for all of the outcomes except hospital admission for MI.

Table A6-16, A6-17 and A6-18 in Appendix 6 show the p-values of the Grambsch and Therneau 1994 test for non-proportionality for all the models and outcomes. Both a baseline heart rate ≥80bpm and an elevated continuous baseline heart rate showed evidence of non-proportionality of hazards over time for the combined endpoint CV death or hospital admission for HF, all-cause hospital admission, CV hospital admission, and the combined endpoint CV death, hospital admission for HF, or hospital admission for MI. A baseline heart rate ≥80bpm also exhibited evidence of non-proportionality for hospital admission for HF.

Examination of the plots of the smoothed curve and corresponding 95% CIs of the Schoenfeld residuals illustrated that the effect of a baseline heart rate ≥80bpm was highest at the beginning of follow-up, and then decreased over time. The effect of an elevated continuous baseline heart rate followed a similar pattern. Figure 8-8 shows the Schoenfeld residual plots for a baseline heart rate ≥80bpm, and provides an illustration of this finding. No violations of the proportional hazard assumption for any of the other heart rate variables that were associated with risk of outcome were observed.

Figure 8-8: The Schoenfeld residuals plots for a baseline heart rate ≥80bpm for each of the outcomes where evidence of non-proportionality of the effect of heart rate over time was observed in the SHIFT placebo population.



The horizontal dotted lines represent the previously calculated 'average' hazard ratio of each outcome. AC = All-Cause; CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction.

8.4 A Pooled Analysis of the Predictive Value of Baseline and Time-Updated Heart Rate Measurements in Patients with Left-Ventricular Systolic Dysfunction and Stable Coronary Heart Disease, Chronic Heart Failure or Both

A pooled analysis of individual trial placebo data from the BEAUTIFUL and SHIFT trials was carried out to permit a more detailed assessment of the relation of heart rate with outcome in subjects with LVSD. This analysis included 8,699 patients.

The following outcomes were able to be evaluated in the pooled analysis: all-cause mortality; CV mortality; hospital admission for HF; hospital admission for non-fatal MI; CV death or hospital admission for HF; CV death or hospital admission for non-fatal MI; and CV death or hospital admission for HF or non-fatal MI.

Table 8-5 shows the characteristics and inclusion criteria of BEAUTIFUL and SHIFT. Both trials were similar in terms of length of follow-up. BEAUTIFUL was slightly larger than SHIFT in regards to the number of patients randomised, had a slightly older population, included more males and slightly fewer patients on beta-blockers. Patients in both trials were required to have LV dysfunction, however BEAUTIFUL recruited subjects with CHD and an LVEF ≤40%, while SHIFT recruited those in HF with an LVEF ≤35% (although many of the BEAUTIFUL subjects also had HF). The mean LVEF of the SHIFT patients was hence slightly lower than that of the BEAUTIFUL patients. Patients in both trials had to be in sinus rhythm, however SHIFT patients had to have a baseline heart rate of at least 70bpm, while BEAUTIFUL patients could have a heart rate of 60bpm or greater.

Table 8-5: Principal characteristics, key inclusion criteria, and main features of the BEAUTIFUL and SHIFT populations.

n = 8699	BEAUTIFUL n = 5438	SHIFT n = 3216
Trial Characteristics		
No. of patients randomised	10917 (5479 iabradine, 5438 placebo)	6558 (3268 ivabradine, 3290 placebo before exclusions – 3264 after exclusions)
Follow-up (months)	19	22.9
Study treatments	Ivabradine and placebo	Ivabradine and placebo
Patient Characteristics		
Mean age (years)	65.2	60
Percentage of males	83%	76.5%
Mean LVEF	32.4%	29%
Percentage receiving beta-blockers	87%	89.5%
Inclusion Criteria		
Primary diagnosis	CHD and LVEF ≤40%	Chronic HF and LVEF ≤35%
Age	≥55 years ≥18 years if diabetic	≥18 years
Main inclusion criteria	CHD: previous MI; previous percutaneous or surgical coronary revascularisation; or angiographic evidence that ≥1 major coronary artery had narrowed by 50% or more LVEF ≤40%, end diastolic short-axis internal dimension of >56mm by echocardiography, in sinus rhythm with a resting heart rate ≥60bpm Any angina or symptoms of HF should have received appropriate conventional cardiovascular medication at stable doses for at least 1 month	Stable symptomatic chronic HF of 4 or more weeks' duration, a previous admission to hospital for worsening HF within the previous 12 months, and an LVEF of ≤35%, in sinus rhythm with a resting heart rate ≥70bpm, on stable background treatment included a beta-blocker if tolerated

The number of the subjects given in the first row of the table are the number that had baseline heart rate measurements available who are included in the present analysis. The follow-up duration is the median length of follow-up. 3,290 patients were randomly assigned to the placebo group in SHIFT, but data was only available for 3,264 since 26 patients were excluded because the study drug was not dispensed or because of invalid data caused by misconduct at study centres.

CHD = Coronary Heart Disease; HF = Heart Failure; LVEF = Left-Ventricular Ejection Fraction; MI = Myocardial Infarction.

Patients were categorised into the following six baseline heart rate groups: <65bpm, 65-69bpm, 70-74bpm, 75-79bpm, 80-84bpm and ≥85bpm. It was not appropriate to divide the pooled population of patients into two groups based on the median heart rate value of the population, as was done in the individual analyses of BEAUTIFUL and SHIFT presented in Sections 8.2 and 8.3, since the distribution of baseline heart rate in each trial population differed. The patients in BEAUTIFUL were required to have a heart rate of at least 60bpm to be enrolled in the trial, whereas in SHIFT they were required to have a heart rate of at least 70bpm. Thus, it was decided that the pooled population would be divided into multiple baseline heart rate groups, which also allows the observation of a finer relationship between heart rate and risk. The baseline heart rate distribution of the pooled population was explored, and the six groups were decided upon as they resulted in a similar number of patients being assigned to each category.

The baseline characteristics of the patients in each of the six baseline heart rate groups are shown by Table 8-6. There were significant differences among the six groups of patients for all of the baseline characteristics excluding hypertension and intake of ARBs. Patients in the highest heart rate group (≥85bpm) were younger, with a lower SBP, a higher DBP, and a lower LVEF. They were more likely to smoke, and be in NYHA class III or IV, have diabetes, and be taking diuretics or anti-aldosterone agents. They were less likely to be in NYHA class I or II, have had a previous MI, and be taking beta-blockers or ACE inhibitors at randomisation. Note that these analyses also compared the values of each characteristic between BEAUTIFUL and SHIFT patients to some extent since Group 1 and Group 2 only contained BEAUTIFUL patients, and study was not adjusted for in the ANOVA or chi-square tests.

Table 8-6: Baseline characteristics of the pooled left-ventricular dysfunction placebo population by heart rate group.

	Group 1 <65bpm n = 1510	Group 2 65-69bpm n = 1238	Group 3 70-74bpm n = 2132	Group 4 75-79bpm n = 1436	Group 5 80-84bpm n = 960	Group 6 ≥85bpm n = 1423	P-value
Demographic Characteristics							
Age (years)	65.8 (8.1)	65.4 (8.4)	63.2 (10.2)	62.4 (10.5)	62.7 (9.8)	60.6 (11.0)	<0.001
Sex (male)	1255 (83%)	1046 (84%)	1670 (78%)	1142 (80%)	777 (81%)	1123 (79%)	<0.001
Smoking (current)	181 (12%)	172 (14%)	312 (15%)	240 (17%)	186 (19%)	320 (22%)	<0.001
BMI	28.3 (4.1)	28.4 (4.3)	28.3 (4.7)	28.0 (4.8)	28.3 (4.6)	28.5 (5.4)	<0.001
Cardiac Parameters							
Heart rate (bpm)	62.0 (1.6)	66.8 (1.4)	71.8 (1.4)	76.6 (1.4)	81.7 (1.5)	93.4 (8.0)	-
SBP	127.1 (15.5)	127.3 (14.9)	124.8 (15.7)	124.7 (16.0)	125.9 (16.2)	123.5 (16.9)	<0.001
DBP	76.5 (9.2)	76.9 (9.2)	76.4 (9.2)	76.7 (9.2)	77.3 (9.3)	77.3 (9.9)	<0.001
LVEF (%)	32.8 (5.3)	32.6 (5.4)	30.8 (5.3)	30.4 (5.8)	30.4 (5.4)	29.4 (5.8)	<0.001
NYHA Class							**<0.001**
I	282 (19%)	185 (15%)	152 (7%)	88 (6%)	59 (6%)	75 (5%)	
II	959 (64%)	787 (52%)	1221 (57%)	817 (57%)	504 (53%)	655 (46%)	
III or IV	269 (18%)	266 (18%)	759 (36%)	531 (37%)	397 (41%)	693 (49%)	
Medical History							
Previous MI	1345 (89%)	1125 (91%)	1542 (72%)	1020 (71%)	682 (71%)	939 (66%)	<0.001
Hypertension	1063 (70%)	851 (69%)	1471 (69%)	981 (68%)	674 (70%)	949 (67%)	0.32
Diabetes	449 (30%)	416 (34%)	710 (33%)	503 (35%)	359 (37%)	588 (41%)	<0.001
Previous stroke	258 (17%)	210 (17%)	273 (13%)	167 (12%)	153 (16%)	203 (14%)	<0.001
Treatment at Randomisation							
Beta-blocker	1371 (91%)	1097 (89%)	1926 (90%)	1288 (90%)	828 (86%)	1149 (81%)	<0.001
ACE inhibitor	1215 (80%)	968 (78%)	1707 (80%)	1169 (81%)	732 (76%)	1083 (76%)	0.0010
ARB	180 (12%)	145 (12%)	269 (13%)	170 (12%)	143 (15%)	205 (14%)	0.058
Diuretics	825 (55%)	668 (54%)	1522 (71%)	1028 (72%)	727 (76%)	1117 (78%)	<0.001
Anti-aldosterone agents	353 (23%)	314 (25%)	915 (43%)	633 (44%)	419 (44%)	771 (54%)	<0.001

This table shows the clinical and demographic characteristics of the patients in each of the six baseline heart rate groups, including only patients who had their baseline resting heart rate measured. Data are the number of patients with the corresponding percentage, or the mean with the standard deviation, depending on whether the variable was categorical or continuous, respectively. The values of each characteristic were compared between the six baseline heart rate groups of patients using ANOVA and chi-square tests for continuous and categorical variables, respectively. Note that these analyses also compared the values of each characteristic between BEAUTIFUL and SHIFT patients to some extent since Group 1 and Group 2 only contained BEAUTIFUL patients, and study was not adjusted for in the tests.

One of the SHIFT placebo patients had an NYHA class that was “missing or Class I” and is not included in the table, while all of the others were NYHA Class II, III or IV; BEAUTIFUL did not include any subjects with NYHA Class IV.

ACE = Angiotensin-Converting Enzyme; ARB = Angiotensin II Receptor Blocker; BMI = Body Mass Index; DBP = Diastolic Blood Pressure; LVEF = Left Ventricular Ejection Fraction; MI = Myocardial Infarction; NYHA = New York Heart Association; SBP = Systolic Blood Pressure.

The number of events that occurred in each of the six baseline heart rate groups, as well as in the total pooled population, is presented by Table 8-7. For all of the events with the exception of hospital admission for non-fatal MI, the percentage of patients in each group who experienced the event increased with increasing heart rate group. Accordingly, patients in the highest heart rate group experienced the highest percentage of each of the events, except hospital admission for non-fatal MI. The percentage of patients who experienced a hospital admission for non-fatal MI event was similar across all six groups.

Table 8-7: The number of first events that occurred in the pooled left-ventricular dysfunction placebo population and each of the baseline heart rate groups.

	Subjects Separated by Baseline Heart Rate Group						
	Pooled Population	**Group 1 <65bpm**	**Group 2 65-69bpm**	**Group 3 70-74bpm**	**Group 4 75-79bpm**	**Group 5 80-84bpm**	**Group 6 ≥85bpm**
	n = 8699	**n = 1510**	**n = 1238**	**n = 2132**	**n = 1436**	**n = 960**	**n = 1423**
Individual Endpoints							
All-cause death	1098 (13%)	120 (8%)	103 (8%)	240 (11%)	176 (12%)	155 (16%)	300 (21%)
CV death	926 (11%)	85 (6%)	87 (7%)	206 (10%)	147 (10%)	134 (14%)	264 (19%)
Hospital admission for HF	1098 (13%)	78 (5%)	79 (6%)	236 (11%)	211 (15%)	149 (16%)	341 (24%)
Hospital admission for non-fatal MI	312 (6%)	56 (4%)	39 (3%)	75 (4%)	57 (4%)	37 (4%)	48 (3%)
Combined Endpoints							
CV death or hospital admission for HF	1659 (19%)	138 (9%)	144 (12%)	372 (17%)	285 (20%)	232 (24%)	479 (34%)
CV death or hospital admission for non-fatal MI	1143 (13%)	130 (9%)	114 (9%)	258 (12%)	184 (13%)	160 (17%)	294 (21%)
CV death or hospital admission for HF or non-fatal MI	1809 (21%)	170 (11%)	165 (13%)	404 (19%)	314 (22%)	252 (26%)	495 (35%)

This table shows the total number of LV dysfunction placebo patients with available baseline resting heart rate data who experienced any pre-specified events of interest, as well as the number in relation to baseline heart rate group. Data are number of patients who experienced each event as a first event, with the corresponding percentage. Note that Group 1 and Group 2 only contained BEAUTIFUL patients. Note that first event refers to the first event of each type: for example, a patient may have been admitted to hospital for a non-fatal MI, and then subsequently been admitted to hospital for HF at a later date.

CV = Cardiovascular; HF = Heart Failure; LV = Left-Ventricular; MI = Myocardial Infarction.

The Cox models were adjusted for the variables which were significantly different between the heart rate groups at baseline ($p<0.05$): age; sex; smoking; BMI; SBP; DBP; LVEF; NYHA class; previous MI; diabetes; previous stroke; and intake of beta-blockers; ACE inhibitors; diuretics; and anti-aldosterone agents at randomisation. Models were also adjusted for study.

The linearity of effect for each continuous heart rate variable was evaluated by plotting the Martingale residuals (a linear transformation of Cox-Snell residuals)[252,253] of each model against the heart rate values. No violations of the linearity assumption were observed.

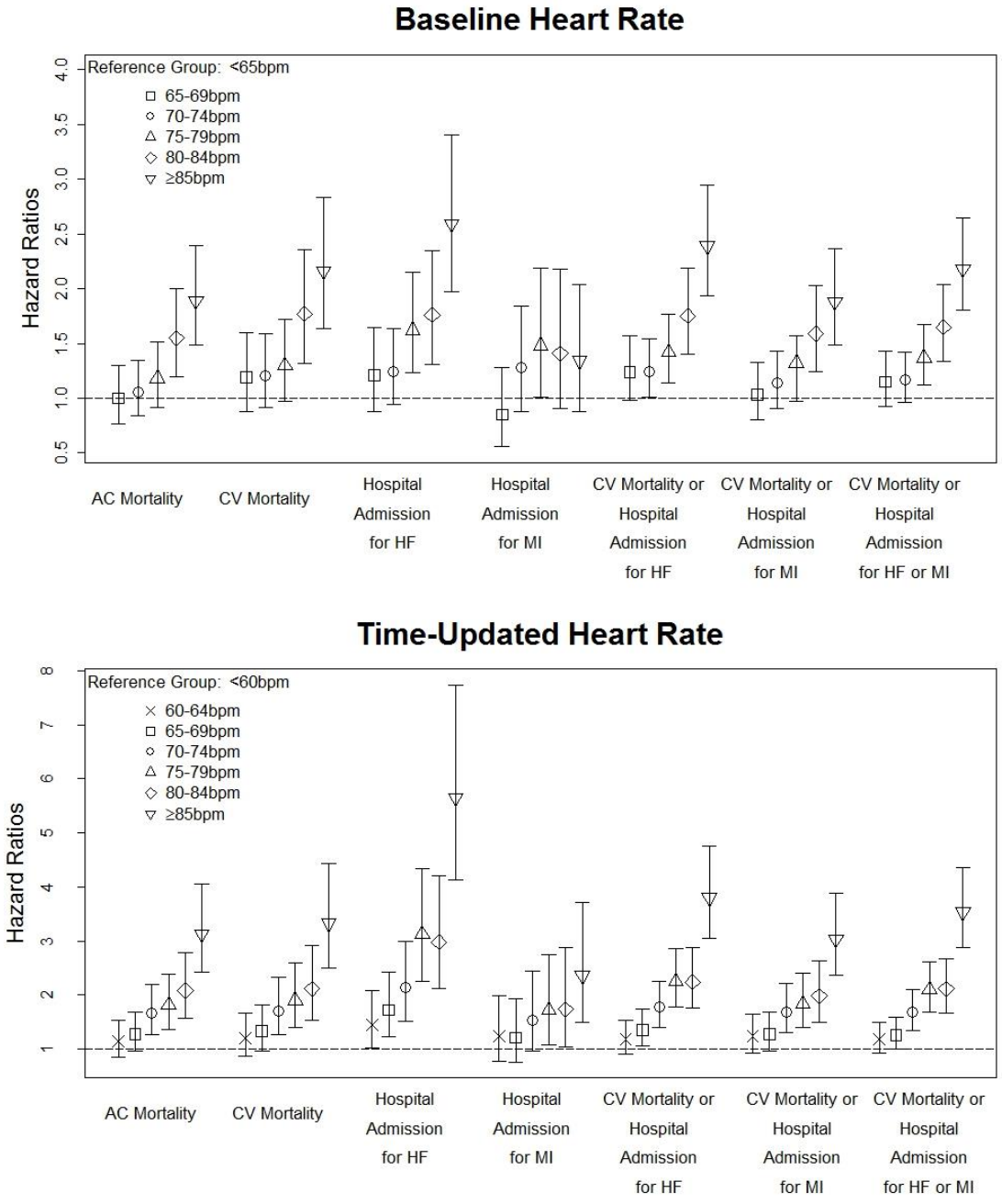
For time-updated heart rate, where regression to the mean resulted in lower heart rates observed at follow-up, it was possible to split the lowest heart rate group (<65bpm) into two groups: <60bpm and 60 to 64bpm. Comparing the risk of the outcomes between patients in each of the heart rate groups greater than or equal to 60bpm (65bpm for baseline), to those in the <60bpm heart rate group (<65bpm for baseline), produced the HRs, 95% CIs and p-values shown by Figure 8-9 and Figure 8-10, and in Table A6-19 provided in Appendix 6.

Patients in each of the baseline heart rate groups ≥70bpm were found to be at a higher risk of the composite of CV death or hospital admission for HF compared to those with a baseline heart rate <65bpm. The risk of hospital admission for HF, and the rate of the combined endpoint of CV death or hospital admission for HF or non-fatal MI, was higher in subjects who had a baseline heart rate in the 75 to 79bpm group or above. Patients in each of the baseline heart rate groups ≥80bpm were at a higher risk of all-cause mortality, CV mortality, and the combination of CV mortality or hospital admission for non-fatal MI. Only patients with a baseline heart rate between 75 and 79bpm were found to be at a higher risk of hospital admission for non-fatal MI compared to those with a baseline heart rate <65bpm (HR 1.48, 95% CI 1.01 to 2.19, $p = 0.047$).

Patients with a time-updated heart rate ≥60bpm were found to be at a higher risk of hospital admission for HF, and those with a time-updated heart rate ≥65bpm were shown to be at a higher risk of the composites of CV death or hospital admission for HF, and CV death or hospital admission for HF or MI, compared to those with a time-updated heart rate <60bpm. The associations with hospital admission for HF and CV death or hospital admission for HF remained the same after adjustment for baseline group, but only a time-updated heart rate group ≥70bpm was associated with an increase in the risk of CV death or hospital admission for HF or MI after adjustment for baseline group. When previous heart rate group was adjusted for, only a time-updated heart rate group ≥70bpm was associated with an increase in risk of each of these three endpoints.

A time-updated heart rate ≥70bpm, unadjusted or adjusted for baseline or the previous heart rate group, was associated with an increase in the risk of all-cause mortality, CV mortality, and CV mortality or hospital admission for non-fatal MI. Finally, a time-updated heart rate ≥75bpm was associated with an increased risk of hospital admission for non-fatal MI. When the model was adjusted for baseline group only the 75 to 79bpm and ≥85bpm groups were associated with an increase in risk; when the model was adjusted for the previous time-updated group, only a heart rate ≥85bpm was associated with an increase in risk.

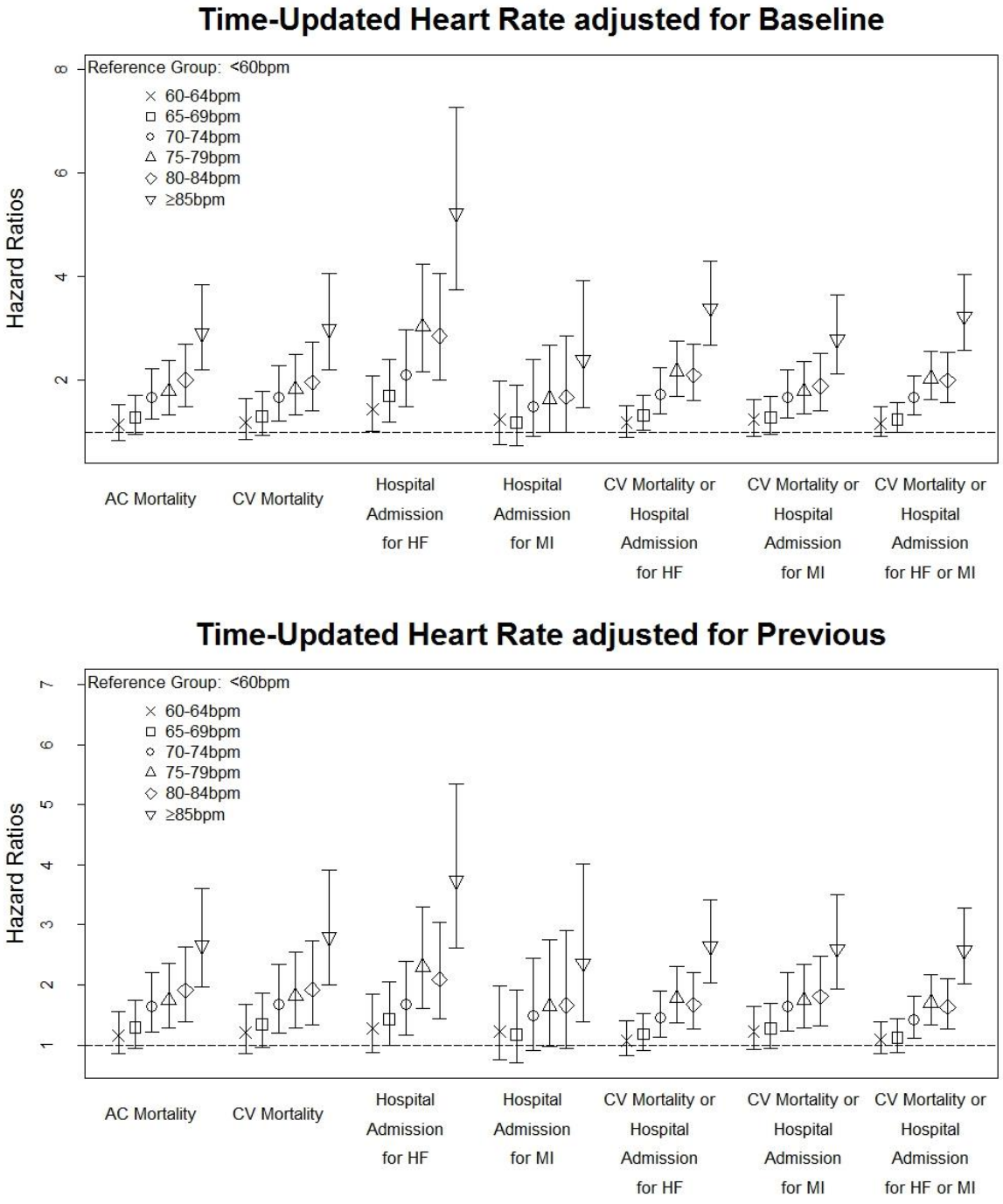
Figure 8-9: Results of fitting Cox proportional hazards models. Hazard ratios with corresponding 95% confidence intervals for each of the five baseline heart rate groups greater than or equal to 65bpm, relative to <65bpm, and each of the six time-updated heart rate groups greater than or equal to 60bpm, relative to <60bpm, in the pooled left-ventricular dysfunction placebo population.



AC = All-Cause; CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction.

Models were additionally adjusted for: age; sex; smoking; body mass index (BMI); systolic blood pressure (SBP); diastolic blood pressure (DBP); left-ventricular ejection fraction (LVEF); New York Heart Association (NYHA) class; previous myocardial infarction (MI); diabetes; previous stroke; and intake of beta-blockers; angiotensin-converting enzyme (ACE) inhibitors; diuretics; and anti-aldosterone agents at randomisation; and study.

Figure 8-10: Results of fitting Cox proportional hazards models. Hazard ratios with corresponding 95% confidence intervals for each of the six time-updated heart rate groups greater than or equal to 60bpm, relative to <60bpm, in the pooled left-ventricular dysfunction placebo population.

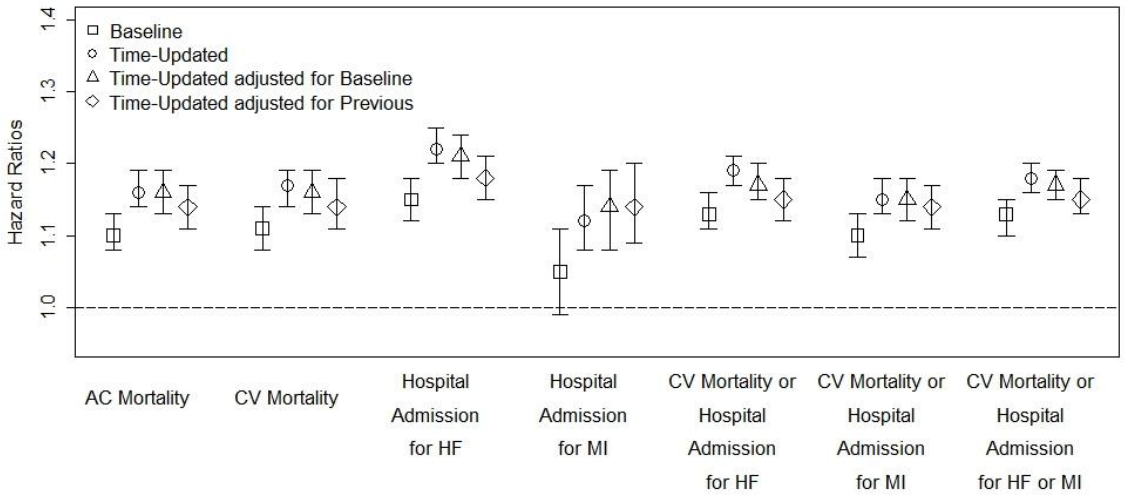


AC = All-Cause; CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction.

Models were additionally adjusted for: age; sex; smoking; body mass index (BMI); systolic blood pressure (SBP); diastolic blood pressure (DBP); left-ventricular ejection fraction (LVEF); New York Heart Association (NYHA) class; previous myocardial infarction (MI); diabetes; previous stroke; and intake of beta-blockers; angiotensin-converting enzyme (ACE) inhibitors; diuretics; and anti-aldosterone agents at randomisation; and study.

Analysing continuous heart rate measurements produced the HRs and 95% CIs shown by Figure 8-11 and in Table A6-20 provided in Appendix 6.

Figure 8-11: Results of fitting Cox proportional hazards models. Hazard ratios with corresponding 95% confidence intervals for a 5bpm higher heart rate in the pooled left-ventricular dysfunction placebo population.



AC = All-Cause; CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction.

Models were additionally adjusted for: age; sex; smoking; body mass index (BMI); systolic blood pressure (SBP); diastolic blood pressure (DBP); left-ventricular ejection fraction (LVEF); New York Heart Association (NYHA) class; previous myocardial infarction (MI); diabetes; previous stroke; and intake of beta-blockers; angiotensin-converting enzyme (ACE) inhibitors; diuretics; and anti-aldosterone agents at randomisation; and study.

An elevated continuous heart rate was associated with a higher risk of all of the endpoints, with the exception of hospital admission for MI, in all models. Time-updated heart rate strengthened the association between heart rate and risk of each of these endpoints compared to using baseline heart rate. An elevated continuous baseline heart rate was not associated with a higher risk of hospital admission for MI, however, a 5bpm higher time-updated heart rate was associated with a 12% ($p<0.001$) increase in risk. The association remained significant after adjustment for baseline heart rate ($p<0.001$) and the previous heart rate measurements ($p<0.001$).

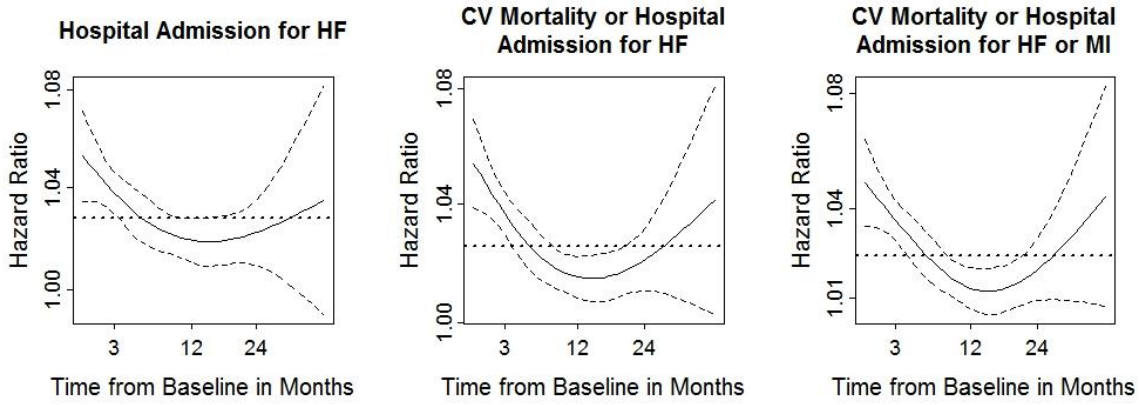
The discrimination and calibration of the models were evaluated using Harrell's C-statistic and likelihood ratio tests, respectively. Table A6-21 provided in Appendix 6 shows Harrell's C-statistics for the model excluding resting heart rate, and the model

including the heart rate groups variable, for each outcome. Regardless of whether resting heart rate group was included, the models had the greatest predictive ability for hospital admission for HF, and the combined endpoint of CV mortality or hospital admission for HF: the C-statistics of the models both excluding and including heart rate ranged from 0.739 to 0.777, and 0.708 to 0.740 for each of these outcomes, respectively. The C-statistics of the models for the other outcomes ranged from 0.661 to 0.723. The addition of resting heart rate group improved discrimination for all of the outcomes compared to the model excluding heart rate. The models including time-updated heart rate group adjusted for the previous heart rate group had the best discrimination for all of the outcomes (although the time-updated heart rate model adjusted for baseline group had the same discrimination for hospital admission for MI). The greatest improvement in discrimination was observed for hospital admission for HF, with the C-statistic increasing from 0.739 to 0.777, and the smallest was observed for hospital admission for MI, with the C-statistic increasing from 0.661 to 0.675. The likelihood ratio test statistics and corresponding p-values for the addition of the heart rate group variables to the models are also presented in Table A6-21. The addition of any of the heart rate group variables resulted in statistically significant improvements in the calibration of the models for all of the outcomes except hospital admission for MI: only the addition of the time-updated heart rate group variable, with or without adjustment for baseline or the previous heart rate group, improved the calibration of the models for MI.

Harrell's C-statistics for the model excluding resting heart rate, and the model including the continuous heart rate variables for each outcome are shown in Table A6-22 provided in Appendix 6, along with the likelihood ratio test statistics and corresponding p-values for the addition of the continuous heart rate variables to the models. The results were very similar to those observed for the resting heart rate groups.

Table A6-23 and A6-24 show the p-values of the Grambsch and Therneau 1994 test for non-proportionality for all the models and outcomes. Evidence of non-proportionality of the effect of heart rate over time was observed using a number of the different models for hospital admission for HF, and the combined endpoints of CV death or hospital admission for HF, and CV death or hospital admission for HF or MI. Examination of the plots of the smoothed curve and corresponding 95% CIs of the Schoenfeld residuals for each model and outcome showed that the effect of elevated heart rate was highest at the beginning of follow-up, and then decreased over time. Figure 8-12 shows the Schoenfeld residual plots for a 5bpm higher baseline heart rate, and provides an illustration of this finding.

Figure 8-12: The Schoenfeld residuals plots for a 5bpm higher baseline heart rate for each of the outcomes where evidence of non-proportionality of the effect of heart rate over time was observed in the pooled left-ventricular dysfunction placebo population.



The horizontal dotted lines represent the previously calculated 'average' hazard ratio of each outcome. CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction.

Table A6-25 provided in Appendix 6 displays the p-values for the likelihood ratio tests for the interaction of heart rate with study using the heart rate group variables, and the continuous heart rate variables, for each outcome. There were no significant interactions observed between any of the heart rate variables and study for any of the outcomes, indicating that the results did not significantly differ between the two populations of patients.

8.5 Discussion

In the placebo population of patients with CHD and LVSD from BEAUTIFUL, an elevated resting heart rate was associated with an increase in risk of all of the endpoints evaluated. The addition of any of the resting heart rate variables improved discrimination for all of the outcomes compared to the model excluding heart rate. In general, the time-updated heart rate models, unadjusted or adjusted for baseline or the previous heart rate measurement, yielded the highest and similar C-statistics, and thus had the best discriminative ability.

Both an elevated baseline and time-updated resting heart rate, analysed categorically or continuously, were associated with an increase in the risk of all-cause death, CV death, cardiac death, admission to hospital for HF, admission to hospital for MI or unstable angina, revascularisation, and the combined endpoints of CV death or admission to hospital for HF, and CV death or admission to hospital for MI or HF. The addition of any of the resting heart rate variables resulted in statistically significant improvements in the calibration of the models for all of these outcomes excluding revascularisation. For revascularisation, each of the models including a categorical heart rate variable had a better calibration than that of the model excluding heart rate, except that which included time-updated heart rate category along with the previous time-updated heart rate category; the addition of any of the continuous heart rate variables improved the calibration of the model. Time-updated heart rate strengthened the associations for each of these outcomes, and remained a significant predictor for each, after adjustment for baseline heart rate or the previous heart rate measurement (with the exception of a time-updated heart rate ≥70bpm for coronary revascularisation, and admission to hospital for MI or unstable angina, which were attenuated after adjustment for either of the other heart rate variables).

Patients with a baseline or time-updated heart rate ≥70bpm were additionally found to be at a higher risk of admission to hospital for MI. Similarly, time-updated heart rate

strengthened the association, and remained a significant predictor after adjustment for baseline or the previous heart rate group. As was previously found in the BEAUTIUFL baseline heart rate analysis[184], an elevated continuous baseline heart rate was only borderline significantly associated with a higher risk of admission to hospital for MI. However, an elevated time-updated heart rate, unadjusted or adjusted for the baseline or previous heart rate measurement, was strongly associated with an elevation in risk. A 5bpm higher time-updated heart rate after adjustment for baseline, for example, was associated with a 15% ($p<0.001$) increase in risk. In accordance with these results, the addition of any of the heart rate category variables resulted in statistically significant improvements in the calibration of the models for MI, while only the continuous time-updated heart rate variable, with or without adjustment for baseline or the previous heart rate measurement, improved the calibration.

In the placebo population of patients with chronic HF and LVSD from SHIFT, an elevated resting heart rate was associated with an increase in risk of all the endpoints evaluated.

Both elevated baseline and time-updated resting heart rates, analysed categorically or continuously, were associated with an increase in the risk of all of the endpoints, excluding hospital admission for non-fatal MI. Time-updated heart rate strengthened the associations, and remained a significant predictor for each of these outcomes after adjustment for baseline heart rate or the previous heart rate measurement. The addition of any of the resting heart rate variables improved both discrimination and calibration compared to the model excluding heart rate. In the main, the time-updated heart rate models adjusted for baseline or the previous heart rate measurement, yielded the highest and similar C-statistics, and thus had the best discriminative ability.

No significant associations were observed between a baseline or time-updated heart rate ≥80bpm, unadjusted or adjusted for the baseline or previous heart rate group, and risk of hospital admission for non-fatal MI. Similarly, there was no improvement in discrimination or calibration for hospital admission for non-fatal MI with the addition of

any of the heart rate category variables. No association between an elevated continuous baseline heart rate and risk was observed either. In contrast, a higher continuous time-updated heart rate, unadjusted or adjusted for the baseline or previous heart rate measurement, was associated with an increase in risk. For example, a 5bpm higher time-updated heart rate adjusted for baseline was associated with a 12% ($p = 0.010$) increase in risk of hospital admission for non-fatal MI. The addition of continuous time-updated heart rate, with or without adjustment for baseline or the previous heart rate measurement, also improved discrimination for MI (but only by a maximum of 0.003). Furthermore, the addition of continuous time-updated heart rate, with or without adjustment for baseline heart rate, but not previous heart rate measurements, significantly improved calibration.

Similarly, in the pooled population of placebo patients with LVSD and CHD or chronic HF, an elevated resting heart rate was associated with an increase in the risk of all of the endpoints evaluated. The addition of any of the resting heart rate variables improved discrimination for all of the outcomes compared to the model excluding heart rate. On the whole, the time-updated heart rate models adjusted for baseline or the previous heart rate measurement, yielded the highest and similar C-statistics, and thus had the best discriminative ability. No significant differences between BEAUTIFUL and SHIFT, in relation to the effect of heart rate, were observed. Note that a version of these results was published in Hamill et al. 2015[277].

Both elevated baseline and time-updated resting heart rates, analysed categorically or continuously, were associated with an increase in the risk of all the endpoints evaluated with the exception of admission to hospital for non-fatal MI. The addition of any of the heart rate variables resulted in statistically significant improvements in the calibration of the models for these outcomes. Again, time-updated heart rate strengthened the associations for each of the outcomes, and remained a significant predictor for each after adjustment for baseline heart rate or the previous heart rate measurement. No

association between a higher continuous baseline heart rate and risk of hospital admission for MI was observed. However, an elevated time-updated heart rate, unadjusted or adjusted for baseline or the previous heart rate measurement, was associated with an increase in risk. A 5bpm higher time-updated heart rate after adjustment for baseline, for example, was associated with a 14% ($p<0.001$) increase in risk. Consistent with these results, only the addition of the time-updated heart rate variables, with or without adjustment for baseline or the previous heart rate measurement, improved the calibration of the models for MI.

Evidence of non-proportionality of the effect of an elevated heart rate was found for the individual outcome of hospital admission for HF, and the combined outcomes of CV death or admission to hospital for HF, and CV death or admission to hospital for HF or MI in each study. Non-proportionality was also observed for admission to hospital for all causes, and CV causes, in SHIFT. The effect of an elevated heart rate appeared to be highest at the beginning of follow-up, and then decreased over time. Fox et al. 2008 similarly found evidence of non-proportionality for admission to hospital for HF in the BEAUTIFUL baseline heart rate analysis[184]. A baseline heart rate ≥70bpm was associated with an 86% (95% CI 40 to 147%, $p<0.001$) and a 44% (95% CI 2 to 103%, $p = 0.036$) increase in risk in the first and second nine months of follow-up, respectively. After 18 months of follow-up, no association between elevated heart rate and risk of hospital admission for HF was observed.

The BEAUTIFUL results for all-cause death are similar to those found in the prior analysis of resting heart rate among the EUROPA population of CHD subjects with no HF presented in Chapter 5, as well as those previously found by Diaz et al. 2005[148], Ho et al. 2010[149] (in which a small percentage of the patients had HF, some of whom may have had LVSD), and Anselmino et al. 2010 (in the subgroup of CHD patients with diabetes)[150]. The results for CV death and hospital admission for HF are also similar to those found by Diaz et al. 2005[148] and the EUROPA analysis.

In the current analysis, in accordance with Fox et al. 2008[184], elevated baseline and time-updated resting heart rates were associated with an increase in the risk of revascularisation. For example, a 5bpm higher time-updated heart rate was associated with a 13% ($p<0.001$) increase in risk. However, as was previously discussed in Chapters 5 and 6, elevated heart rate was associated with a decrease in the risk of revascularisation in the EUROPA and PROSPER populations (PROSPER included older individuals with, or at an increased risk of, vascular disease, some of whom had CHD). In the discussions of Chapters 5 and 6 (Sections 5.3 and 6.3), it was suggested that this may have been because revascularisation was a marker for different conditions in these studies, since the BEAUTIFUL trial began in 2004, around seven years after the EUROPA and PROSPER trials: revascularisation was mainly used to treat angina before 2000, but was later used more frequently to treat MI[276]. However, further investigation is necessary to truly understand these contrasting results.

Fox et al. 2008[184] showed previously that patients with a baseline resting heart rate ≥70bpm were at a 46% ($p = 0.0066$) higher risk of admission to hospital for MI, and the current analysis found that patients with a time-updated heart rate ≥70bpm were at a 48% ($p = 0.0084$) higher risk. In addition, a 5bpm higher time-updated heart rate adjusted for baseline heart rate was associated with a 15% ($p<0.001$) increase in risk. Moreover, a 5bpm higher time-updated heart rate adjusted for baseline heart rate was associated with a 10% ($p<0.001$) increase in risk of hospital admission for MI or unstable angina, although hospital admission for unstable angina alone was not evaluated. Neither the EUROPA analysis presented in Chapter 5, or the previous studies by Diaz et al. 2005[148] and Ho et al. 2010[149], observed any associations between resting heart rate and the risk of MI, or unstable angina This suggests that there could be differences in the association between resting heart rate and risk of MI or unstable angina in CHD patients without HF or a reduced EF, and CHD patients with HF or reduced EF, although a small percentage of patients included in the Ho et al. 2010[149] analysis had HF, and

some may have had LVSD. Further studies would therefore be required to substantiate this possibility.

None of the studies of CHD patients identified in Chapter 2, or the prior EUROPA analysis, evaluated the relationship between resting heart rate and risk of cardiac death. The present analysis demonstrated that patients with a time-updated heart rate ≥70bpm adjusted for baseline were at a great 225% ($p<0.001$) higher risk of cardiac death compared to those with a time-updated heart rate <70bpm. Furthermore, a 5bpm higher time-updated heart rate adjusted for baseline was associated with a 27% ($p<0.001$) increase in risk of cardiac death. These were the most substantial increases in risk observed in the present study. Further analyses of the risk of cardiac death in patients without LVSD would be interesting.

The patients enrolled in SHIFT had LVSD and were in sinus rhythm. Only two of the studies identified in the systematic review in Chapter 2 presented results regarding the association between baseline resting heart rate and risk of adverse CV outcomes in patients with chronic HF and LVSD who were in sinus rhythm[174,176]. Maeder and Kaye 2012 illustrated that such patients with a baseline heart rate >87bpm were at a 16% (95% CI 2 to 31%) and 31% (95% CI 15 to 50%) higher risk of all-cause death and hospital admission for HF, respectively[174]. In the current analysis, patients with a resting heart rate ≥80bpm were found to be at a much higher risk of these outcomes. For example, patients with a baseline heart rate ≥80bpm were shown to be at a 78% ($p<0.001$) and 68% ($p<0.001$) higher risk of all-cause death, and hospital admission for HF, respectively, and those with a time-updated heart rate ≥80bpm, adjusted for baseline heart rate, were shown to be at an even greater 73% ($p<0.001$) and 120% ($p<0.001$) higher risk. Takada et al. 2014 showed that patients with a baseline resting heart rate in the highest third of the distribution were at a similar 80% (95% CI 17 to 178%) higher risk of all-cause death. However, no associations between baseline resting heart rate and the risk of CV death, HF death, or hospital admission for HF were observed[176]. In

contrast, the current analysis established that patients with a baseline resting heart rate ≥80bpm were at an 81% ($p<0.001$) and 112% ($p<0.001$) higher risk of CV death and HF death, respectively.

In a population of chronic HF patients with reduced or preserved EF, in sinus rhythm or AF, Vazir et al. 2014 recently determined that a 5bpm higher time-updated resting heart rate, adjusted for baseline heart rate, was associated with a 9% ($p<0.001$) increase in the risk of all-cause death, and CV death, and a 6% increase in the risk of hospital admission for HF, MI, and the composite of CV death or hospital admission for HF ($p<0.001$ for hospital admission for HF and the combined endpoint; $p = 0.014$ for MI)[215]. The present study confirmed these results in chronic HF patients with LVSD in sinus rhythm, but found somewhat higher increases in risk: a 5bpm higher time-updated heart rate, adjusted for baseline, was associated with a 16% ($p<0.001$) increase in the risk of all-cause death and CV death, a 22% ($p<0.001$) increase in the risk of hospital admission for HF, a 12% ($p = 0.010$) increase in the risk of MI, and a 19% ($p<0.001$) increase in the risk of the composite of CV death or hospital admission for HF.

8.5.1 Chapter Summary and Conclusions

This chapter investigated the prognostic value of baseline and time-updated resting heart rate in the BEAUTIFUL and SHIFT placebo populations. Both trials enrolled patients with LVSD who were in sinus rhythm: the BEAUTIFUL subjects had CHD, and the SHIFT subjects had chronic HF, although some of the BEAUTIFUL subjects also had HF. Analysis of each individual trial was performed, and since both studies included patients with LVSD in sinus rhythm, a pooled individual patient meta-analysis of the two placebo populations was additionally executed.

Across all analyses, both baseline and time-updated resting heart rate, regardless of whether the baseline or previous heart rate measurements were adjusted for, were demonstrated to be directly associated with a higher risk of death and all of the other

adverse CV outcomes examined, excluding hospital admission for MI. The associations were weaker for hospital admission for MI: for example, in each of the three analyses, no association between an elevated continuous baseline heart rate and risk was observed, while a higher continuous time-updated heart rate was associated with an increase in risk.

The final and following analysis chapter, Chapter 9, presents meta-analyses of the risk of death from any cause and death from CV causes associated with baseline and time-updated resting heart rate in a variety of populations, including the published prospective evidence identified in the systematic review of Chapter 2, as well as the results from this chapter and Chapters 4 to 7.

Chapter 9

Meta-Analyses of the Associations between Resting Heart Rate and All-Cause and Cardiovascular Mortality

9.1 Introduction

Chapter 2 presented a systematic review of studies that focused on the prognostic value of resting heart rate for mortality and adverse CV outcomes. Studies that used a single heart rate measurement to predict risk were distinguished from those that used multiple heart rate measurements. The majority of the studies included in the review showed that an elevated resting heart rate measured at a single point in time is associated with an increase in the risk of death and adverse CV outcomes in the general population, as well as in patients with certain pre-existing diseases or conditions. The studies by Ho et al. 2014[204] and Vazir et al. 2014[215] showed that time-updated heart rate was able to predict events where a single heart rate measurement was not. Time-updated heart rate may be more relevant to clinical practice, since heart rate varies over time, and so risk may be more closely related to newly measured levels.

Each of the studies identified in the review included individuals from specific populations. The aim of this analysis was to assess the overall association between an elevated resting heart rate and the risk of all-cause and CV death across different patient populations. Following on from the systematic review of Chapter 2, a meta-analysis of the published prospective evidence on the association between baseline resting heart rate and risk of these endpoints was carried out and is presented in Section 9.2. A similar meta-analysis of time-updated resting heart rate was performed and is presented in Section 9.3. The results from Chapters 4 to 8 were also included in the analyses. The PRISMA guidelines[94,95] were followed as extensively as possible; the PRISMA 2009 checklist is given in Table A7-1 provided in Appendix 7.

9.2 A Meta-Analysis of 28 Studies that Analysed Baseline Resting Heart Rate as a Prognostic Risk Marker for All-Cause and Cardiovascular Mortality

9.2.1 Study Selection and Data Extraction

The 118 studies that were reviewed in Chapter 2 were considered for inclusion in this meta-analysis. Each publication was read in full to assess its eligibility. Studies were accepted for inclusion if they presented a HR from a Cox model for all-cause and/or CV death for a change in continuous baseline heart rate, with a corresponding 95% CI. Only studies published from 1990 onwards were included. The study population had to include both men and women. Studies were excluded if the study population consisted of only men or women, or if HRs were presented separately for men and for women. Studies were also excluded if they presented results only for specific subgroups of individuals, such as individuals who smoked and individuals who did not. Short-term mortality events such as in-hospital death were not of interest, and studies which presented results only for such endpoints were not included.

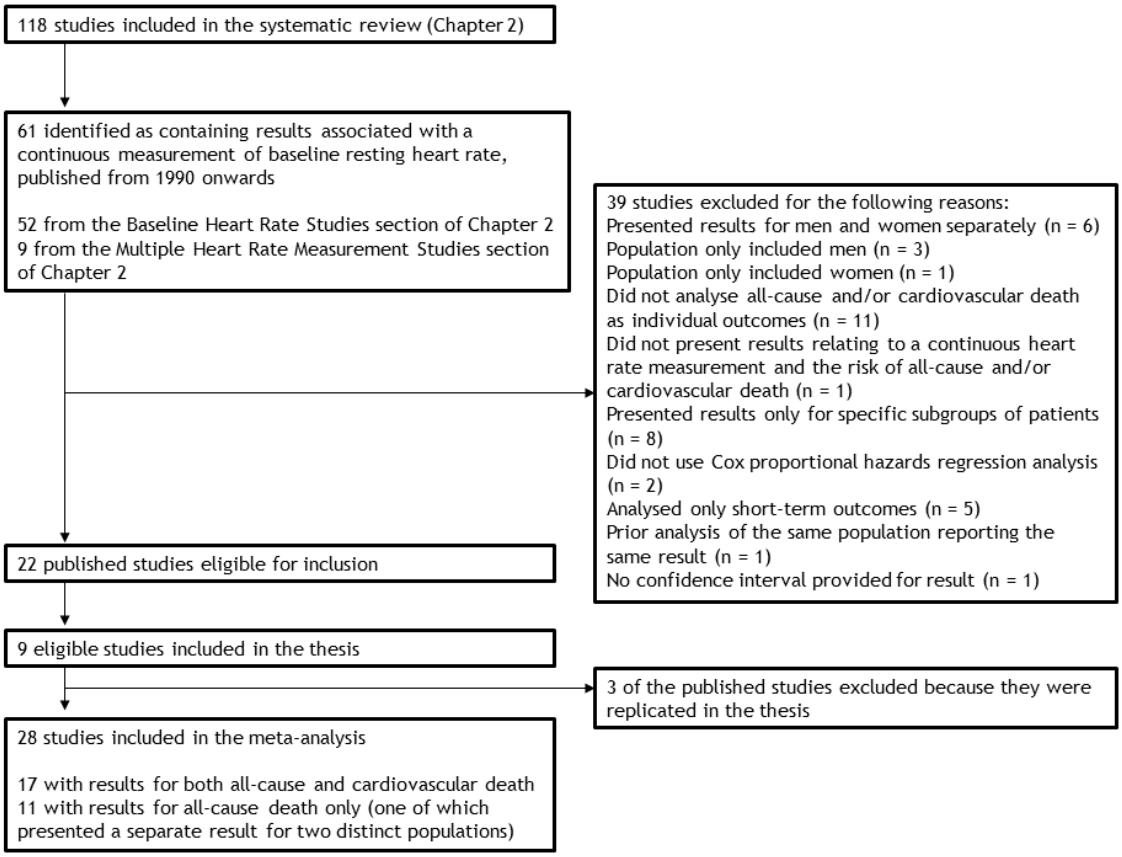
The HRs and 95% CIs for all-cause and/or CV death associated with a change in continuous baseline heart rate were obtained. Generally, the result found using the most adjusted model was selected. The following data were also extracted from each publication where possible: the first author's last name; the year of publication; the mean or median length of follow-up; the covariates additionally adjusted for in the model; the number of first all-cause and/or CV death events; the number of subjects included in the study; and the method of heart rate measurement.

9.2.2 Results

As shown by Figure 9-1, 61 of the 118 publications described in Chapter 2 were identified as containing results associated with a continuous measurement of baseline resting heart rate. A total of 52 of these publications were described in the Baseline

Heart Rate Studies section of Chapter 2 (Section 2.3.1), and the remaining nine were described in the Multiple Heart Rate Measurement Studies section (Section 2.3.2).

Figure 9-1: Flow chart of the selection process of the studies included in the meta-analysis of baseline resting heart rate.



Thirty-nine of these studies were excluded for the reasons outlined in Figure 9-1. Thus, 22 publications were eligible for inclusion in the meta-analysis, each of which were prospective in design. Table A7-2 provided in Appendix 7 gives the details of these studies, including their quality, as appraised using the Newcastle-Ottawa scale[96] (see Tables A1-3 and A1-15 for breakdown), along with HRs and 95% CIs for a 5bpm higher baseline heart rate for all-cause and/or CV death, the number of corresponding first events, and the other covariates adjusted for in the models. Note that the publication by Fosbol et al. 2010[183] is included twice in Table A7-2 since it was an analysis of two patient populations (DIAMOND-MI and DIAMOND-HF), and presented distinct results for each population. Study quality was high, ranging from 7 to 8 stars.

The HRs and 95% CIs calculated for a 5bpm higher baseline heart rate presented in Chapters 4, 5, 6, 7 and Chapter 8 Sections 8.2 and 8.3 of this thesis were also eligible for inclusion in the meta-analysis. The pooled analysis in Chapter 4 did not calculate results for all-cause and CV death for EPHESUS, OPTIMAAL or VALIANT individually. Thus, HRs and 95% CIs for a 5bpm higher heart rate for all-cause and CV death were calculated for each of these populations and included in the analysis. The results for all-cause and CV death for these three populations and the six other populations are summarised in Table A7-3.

The previously published PROSPER[138], PERFORM[191], and BEAUTIFUL[184] studies of baseline resting heart rate were subsequently excluded from the analysis as they were replicated in the thesis. The results presented for PROSPER, PERFORM and BEAUTIFUL are therefore those previously calculated in Chapters 6, 7 and 8, as opposed to those presented in the original baseline heart rate publications[138,191,184] (note that there were some slight differences between these results).

Thus, a total of 28 studies were included in this meta-analysis: 17 of which presented results for both all-cause and CV mortality, and 11 of which presented results for all-cause mortality only (with Fosbol et al. 2010[183] providing two separate results for all-cause mortality).

9.2.2.1 All-Cause Death

A 5bpm higher baseline resting heart rate was associated with a 7.9% increase in the risk of all-cause death (number of studies = 29, HR = 1.079, 95% CI = 1.068 to 1.091, $p<0.001$), as shown by Figure 9-2. There was a substantial degree of true between-study heterogeneity ($I^2 = 70\%$), which was statistically significant ($Q = 99.64$, $p<0.001$). Note that these results were obtained using the 1-year results from Antoni et al. 2012[169] and Seronde et al. 2013[171]. When the 4-year and 5-year results from Antoni[169] and Seronde[171], respectively, were used, the pooled risk of all-cause death associated with a 5bpm higher resting heart rate (and the associated 95% CI) remained the same, but the

degree of true between-study heterogeneity was larger (I^2 = 75%), as was the Q-statistic (Q = 101.10, p<0.001).

The results from Jensen et al. 2013[170], Antoni et al. 2012[169], Parodi et al. 2010[159] and Palatini et al. 2002[147] were visually identified as outliers. Each of these studies included only a small number of deaths (Jensen et al. 2013 did not state the number of deaths that occurred[170]) and reported a substantially higher increase in risk of death compared to the other studies. Excluding these studies reduced the degree of heterogeneity (I^2 = 54%), although it remained significant (Q = 49.50, p = 0.002). Among the remaining studies, a 5bpm higher baseline heart rate was associated with a similar 7.2% (95% CI 6.3 to 8.1%, p<0.001) increase in the risk of all-cause death.

To explore the heterogeneity further, summary HRs were calculated for each population of patients that included two or more studies. The results are shown by Figure 9-3. As can be seen, the populations that contained the most between-study heterogeneity were the post-MI or ACS patients, the patients with CHD and LVSD, HF or both, the individuals drawn from the general population, and the individuals with hypertension. A 5bpm higher baseline heart rate was associated with around a 6 to 9% increase in the risk of all-cause death in the majority of the subgroups. In the post-MI or ACS and hypertensive subgroups of patients, a 5bpm higher baseline heart rate was associated with a 16.9% (95% CI 6.3 to 27.6%) and an 11.8% (95% CI 3.6 to 20.0%) increase in the risk of all-cause death, respectively. Excluding Jensen et al. 2013[170], Antoni et al. 2012[169] and Parodi et al. 2010[159] from the post-MI or ACS subgroup (the studies within this subgroup that there visually identified as outliers) a 5bpm higher baseline heart rate was associated with a 6.7% (95% CI 4.0 to 9.3%). Excluding Palatini et al. 2002[147] from the hypertensive subgroup (the other study visually identified as an outlier) left only the study by Julius et al. 2012, which reported that a 5bpm higher baseline heart rate was associated with a 9.0% (95% CI 7.0 to 10.0%) higher risk of all-cause death[212].

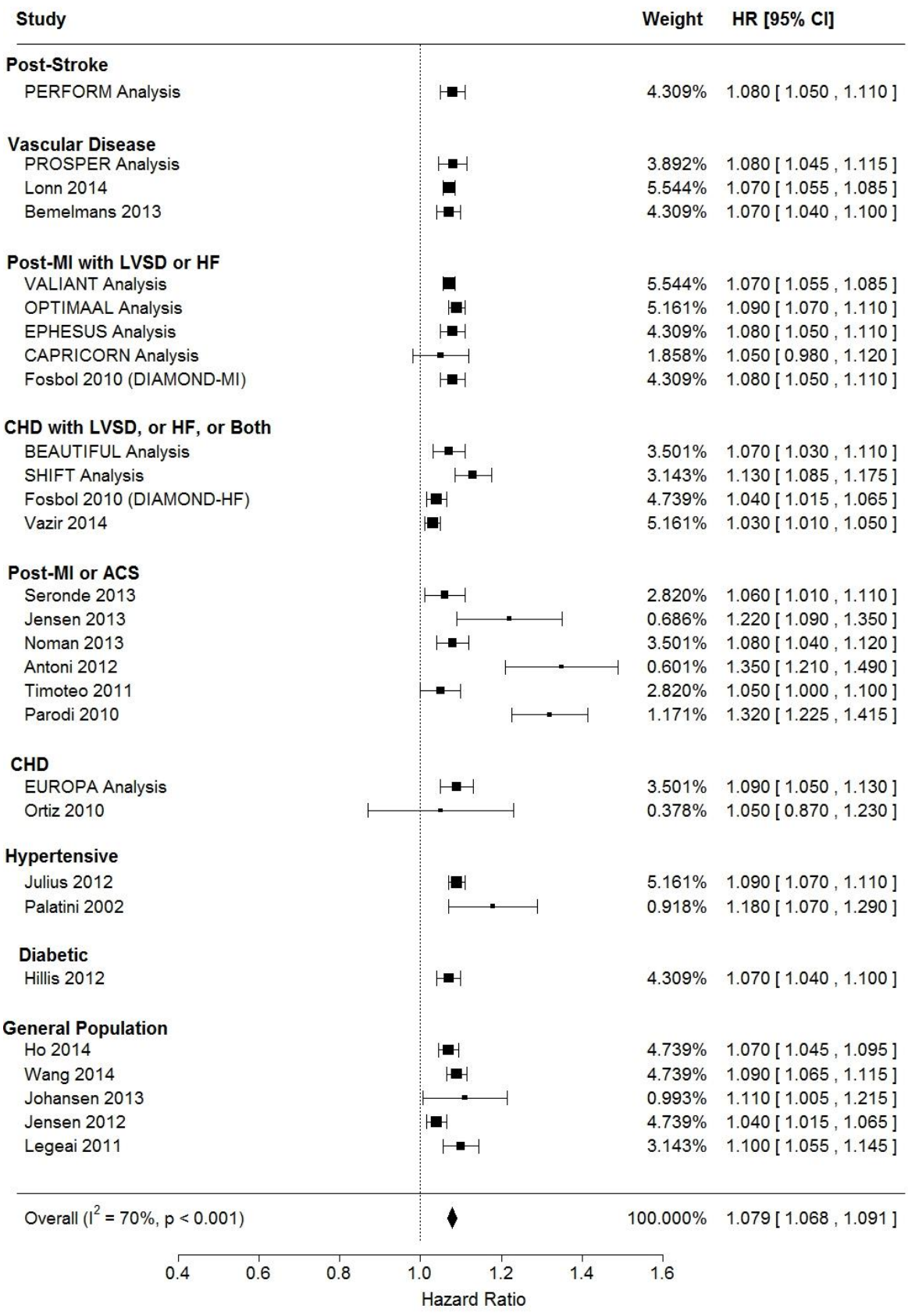
9.2.2.2 Cardiovascular Death

A 5bpm higher baseline resting heart rate was also associated with an 8.0% increase in the risk of CV death (number of studies = 17, HR = 1.080, 95% CI = 1.065 to 1.095, p<0.001), as shown by Figure 9-4. There was a substantial degree of true between-study heterogeneity (I^2 = 63%) which was statistically significant (Q = 44.04, p<0.001). Note that these results were obtained using the 1-year results from Antoni et al. 2012[169]. When the 4-year result was used, the pooled risk of CV death and the associated 95% CI was the same; the between-study heterogeneity was slightly larger (I^2 = 64%) as was the Q-statistic (44.22, p<0.001).

Excluding the result from Antoni et al. 2012, which was the only apparent outlier, did not alter the degree of heterogeneity (I^2 = 63%). Among the remaining studies, a 5bpm higher baseline heart rate was associated with a similar 7.8% increase in risk, and the width of the 95% CI was slightly reduced (95% CI 6.4 to 9.3%).

The summary HRs for each population of patients that included two or more studies are shown by Figure 9-5, and were similar across all populations. The populations of patients that contained the most between-study heterogeneity were those with CHD and LVSD, HF or both, and those who had previously experienced an MI who had LVSD, HF or both.

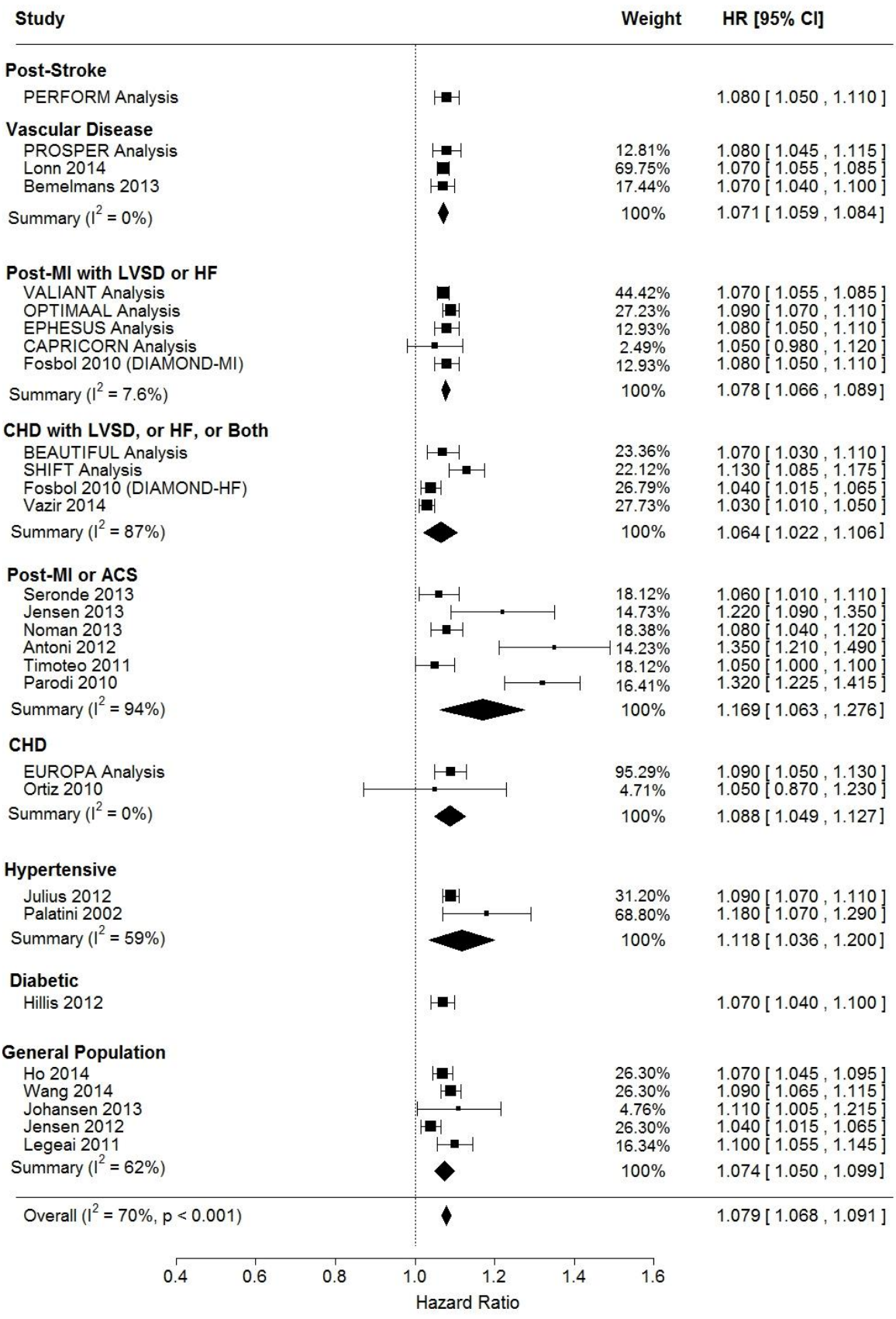
Figure 9-2: Forest plot representing the individual and pooled risk of all-cause death associated with a 5bpm higher baseline resting heart rate.



Note that the results for Antoni et al. 2012[169] and Seronde et al. 2013[171] are the ones for 1-year all-cause mortality, as opposed to 4- and 5-year mortality, respectively.

ACS = Acute Coronary Syndrome; CHD = Coronary Heart Disease; CI = Confidence Interval; HF = Heart Failure; HR = Hazard Ratio; LVSD = Left-Ventricular Systolic Dysfunction; MI = Myocardial Infarction.

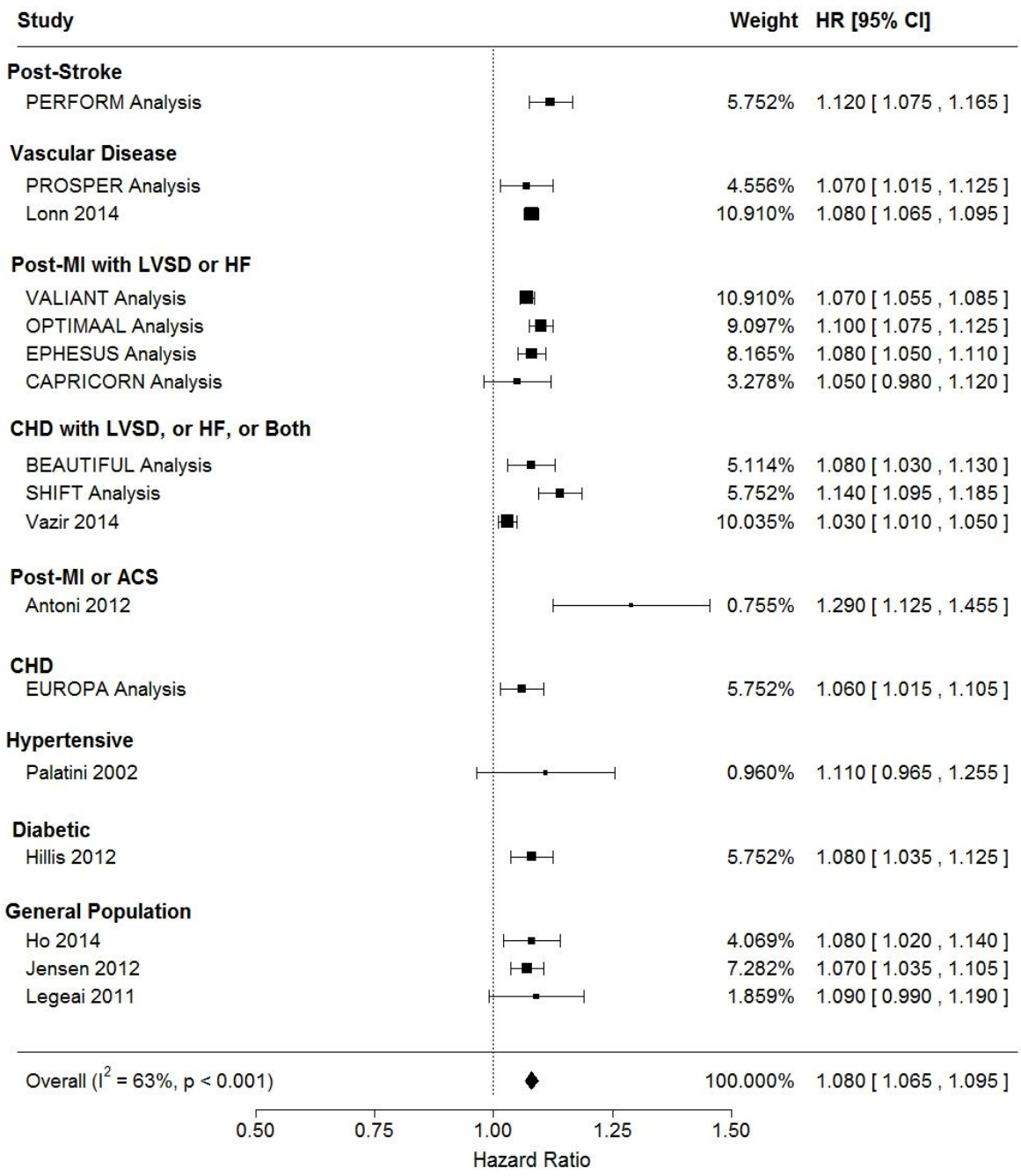
Figure 9-3: Forest plot representing the individual and pooled risk of all-cause death associated with a 5bpm higher baseline resting heart rate, overall and by patient population.



Note that the results for Antoni et al. 2012[169] and Seronde et al. 2013[171] are the ones for 1-year all-cause mortality, as opposed to 4- and 5-year mortality, respectively.

ACS = Acute Coronary Syndrome; CHD = Coronary Heart Disease; CI = Confidence Interval; HF = Heart Failure; HR = Hazard Ratio; LVSD = Left-Ventricular Systolic Dysfunction; MI = Myocardial Infarction.

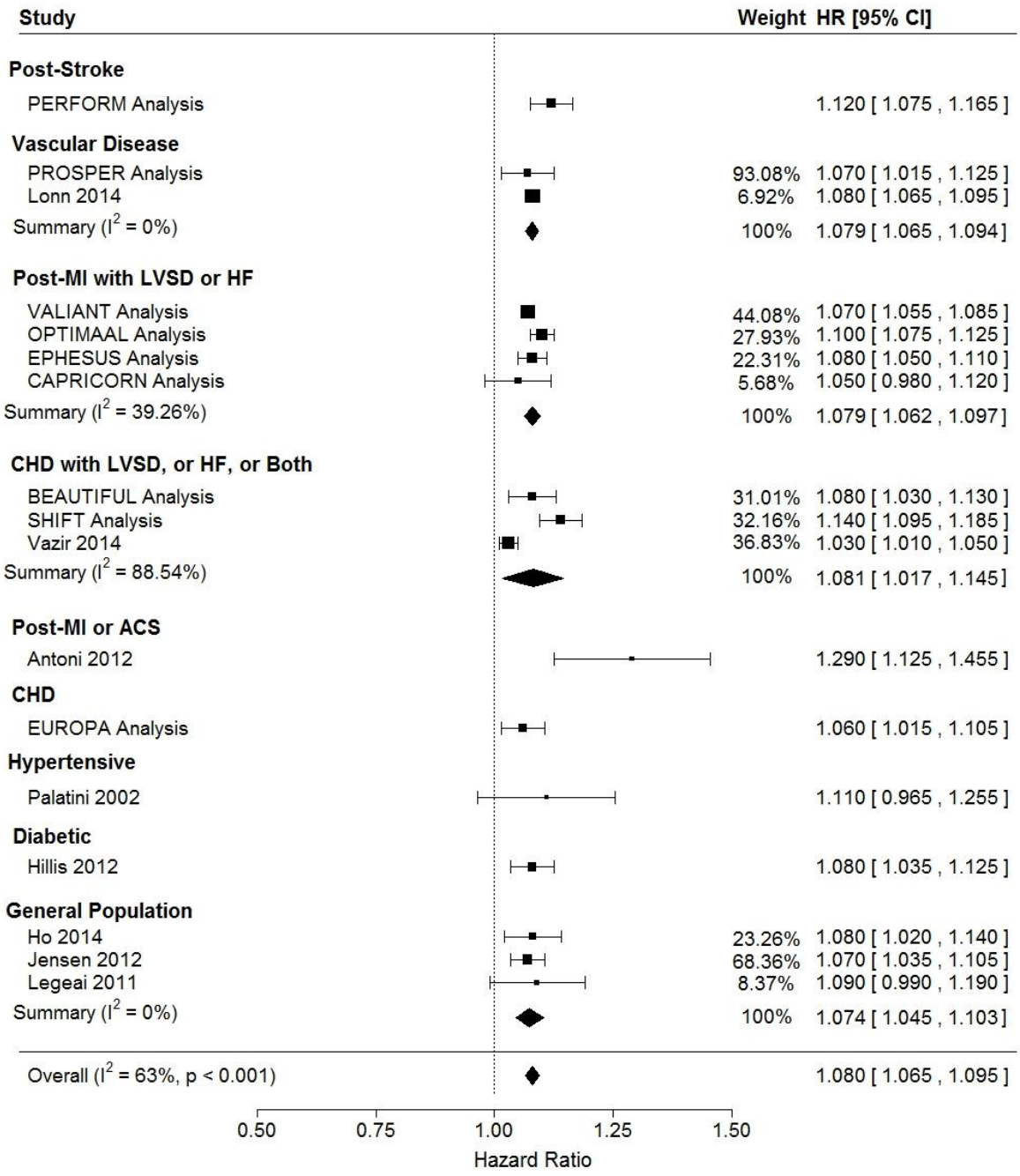
Figure 9-4: Forest plot representing the individual and pooled risk of cardiovascular death associated with a 5bpm higher baseline resting heart rate.



Note that the result for Antoni et al. 2012[169] is the one for 1-year cardiovascular mortality.

ACS = Acute Coronary Syndrome; CHD = Coronary Heart Disease; CI = Confidence Interval; HF = Heart Failure; HR = Hazard Ratio; LVSD = Left-Ventricular Systolic Dysfunction; MI = Myocardial Infarction.

Figure 9-5: Forest plot representing the individual and pooled risk of cardiovascular death associated with a 5bpm higher baseline resting heart rate, overall and by patient population.



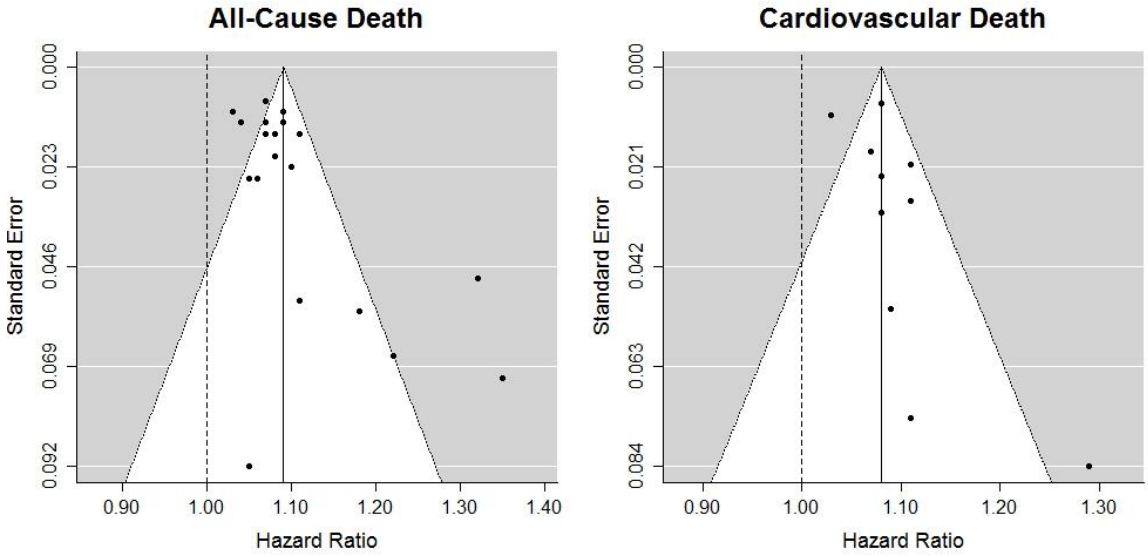
Note that the result for Antoni et al. 2012[169] is the one for 1-year cardiovascular mortality.

ACS = Acute Coronary Syndrome; CHD = Coronary Heart Disease; CI = Confidence Interval; HF = Heart Failure; HR = Hazard Ratio; LVSD = Left-Ventricular Systolic Dysfunction; MI = Myocardial Infarction.

9.2.2.3 Publication Bias

There was evidence of publication bias for all-cause death and CV death, including only the studies and corresponding results in Table A7-2, since the results in Table A7-3 have not been published (using the 1-year post-MI population results of Antoni[169] and Seronde[171]) ($p<0.001$ for all-cause death and $p = 0.017$ for CV death). Including only the published results, the pooled risks of all-cause and CV death associated with a 5bpm higher resting heart rate were 1.091 (95% CI 1.067 to 1.114, $p<0.001$) and 1.080 (95% CI 1.060 to 1.101, $p<0.001$), respectively. The funnel plots are shown by Figure 9-6.

Figure 9-6: Funnel plots showing the degree of publication bias for all-cause death and cardiovascular death, assessed from the results in Table A7-2.



The white triangular areas of the funnel plots indicate where 95% of studies would be expected to lie assuming that the heterogeneity within the analysis fit the assumptions of the random-effects model, and that no publication bias was present[278]. Studies that lie outside of this area can be thought of as statistical outliers[275]. The vertical line of symmetry in each triangle corresponds to the pooled risk of all-cause and CV death associated with a 5bpm higher baseline heart rate, including only the published results (1.091 and 1.080 for all-cause and CV death, respectively, as stated in the previous paragraph). In theory, this line would correspond to the true risk associated with a 5bpm higher heart rate, and studies would be symmetrically scattered around it.

Smaller studies represented by those with larger standard errors would be spread out at the bottom, and larger, more powerful studies would be gathered more tightly at the top as their standard errors decreased[279]. In practice, the true size of the association is unknown, and often only published studies are represented. If publication bias is present, parts of the funnel plot will be bare. The dashed vertical line at a hazard ratio of one corresponds to their being no association between baseline resting heart rate and risk.

As can be seen from Figure 9-6, the majority of the studies included in the analyses were large, with small standard errors: most of the studies are grouped quite tightly around the top of each triangle - more so for all-cause death. The bottom of each triangle is quite bare, suggesting that smaller studies with larger standard errors are lacking or missing. All of the studies lie on the right of the dashed vertical line, indicating that they each reported a positive association between baseline resting heart rate and risk of all-cause or CV death, even if it was not statistically significant (as was the case with the study by Ortiz et al. 2010[151] in relation to all-cause death, and Palatini et al. 2002[147] and Legeai et al. 2011[206] in relation to CV death).

Regarding all-cause death, the two results that lie outside the white triangle to its right are from the studies by Parodi et al. 2010 (HR 1.32, 95% CI 1.23 to 1.42)[159] and Antoni et al. 2012 (HR 1.35, 95% CI 1.22 to 1.50 after 1 year of follow-up)[169]. These studies were visually identified as being outliers in Section 9.2.2.1. Three results appear to lie outside the triangle to its left, but in actual fact there are four, from the studies by Vazir et al. 2014[215], Jensen et al. 2012[128] and Fobsol et al. 2010 (DIAMOND-HF)[183] – which reported the same hazard ratio and had the same standard error – and Lonn et al. 2014[216]. The hazard ratio that each of these studies reported is smaller than expected given their large size and small standard errors. Similarly, in relation to CV death, the result lying outside of the triangle to its right is from Antoni et al. 2012 (HR 1.29, 95% CI 1.13 to 1.46)[169], which was also visually identified as being an outlier in Section 9.2.2.2.

The result lying outside and to the left of the triangle is again from Vazir et al. 2014[215], which reported a hazard ratio smaller than excepted given its large size and small standard error.

Using the L_0 estimator of the number of missing studies, the trim and fill method estimated that zero and five studies were theoretically missing for all-cause and CV death, respectively. Incorporating these five theoretical missing studies into the analysis slightly reduced the pooled HR for CV death to 1.067 (95% CI 1.047 to 1.087), p<0.001). Conversely, using the R_0 estimator, the trim and fill method estimated that three and zero studies were theoretically missing for all-cause and CV death, respectively. In this case, incorporating the three theoretical missing studies into the analysis, the pooled HR for all-cause death was slightly reduced to 1.075 (95% CI 1.035 to 1.115, p<0.001).

9.3 A Meta-Analysis of 10 Studies that Analysed Time-Updated Resting Heart Rate as a Prognostic Risk Marker for All-Cause and Cardiovascular Mortality

9.3.1 Study Selection and Data Extraction

The seven time-updated heart rate studies that were identified in Chapter 2 were considered for inclusion in this meta-analysis. Each publication was read in full to assess its eligibility. Studies were accepted for inclusion if they presented a HR for all-cause and/or CV death for a change in continuous time-updated resting heart rate entered as a time-dependent variable in the extended Cox proportional hazards regression model[205], with a corresponding 95% CI.

The HRs and 95% CIs for all-cause and/or CV death associated with a change in continuous time-updated heart rate were obtained. The result found using the most adjusted model was selected. The following data were also extracted from each publication where possible: the first author's last name; the year of publication; the mean or median length of follow-up; the covariates additionally adjusted for in the

model; the number of first all-cause and/or CV death events that occurred; the number of subjects included in the study; and the method of heart rate measurement.

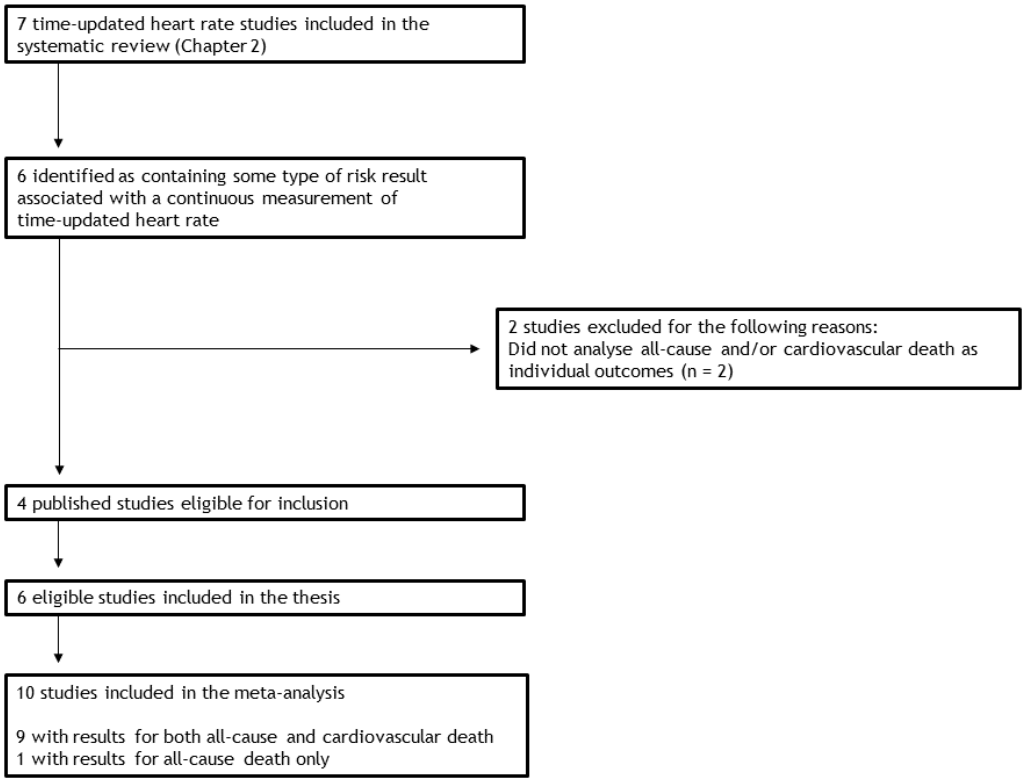
9.3.2 Results

As shown by Figure 9-7, six of the seven time-updated heart rate studies identified in Chapter 2 were identified as containing results associated with a continuous measurement of resting heart rate. Two of these were excluded for the reasons outlined in Figure 9-7. Thus, four publications remained eligible for inclusion in the meta-analysis. All of the studies that satisfied the inclusion criteria included both male and female participants and were prospective in design. Table A7-4 gives the details of these four studies, including their quality, as appraised using the Newcastle-Ottawa scale[96] (see Tables A1-3 and A1-15 for breakdown), along with HRs and 95% CIs for a 5bpm higher time-updated resting heart rate for all-cause and/or CV mortality, the number of corresponding first events, and the other covariates adjusted for in the models. The studies by Okin et al. 2010[210] and Vazir et al. 2014[215] additionally adjusted the time-dependent heart rate models for baseline heart rate. Study quality was high, ranging from 7 to 8 stars.

The HRs and 95% CIs calculated for a 5bpm higher time-updated heart rate presented in Chapter 4 Section 4.3, Chapters 5, 6, 7 and Chapter 8 Sections 8.2 and 8.3 of this thesis were also eligible for inclusion in the meta-analysis. The results for all-cause and CV death for the six populations are summarised in Table A7-5. The result found using the time-updated models unadjusted and adjusted for baseline heart rate are presented since two of the published papers presented results additionally adjusted for baseline heart rate[210,215], while the other two did not[204,207]. The models that adjust for baseline heart rate are more revealing since they provide information on whether the current heart rate measurement contributes significant additional information about risk of death, despite knowing the baseline heart rate measurement.

Thus, a total of ten distinct studies were therefore included in this meta-analysis: nine of which presented results for both all-cause and CV mortality, and one of which presented a result for all-cause mortality only.

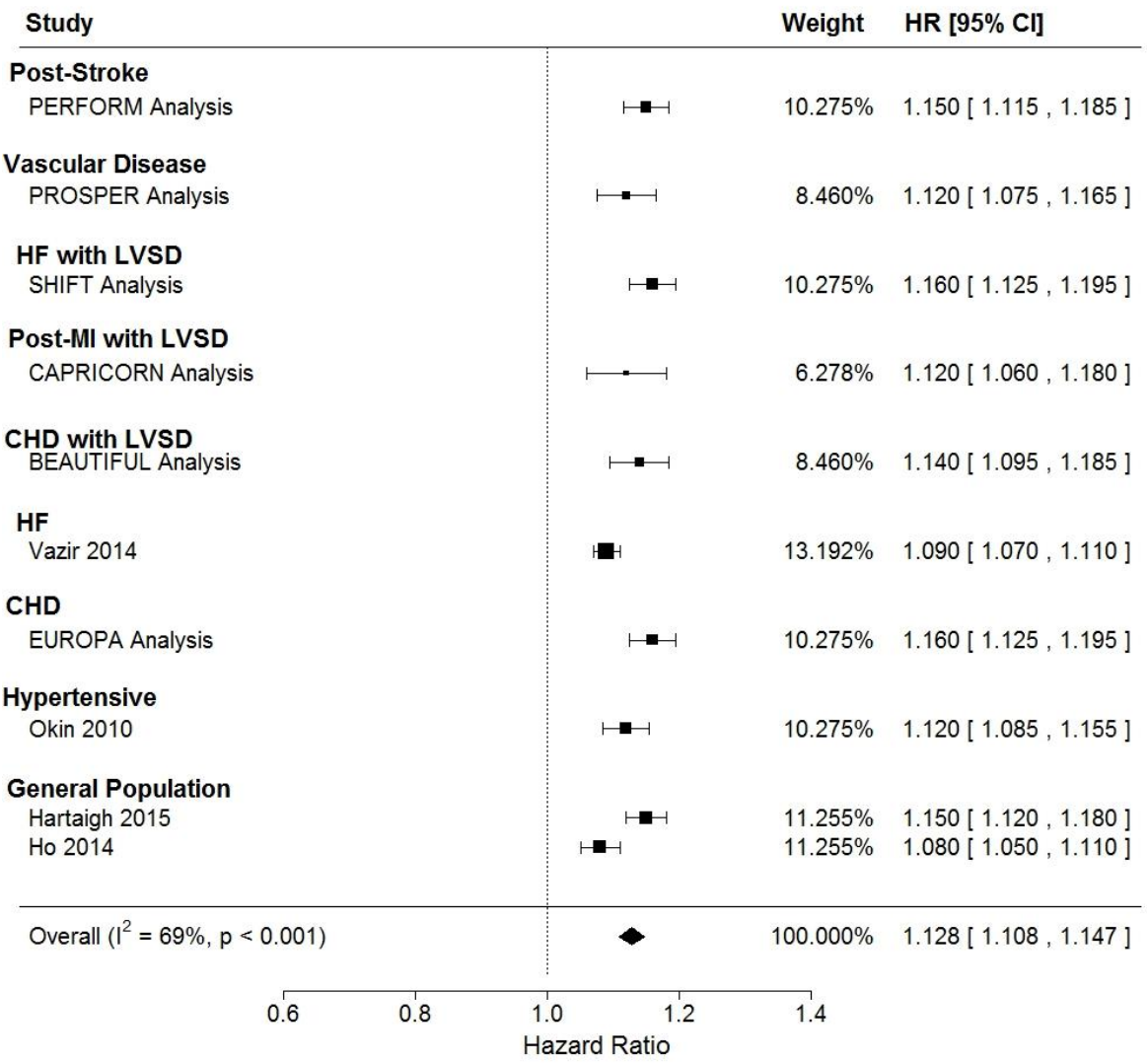
Figure 9-7: Flow chart of the selection process of the studies included in the meta-analysis of time-updated resting heart rate.



9.3.2.1 All-Cause Death

A 5bpm higher time-updated resting heart rate was associated with a 12.8% increase in the risk of all-cause death (number of studies = 10, HR = 1.128, 95% CI = 1.108 to 1.147, p<0.001), as shown by Figure 9-8. There was a substantial degree of true between-study heterogeneity (I^2 = 69%), which was statistically significant (Q = 32.86, p<0.001). These are the results obtained using the models additionally adjusted for baseline heart rate from this thesis. When the results not additionally adjusted for baseline from this thesis were used, the pooled risk of all-cause death associated with a 5bpm increase in time-updated resting heart rate (and the associated 95% CI) remained the same, but the degree of true between-study heterogeneity was larger (I^2 = 73%) as was the Q-statistic (Q = 34.23, p<0.001).

Figure 9-8: Forest plot representing the individual and pooled risk of all-cause death associated with a 5bpm higher time-updated resting heart rate.



Note that the results from the analyses in Chapters 4 to 8 are the ones that were obtained when baseline resting heart rate was additionally adjusted for.

CHD = Coronary Heart Disease; CI = Confidence Interval; HF = Heart Failure; HR = Hazard Ratio; LVSD = Left-Ventricular Systolic Dysfunction.; MI = Myocardial Infarction.

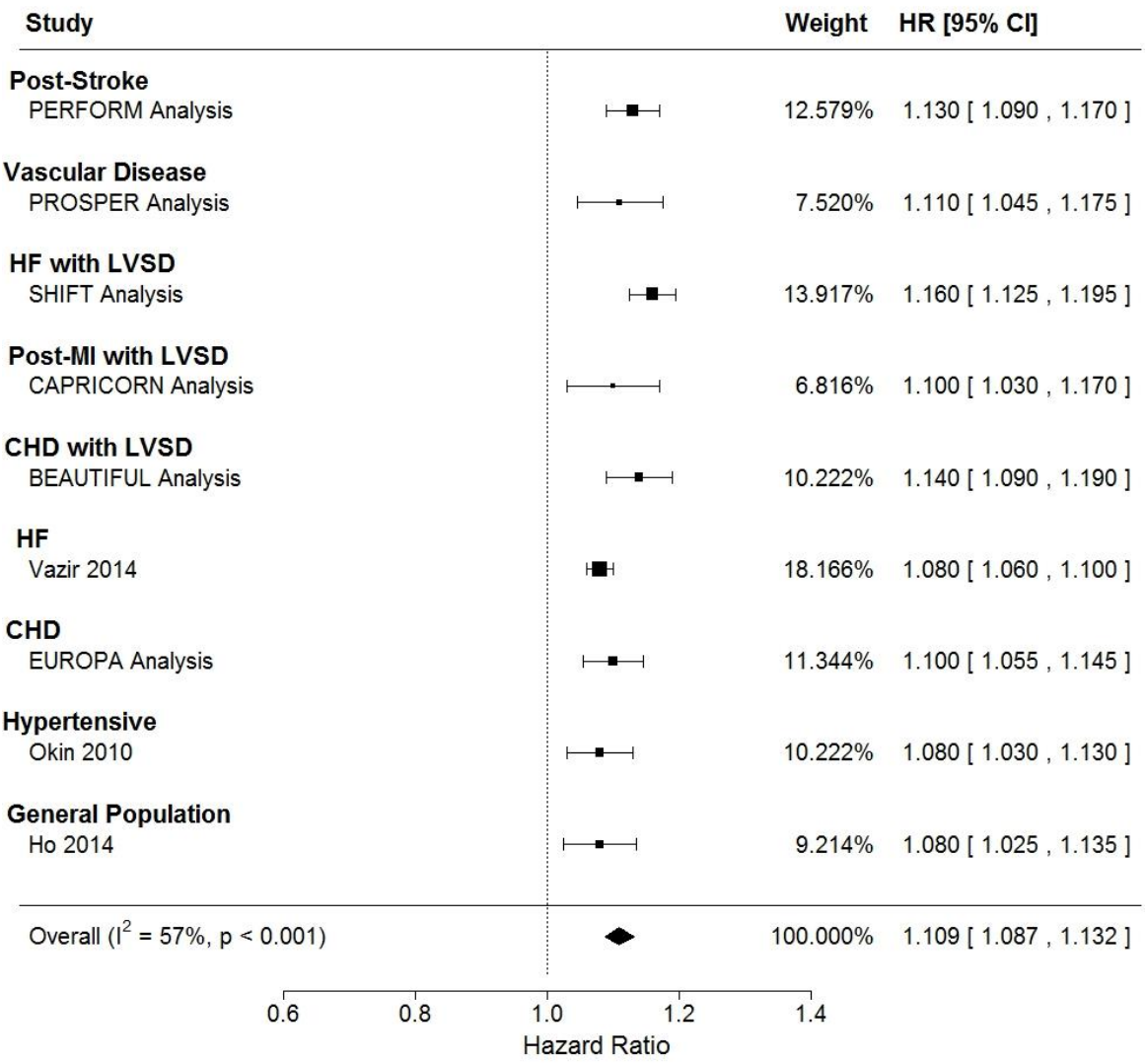
9.3.2.2 Cardiovascular Death

A 5bpm higher time-updated resting heart rate was associated with a 10.9% increase in the risk of CV death (number of studies = 9, HR = 1.109, 95% CI 1.087 to 1.132, p<0.001), as shown by Figure 9-9. There was a substantial degree of true between-study heterogeneity (I^2 = 57%) which was statistically significant (Q = 20.67, p = 0.008). These are the results obtained using the models additionally adjusted for baseline heart rate from this thesis. When the results unadjusted for baseline from this thesis were used, the pooled risk of CV death associated with a 5bpm higher time-updated resting heart rate was 11.5% (95% CI 9.1 to 14.0%). The degree of true between-study heterogeneity was much larger (I^2 = 78%) as was the Q-statistic (Q = 33.48, p<0.001).

9.3.2.3 Publication Bias

It was not appropriate to assess publication bias since only the results from the four studies described in Table A7-4 have been published. Tests for publication bias should only be applied when ten or more studies are included in the analysis[275].

Figure 9-9: Forest plot representing the individual and pooled risk of cardiovascular death associated with a 5bpm higher time-updated resting heart rate.



Note that the results from the analyses in Chapters 4 to 8 are the ones that were obtained when baseline resting heart rate was additionally adjusted for.

CHD = Coronary Heart Disease; CI = Confidence Interval; HF = Heart Failure; HR = Hazard Ratio; LVSD = Left-Ventricular Systolic Dysfunction.; MI = Myocardial Infarction.

9.4 Discussion

The meta-analysis presented in Section 9.2 showed that a 5bpm higher baseline heart rate was associated with a 7.9% and an 8.0% increase in the risk of all-cause and CV death, respectively, after adjustment for conventional baseline risk factors, across different patient populations.

In Section 9.3, it was found that a 5bpm higher time-updated resting heart rate was associated with a 12.8% increase in the risk of all-cause death, and a 10.9% increase in the risk of CV death, after adjustment for baseline risk factors as well as baseline resting heart rate (only two out of the ten studies included in the meta-analyses of time-updated heart rate did not additionally adjust for baseline heart rate[204,207]).

These findings demonstrate that measurement of resting heart rate can identify patients at a higher risk of death, irrespective of whether or not they have a pre-existing CV-related condition. Furthermore, the results of the meta-analyses of time-updated heart rate illustrate that, despite knowing an individual's baseline heart rate, updated measurements of heart rate offer additional information about their risk of all-cause and CV death.

There was a substantial degree of true between-study heterogeneity for all analyses. In the meta-analysis of baseline heart rate and risk of all-cause death, the results from Palatini et al. 2002[147], Parodi et al. 2010[159], Antoni et al. 2012[169] and Jensen et al. 2013[170] appeared to account for a considerable proportion of the heterogeneity, and were visually identified as outliers. Each of these studies included only a small number of deaths (Jensen et al. 2013 did not state the number of deaths that occurred[170]) and reported a substantially higher increase in risk of death compared to the other studies. Repeating the analysis without these studies reduced the degree of heterogeneity by 16%, but the heterogeneity that remained was still significant. The pooled HR was reduced to 7.2% (95% CI 6.3 to 8.1%) from 7.9% (95% CI 6.8 to 9.1%). In the meta-

analysis of baseline heart rate and CV death, the result from Antoni et al. 2012[169] was the only apparent outlier. Neither Parodi et al. 2010[159] or Jensen et al. 2013[170] evaluated the risk of CV death. Removing Antoni et al. 2012[169] from the analysis did not alter the degree of heterogeneity; the pooled HR for CV death was slightly reduced from 8.0% (95% CI 6.5 to 9.5%) to 7.8% (6.4 to 9.3%). None of the studies of time-updated heart rate appeared to be outliers in regards to either endpoint.

The heterogeneity was further examined by calculating the summary HR for a 5bpm higher baseline heart rate and the between-study heterogeneity in each population that included two or more studies. In regards to both all-cause and CV death, the subgroup of patients with, or at increased of, some form of vascular disease, appeared to contain no between-study heterogeneity (I^2 = 0%). Similarly, the subgroup of individuals from the general population, and the subgroup of post-MI patients with LVSD or HF, contained no and a very low degree of between-study heterogeneity in regards to CV death and all-cause death, respectively (I^2 = 0% in the general population subgroup for CV death; I^2 = 7.6% in the post-MI patients with LVSD or HF subgroup for all-cause death).

The post-MI or ACS subgroup of patients, which included the studies by Parodi et al. 2010[159], Antoni et al. 2012[169] and Jensen et al. 2013[170], contained the greatest degree of between-study heterogeneity (I^2 = 94%) in relation to all-cause death. Antoni et al. 2012[169] and Jensen et al. 2013[170] were the only studies within this subgroup that included post-PCI patients and evaluated risk associated with discharge heart rate. Parodi et al. 2010[159], on the other hand, was more similar to Noman et al. 2013[164], in that it included post-PCI patients but assessed the risk associated with admission heart rate. Noman et al. 2013[164], however, found that a 5bpm higher admission heart rate was associated with an 8% increase in the risk of all-cause death, while Parodi et al. 2010[159] found that it was associated with a 32% increase in the risk of death. The other two studies included in this subgroup were slightly different from the others, and from

each other. Seronde et al. 2013[171] included post-MI patients, some of whom had undergone reperfusion therapy but some of whom had not, and evaluated the risk associated with discharge heart rate, while Timoteo et al. 2011[161] included patients admitted to hospital with ACS and evaluated the risk associated with admission heart rate.

The subgroup of patients with CHD and LVSD, or HF, or both, also contained a large degree of between-study heterogeneity in regards to both all-cause (I^2 = 87%) and CV death (I^2 = 88.54%). Although each of the four studies in this subgroup included similar populations of patients, each was somewhat different from the others. Fosbol et al. 2010 (DIAMOND-HF)[183], for example, included patients with acute HF with LVSD (in sinus rhythm or AF), whereas the other three studies included patients with chronic HF. The patients included in SHIFT[182] had both ischemic and non-ischemic chronic HF with LVSD and were in sinus rhythm, whereas the patients included in BEAUTIFUL[184] all had CHD with LVSD in sinus rhythm, some of whom also had chronic HF. Vazir et al. 2014[215] included a much more heterogeneous group of patients compared to the other three studies. While all patients had chronic HF, 60% had a reduced EF and 40% had a preserved EF, with 73% in sinus rhythm and 27% in AF.

The summary HRs for all-cause and CV death were similar across all of the subgroups of patients, with the exception of the post-MI or ACS and hypertensive patients in respect to all-cause death. In the post-MI or ACS subgroup, which included the studies by Parodi et al. 2010[159], Antoni et al. 2012[169] and Jensen et al. 2013[170], which reported much higher increases in the risk of death compared to the others, a 5bpm higher baseline heart rate was associated with a 16.9% (95% CI 6.3 to 27.6%) increase in the risk of all-cause death. Similarly, in the hypertensive subgroup which included the study by Palatini et al. 2002[147], which also reported a higher increase in the risk of death compared to the others, 5bpm higher baseline heart rate was associated with an 11.8% (95% CI 3.6 to 20.0%) increase in the risk of all-cause death.

In general, each study included a different population of participants, which is a possible reason for the heterogeneity observed. While all of the studies were prospective in design, some were epidemiological studies of subjects from the general population; others were post-hoc studies of patients with certain diseases and conditions enrolled in clinical trials, some of whom were stable and some of whom were unstable. Another possible contribution to the heterogeneity was the difference in the underlying risk of each population. Additionally, each study followed patients up for different lengths of time, and those with the longest follow-up would have had lower event rates compared to those with the shortest follow-up which would have had much higher event rates. It is also possible that some of the previously published HRs may have contained underlying non-proportionality, and thus would have been dependent on length of follow-up. The previously published HRs calculated using time-updated heart rate are less likely to contain underlying non-proportionality since the updated measurements of heart rate pick up changes in the risk of patients at different points in time throughout follow-up. However, individual patient data would be required to explore this possibility further. In addition, studies most likely differed in regards to the events that made up the total number of all-cause and CV deaths. Certain studies may have included a higher number of non-CV deaths, for example, while others may have included a higher number of deaths caused by CV conditions such as HF, MI and stroke. Moreover, each study varied in regards to what covariates were adjusted for in the models. Differences will also have existed with respect to how and when heart rate was measured in each study. Furthermore, the total number of heart rate measurements that were entered into the time-updated heart rate models would have been different in each study, as would the length of time between each measurement. Finally, several of the studies enrolled over 10,000 subjects - when there are a number of large studies included in a meta-analysis, a test for heterogeneity, such as the Q statistic, will likely have excessive power, meaning that it may detect statistically significant heterogeneity that is actually of little practical importance[264,267]. It is further reasoned that, since systematic reviews and meta-analyses always include

studies that differ somewhat in their methodology and clinical characteristics, heterogeneity is inevitable[267,266].

Although the systematic review of Chapter 2 identified a total of 118 studies that investigated the prognostic value of resting heart rate for adverse outcomes, the majority reported results for some form of categorical heart rate measurement, which are more difficult to combine. In addition, deaths from more specific causes and non-fatal outcomes such as MI and stroke were not as consistently reported on compared to all-cause and CV death. Khan et al. 2015[136], however, did recently perform a meta-analysis of seven studies which reported on the association between resting heart rate and risk of incident HF. The pooled RR of incident HF was 1.40 (95% CI 1.19 to 1.64) comparing individuals in the top quartile of resting heart rate to those in the bottom quartile. Further meta-analyses of the association between resting heart rate and risk of other endpoints would be interesting and informative.

9.4.1 Strengths and Limitations

The current meta-analyses are subject to the same limitations as the systemic review in Chapter 2. Namely, that the review was limited to full-text articles that were available in English, and did not search for, or include, studies of risk models that may have included heart rate, but did not highlight its inclusion in the title of the publication. This may have contributed to the observed publication bias for all-cause and CV death in relation to baseline heart rate, since studies that found a significant association between heart rate and risk may have been more likely to highlight its inclusion in the title of the publication. However, the literature search was extensive, and the meta-analyses did include some studies that did not observe a significant association between heart rate and risk, so bias should be limited. One possible reason for the observed publication bias is that there is a true strong effect of baseline resting heart rate on the risk of all-cause and CV death. Even after incorporating theoretical missing studies into the analysis using the trim and fill method, the observed association, while slightly

reduced, remained strongly significant. It was not appropriate to assess publication bias for all-cause or CV death in relation to time-updated heart rate since few of the results had previously been published[275]. Finally, while the post-hoc clinical trial analyses generally excluded treatment-group patients if the treatment directly affected heart rate, other treatment- and placebo-assigned patients may have been on background therapy that affected heart rate. In SHIFT, for example, almost all of the placebo-assigned patients were taking beta-blockers at baseline and throughout the trial. Subjects in the epidemiological studies could also have been taking heart rate-affecting drugs at baseline, or may have started taking such drugs during follow-up. Use of such medications at baseline were usually adjusted for in the models applied, but if an individual began to take such medications during follow-up, this would not have been taken into account in the estimation of the association. Finally, none of the sensitivity analyses were pre-specified.

9.4.2 Chapter Summary and Conclusions

Following on from the systematic review of Chapter 2, this chapter firstly presented meta-analyses of the associations between baseline resting heart rate and risk of death from any cause, and death from CV causes, including the published prospective evidence identified in the review as well as the results from Chapters 4 to 8. Similar meta-analyses of time-updated resting heart rate were also described.

Both an elevated baseline resting heart rate and time-updated resting heart rate, after adjustment for baseline, were associated with an increase in the risk of death from all-causes and CV causes across a variety of populations. These findings emphasise the potential that heart rate has for assessing future risk of death in both healthy individuals and disease-specific groups.

The subsequent and final chapter, Chapter 10 discusses the thesis as a whole.

Chapter 10

Discussion

10.1 Background, Justification and Overview

Heart rate is inversely correlated with life span across mammal species, with humans being an outlier to the general pattern, having a longer lifespan than would be expected given their average heart rate[2]. The most likely explanation of this is that humans have been able to extend their lives through improvements to living standards, healthcare, food production and the general application of modern scientific techniques. In the last 100 years alone, Western man has been able to increase life expectancy by around 30 years[5]. During the 20th century, aside from access to more nutritious diets, cleaner drinking water, and vaccines that prevent potentially life-threatening infectious diseases, techniques and treatments found to effectively intervene in the process of heart disease were discovered. Nevertheless, CV disease remains to be one of the leading causes of death in the Western world[8,10,11].

Resting heart rate has been shown to independently predict the development of established risk factors for CV disease such as hypertension, diabetes, and kidney disease. In addition, other risk factors such as smoking, excessive consumption of alcohol, and leading a sedentary lifestyle, have been shown to increase heart rate. Furthermore, the systematic review of studies that assessed resting heart rate as a prognostic risk marker, described in Chapter 2, demonstrated that an elevated heart rate is associated with an increase in the risk of death and adverse CV events, in a number of different populations, independent of other risk factors.

In view of this evidence, and the fact that it can be inexpensive and simple to measure, resting heart rate as a risk marker is given less consideration in clinical practice than perhaps it should be. The ESC guidelines relating to CV disease prevention in clinical practice[31], diabetes[217], arterial hypertension[218], stable CHD[219], STEMI[220], and HF[221], as

well as the ACC/AHA guidelines for stable CHD[222] and CABG surgery[223], currently recognise elevated heart rate as an indicator of risk. However, only the ESC guidelines for CV disease prevention in clinical practice, and the management of arterial hypertension, recommend that heart rate be measured as part of the routine physical examination for risk assessment[31,218]. In addition, only the NICE guidelines for the management of ACS, and unstable angina and NSTEMI, mention that formal assessment of risk should include a physical examination where heart rate is measured, alongside blood pressure[224,225]. Moreover, elevated resting heart rate does not appear to be given consideration in the management of post-stroke patients. Neither the NICE guidelines for the management of stroke or TIA[280], or the AHA/ASA guidelines for the prevention of stroke in post-stroke or TIA patients[281], mention heart rate. Furthermore, the ASA and ESO guidelines for the management of ischemic stroke and TIA[282,283] only mention that heart rate should be measured as part of the initial examination, alongside measurement of other vital signs such as temperature and blood pressure.

The majority of studies that were identified in the systematic review of Chapter 2 evaluated the risk associated with resting heart rate measured at a single point in time at the beginning of follow-up using Cox proportional hazards regression. Seven of the studies included in the review examined the prognostic value of multiple heart rate measurements gathered over the duration of follow-up, entered into the extended Cox proportional hazards model[205] as a single time-dependent variable, often referred to as time-updated heart rate. The studies by Vazir et al 2014[215] and Ho et al. 2014[204] showed that time-updated heart rate was associated with adverse events where baseline heart rate was not.

One of the reasons physicians may not give much consideration to heart rate as an indicator of risk is because it can be influenced by a number of different factors. Aside from smoking, alcohol consumption, and physical activity, heart rate can be affected by blood pressure[60,61], gender[62-64], and various conditions, such as anxiety, pain,

dehydration, fever, and CV diseases, such as CHD, MI and HF[65]. If blood cannot travel as easily through the vessels because of a partial occlusion, or if the heart muscle has been damaged and cannot pump as effectively as it once could, the heart attempts to maintain adequate cardiac output by increasing the heart rate[66,67]. It is reasonable to suppose then that a single baseline heart rate measurement may not adequately predict the risk of experiencing an adverse outcome many years in the future. Taking updated measurements of heart rate into account could supply a more appropriate estimate of the risk at any given time. The predictive value of time-updated heart rate measurements may therefore be more pertinent to clinical practice than that of a single heart rate measurement, and further studies of the relationship between time-updated heart rate and risk could motivate medical practitioners to give more consideration to regular assessment of heart rate, an approach that is not currently mentioned in the guidelines.

The study by Khan et al. 2015[136] recently applied meta-analysis techniques to the exploration of the relationship between resting heart rate and risk, and was the only study found in the review of Chapter 2 to use such methods. Another reason that heart rate is not given much consideration in clinical practice may be because studies often include specific populations of subjects, and so general conclusions about its effect as a risk marker cannot be made. Meta-analysis can be used can be used to calculate a single more powerful estimate of the effect of a risk marker by combining the results from different studies. It can also be used to assess consistency of effect across individuals from different populations.

In addition, the majority of studies identified in the review analysed the risk associated with an elevated heart rate in subjects from the general population, often with no evidence of existing CV disease or CHD.

Accordingly, this thesis further examined the role of resting heart rate as a risk marker by performing new analyses of data from nine clinical trials, with the aim of highlighting

its importance as an indicator of risk. Specifically, in Chapter 4, Section 4.3, and Chapters 5 to 8, both the original[74] and extended Cox model[205] were used to assess the predictive value of baseline and time-updated resting heart rate for death and other adverse outcomes. In Chapter 4, Section 4.2, and Chapter 8, Section 8.4, pooled individual patient meta-analyses were performed. The discrimination and calibration of the models applied in Chapters 4 to 8 were evaluated using Harrell's C-statistic[228,229] and likelihood ratio tests, respectively. Finally, following on from the systematic review presented in Chapter 2, meta-analyses of the risk of death from any cause and death from CV causes were presented in Chapter 9 Sections 9.2 and 9.3.

10.2 Main Findings

10.2.1 Associations Between Resting Heart Rate and Risk

Each of the nine trials newly analysed in this thesis recorded data on all-cause deaths, CV deaths and hospitalisations for HF, with the exception of PERFORM which did not report on hospitalisation for HF in its population of post-stroke or -TIA patients. In Chapter 4, an elevated baseline heart rate was seen to be associated with an increase in risk of each of these endpoints in the large pooled population of patients who had recently experienced an MI, and had LVSD, HF or both. In the much smaller CAPRICORN placebo population of post-MI patients with LVSD, no associations between baseline heart rate and risk of all-cause or CV death were observed. However, an elevated time-updated heart rate was associated with an increase in risk of both endpoints, even after adjustment for baseline or the previous heart rate measurement. Both elevated baseline and time-updated heart rates, unadjusted or adjusted for baseline or previous heart rate, were associated with an increase in the risk of hospitalisation for HF. In the EUROPA, PROSPER, PERFORM, BEAUTIFUL and SHIFT populations, as well as the pooled LV dysfunction population of BEAUTIFUL and SHIFT patients, elevated baseline and time-updated heart rates were also associated with an increase in the risk of all-cause death and CV death, regardless of whether baseline or previous heart rate

measurements were adjusted for. Similar results were found for hospital admission for HF in the PROSPER, BEAUTIFUL, SHIFT and LV dysfunction populations, and incorporating time-updated heart rate strengthened each of these associations. Thus, despite knowing the baseline or previous heart rate measurement, current heart rate measurements contribute additional information about the risk of each of these endpoints. In EUROPA, no association between baseline heart rate and risk of hospital admission for HF was discovered, but elevated time-updated heart rate was associated with an increase in risk irrespective of adjustment.

The relationship between resting heart rate and risk of a number of other causes of death were additionally evaluated for some studies. In the CAPRICORN placebo population, the risk of sudden death was assessed, but no relationship between heart rate and risk was observed. The risk of death from HF was also investigated in the CAPRICORN population, and in the SHIFT population of patients with chronic HF and LVSD. In CAPRICORN, only an elevated continuous baseline heart rate was associated with a higher risk of death due to HF, whereas in SHIFT both elevated baseline and time-updated heart rates were associated with an increase in risk. Similarly, in the PROSPER population of older individuals with, or at an increased risk of, vascular disease, elevated baseline and time-updated heart rates were associated with an increase in the risk of CHD death and non-vascular death. On the other hand, only time-updated heart rate adjusted for baseline or previous heart rate was associated with an increase in the risk of cancer death in PROSPER. The risk of stroke death was also explored, but no association with heart rate was seen. Furthermore, the risk of cardiac death was assessed in the PERFORM and BEAUTIFUL populations. No association between baseline heart rate and risk of cardiac death was observed in PERFORM. However, higher time-updated heart rate, and time-updated heart rate adjusted for baseline, was associated with an increase in risk. In the BEAUTIFUL placebo population of patients with CHD and LVSD, some of whom also had HF, both elevated baseline and time-updated heart rates were associated with an increase in risk. In SHIFT, PROSPER

and BEAUTIFUL, including time-updated heart rate measurements strengthened the associations with death due to HF, CHD death and non-vascular death, and cardiac death, respectively.

Information on MI-related endpoints was common across the trials. In the pooled acute-MI population, an elevation in baseline heart rate was associated with an increase in risk of fatal or non-fatal MI. In the PERFORM population, both elevated baseline and time-updated heart rates were associated with an increase in risk of fatal or non-fatal MI, while only a higher time-updated heart rate was associated with a higher risk of non-fatal MI. In each instance, the association with time-updated heart rate did not retain its significance when baseline or previous heart rate was adjusted for. Similarly, in the PROSPER population, only elevated time-updated heart rate, and time-updated heart rate adjusted for baseline, was associated with an increase in risk of non-fatal MI. In BEAUTIFUL, SHIFT and the pooled LV dysfunction population, while no association between an elevated continuous baseline heart rate was observed, time-updated heart rates both unadjusted and adjusted for baseline or previous heart rate measurements were associated with an increase in risk of hospital admission for MI. In contrast, only baseline as opposed to time-updated heart rate was associated with an increase in the risk of non-fatal MI in the CAPRICORN placebo population. No associations between either baseline or time-updated heart rate and risk of fatal or non-fatal MI was observed in the EUROPA population.

The risk of stroke-related endpoints was also evaluated in the pooled acute-MI, EUROPA, PROSPER and PERFORM populations. In comparison to the endpoints previously discussed, the results for such endpoints are much less consistent. In the pooled acute-MI and EUROPA populations, for example, no associations between heart rate and the risk of fatal or non-fatal stroke were observed. Moreover, in the PROSPER population, an association between time-updated heart rate adjusted for baseline and the risk of fatal or non-fatal stroke, non-fatal stroke, and the combined endpoint of fatal or non-

fatal stroke or TIA, was only observed in patients taking anti-arrhythmic drugs and/or beta-blockers at baseline. In addition, patients with a heart rate in the highest third of the distribution were found to be at a lower risk of TIA compared to those with a heart rate in the lowest third. On the other hand, in the PERFORM population, while no significant association between baseline heart rate and risk of fatal or non-fatal stroke, fatal or non-fatal ischemic stroke, or non-fatal ischemic stroke was observed, higher time-updated heart rate was associated with a higher risk of each of these endpoints.

Several other endpoints were investigated in certain studies. In the EUROPA population, the risk of cardiac arrest and unstable angina were assessed. No associations between heart rate and risk of unstable angina were observed. Higher time-updated heart rate adjusted for baseline heart rate, and previous heart rate measurements, was associated with an increase in the risk of cardiac arrest. The risk of hospitalisation due to cardiac causes was examined in the PERFORM population, and while it was not found to be associated with baseline heart rate, a higher time-updated heart rate was associated with an increase in risk, irrespective of adjustment for the other heart rate variables. Finally, the risk of revascularisation was evaluated in the EUROPA, PROSPER and BEAUTIFUL populations. A higher resting heart rate was associated with a decrease in the risk of revascularisation in EUROPA and PROSPER, and an increase in risk in BEAUTIFUL. EUROPA and PROSPER occurred in the late 1990s, when revascularisation was mainly used to treat angina, while BEAUTIFUL occurred in the mid-2000s, when revascularisation was more frequently used to treat acute MI[276]. Thus it was suggested that the difference in findings may have been because revascularisation was more likely to be related to angina in the EUROPA and PROSPER trials, and emergency events such as acute MI in the BEAUTIFUL trial.

In the discussion of Chapter 2, Section 2.4, Table 2-1 and Table 2-2 provided a simplified illustration of the evidence presented in the baseline and multiple heart rate measurement studies, respectively, in relation to each of the main adverse outcomes and populations of subjects. The cells that contained one or more black shapes

indicated where an association between some form of resting heart rate variable and risk had been established, using a multivariate-adjusted model; the blank cells indicated where an association had yet to be established using such a model. Each shape represented a different resting heart rate variable: a rectangle represented baseline resting heart rate; a circle represented a change in resting heart rate over time; a triangle represented the mean of multiple heart rate measurements gathered over time; and a star represented time-updated resting heart rate. To highlight the contributions of the thesis to the field, Table 10-1 provides a similar summary and comparison of the evidence that was previously identified by the review, and the evidence which was presented in Chapters 4 to 8 of the thesis: the previous evidence is represented by the shaded shapes, and the evidence from the thesis is represented by the solid black shapes.

As can be seen from Table 10-1, new associations between baseline resting heart rate and risk of: HF death and recurrent MI were observed in post-MI patients; cardiac death was observed in patients with LVSD; CHD death was observed in patients with vascular disease; and revascularisation was observed in patients with CHD, and vascular disease. Additionally, new evidence of an association between time-updated resting heart rate and risk of numerous outcomes was demonstrated in each of the populations examined in thesis, where measurements of resting heart rate had been recorded over follow-up.

Table 10-1: A summary and comparison of the evidence previously identified in the systematic review of Chapter 2, and the evidence presented in Chapters 4 to 8 of the thesis, on the associations between both baseline and multiple resting heart rate measurements, and risk of each of the main adverse outcomes, in the populations of subjects discussed in the review and in Chapters 4 to 8.

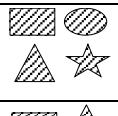
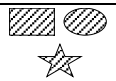
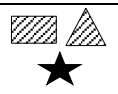
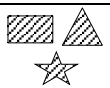
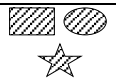
Outcome	Category of Subjects										
	General	Diabetes	Hypertension	CHD	Post-MI/ACS	HF	LV Dysfunction	CABG	Vascular Disease	Post-Stroke	Kidney Disease
Deaths											
All-cause death											
CV/vascular death											
Cardiac death											
CHD death											
HF death											
Sudden death											
Stroke death											

Table continued and footnote provided on the following page.

Table 10-1 (Cont.): A summary and comparison of the evidence previously identified in the systematic review of Chapter 2, and the evidence presented in Chapters 4 to 8 of the thesis, on the associations between both baseline and multiple resting heart rate measurements, and risk of each of the main adverse outcomes, in the populations of subjects discussed in the review and in Chapters 4 to 8.

Outcome	Category of Subjects										
	General	Diabetes	Hypertension	CHD	Post-MI/ACS	HF	LV Dysfunction	CABG	Vascular Disease	Post-Stroke	Kidney Disease
Other											
CV disease/event	▨ △ ☆			▨	▨	▨	▨		▨ △		▨
Cardiac event				★						★	
CHD	▨ ☆		▨								
MI	▨				■	☆	▨ ★		★	▨ ★	
Revascularisation				■ ★			▨ ★		■ ★		
HF	▨ △ ☆		☆	▨ ★	▨ ★	▨ ☆	▨ ★		▨ △ ★		
Stroke	▨				▨	☆			△ ★	▨ ★	

The cells that contain one or more shapes indicate where an association between some form of resting heart rate variable and risk has been established, using a multivariate-adjusted model; the blank cells indicate where an association has yet to be established using such a model. Each shape represents a different resting heart rate variable: a rectangle represents baseline resting heart rate; a circle represents a change in resting heart rate over time; a triangle represents the mean of multiple resting heart rate measurements gathered over time; and a star represents time-updated resting heart rate. The previous evidence is represented by the shaded shapes, and the evidence from the thesis is represented by the solid black shapes. The 'Other' events include combinations of both fatal and non-fatal events, and non-fatal events only.

10.2.2 Model Discrimination and Calibration

In the main, models in which the resting heart rate variable was found to be significantly associated with risk of outcome had better discrimination and calibration than the model excluding resting heart rate. This indicates that these models had a greater ability to differentiate between subjects who experienced the event from those that did not, and that the predictions from these models more accurately reflected the observed event rates, compared to the model not including resting heart rate. In some cases, where baseline resting heart rate was not found to be associated with risk of the event, while an elevated time-updated resting heart rate was, the addition of the baseline heart rate variable did increase the C-statistic of the model, but only the addition of the time-updated heart rate variable resulted in statistically significant improvements in calibration. Overall, the models including time-updated heart rate additionally adjusted for the baseline or previous heart rate measurement generally yielded the highest and similar C-statistics, and thus had the best discriminative ability.

10.2.3 Evidence of Non-Proportionality of Hazards

Non-proportionality of the effect of an elevated resting heart rate was detected for some of the outcomes in several of the studies. In the pooled acute MI population, non-proportionality of an elevated baseline heart rate was observed for all of the outcomes. The effect of an elevated continuous baseline heart rate was also found to be non-proportional in relation to all-cause death in the PROSPER population. Furthermore, in the BEAUTIFUL, SHIFT and pooled LV dysfunction populations, non-proportionality was observed in regards to hospital admission for HF, and the combinations of CV death or hospital admission for HF, and CV death or hospital admission for HF or MI. A higher heart rate was also found to have a non-proportional association for all-cause and CV hospital admissions in the SHIFT population. In each case, plots of the Schoenfeld residuals demonstrated that the effect of an elevated heart rate was highest at the beginning of follow-up, and then declined over time. These findings could potentially

impact the interpretation of results from previous publications, as the proportional hazards assumption is not always assessed. Thus, previous studies have may have reported results of the 'average' effect of heart rate over time, possibly containing some underlying non-proportionality.

10.2.4 Meta-Analyses

In Chapter 9, the meta-analyses of the predictive value of baseline and time-updated resting heart rate demonstrated that elevated resting heart rate is associated with a higher risk of death across individuals from the general populations and patients with different pre-existing conditions. A 5bpm higher baseline heart rate was associated with a 7.9% and an 8.0% increase in the risk of all-cause and CV death, respectively (both $p<0.001$). Furthermore, adjusting for baseline heart rate in eight of the ten studies included in the analysis, a 5bpm higher time-updated heart rate was associated with a 12.8% ($p<0.001$) and a 10.9% ($p<0.001$) increase in the risk of all-cause and CV death, respectively.

10.3 Clinical Implications

These findings should increase support for assessment of resting heart rate in all types of individuals. Given that an elevated time-updated heart rate is in some cases associated with risk of events where baseline heart rate is not, and can provide additional information about the risk of certain events despite knowledge of baseline or previous heart rate measurements, regular assessment of resting heart rate should be considered by physicians as a method of identifying individuals at higher risk.

The addition of resting heart rate to the models where resting heart rate was found to be associated with risk of outcome improved both discrimination and calibration, and in general, the models including time-updated heart rate along with baseline or the previous heart rate measurement had the highest and similar C-statistics, and thus the greatest discriminative ability. The improvements in discrimination with the addition of

resting heart rate - even time-updated resting heart rate – however, were modest. While it is compelling to imagine the use of repeated measurements of resting heart rate in general practice, to identify individuals at higher risk of death and adverse cardiovascular events, prospective validation studies in different populations would very likely be required before clinical application would become a reality. It is possible that the addition of time-updated resting heart rate would make only an incremental improvement to the discriminative and predictive abilities of already established risk scores, although further studies would have to be carried out to properly assess the impact of its contribution. Nonetheless, resting heart rate can be measured simply using pulse palpation, and so would be easy to obtain in routine clinical practice. Therefore, the findings that the addition of time-updated resting heart rate does improve the discrimination and calibration of models for certain outcomes including death, even if only modestly, strengthens the case that it could be added to traditional risk models, and should incite medical practitioners to routinely measure patients' resting heart rate in clinical practice as a means of assessing their risk of adverse events.

The findings of the thesis, however, are of particular importance, and have greater implications for the clinical management of patients with pre-existing disease. It has been shown that elevated resting heart rate measurements gathered over time are associated with higher risk of adverse events in post-MI and -stroke patients, and those with stable CHD, vascular disease, and LVSD. Thus, in sicker patients with such conditions, regular assessment of resting heart rate could be used to guide medical decision-making. An elevated, or increasing heart rate over time, could be used as a tool, potentially alongside other established risk scores, to help doctors identify patient deterioration or those at higher risk who might benefit from more intensive monitoring or treatment re-evaluation. While a higher heart rate could simply be a sign of infection or dehydration (ADD REFs), for example, further investigation would no doubt be of some benefit and could prevent patient decline. In addition, the re-evaluation

and possible alteration of a patient's treatment regime could result in the implementation of more appropriate therapies, which could prevent both fatal or non-fatal events from occurring in the future.

10.4 The Recommended Method for Assessing Risk Associated with Resting Heart Rate

The thesis explored associations between both baseline and time-updated resting heart rate, and risk of death and other adverse events. Risk was compared between baseline and time-updated heart rate groups, and the risk associated with continuous baseline and time-updated heart rate was evaluated. Additional models assessing time-updated resting heart rate were fitted with adjustment for (i) baseline resting heart rate group or baseline heart rate as appropriate, and (ii) the previous heart rate group or the previous measurement. This was done to determine whether the updated heart rate measurements added prognostic value to the information already provided by the baseline or previous heart rate measurement. Finally, in order to assess the risk associated with the direction of change in heart rate at each follow-up visit, models were fitted for 'time-updated categorical heart rate patterns' (see Chapter 3 Section 3.3.3.3 for details), which accounted for the change in heart rate between visits, while also adjusting for the previous visit measurement (which was absorbed into the grouping).

An elevated time-updated heart rate was found to be associated with risk of events where baseline heart rate was not, and provided additional information about the risk of certain events, despite knowledge of baseline or previous heart rate measurements. Furthermore, the models including time-updated heart rate along with baseline or the previous heart rate measurement generally had the highest and similar C-statistics, as well as significantly better calibration than the model not including any of the resting heart rate variables. This suggests that these models had a greater ability to differentiate between subjects who experienced the event from those that did not, and

that the predictions from these models more accurately reflected the observed event rates, compared to the model not including resting heart rate.

Currently, despite the extensive research on resting heart rate as a risk marker for death and adverse CV events, there is no objective cut-off level for the definition of a high resting heart rate, also known as tachycardia[72]. Thus, in each of the different studies presented in the thesis, the categorical heart rate cut-off point was chosen somewhat arbitrarily on the basis of previously published studies (see Chapter 3 Section 3.3.1 for details). The textbook definition of tachycardia is a resting heart rate greater than 100bpm[284]. However, this is not an appropriate cut-off value for a high resting heart rate from an epidemiological point of view - below which an individual's heart rate would be considered normal – since essentially all of the observational studies and post-hoc clinical trial analyses reviewed in Chapter 2, in addition to the studies presented in the thesis, demonstrated that individuals with resting heart rates well below the 100bpm threshold were at a higher risk of death and adverse CV events[72].

Therefore, the models including continuous time-updated resting heart rate adjusted for either baseline or the previous heart rate measurements, also treated as continuous variables, would appear to be the best models to use for the assessment of risk associated with resting heart rate: since adjustment for baseline heart rate is simpler and possibly more intuitive, it is recommended that this method be used.

10.5 Future Research

In the discussion section of each analysis chapter, Chapters 4 to 9, possible future studies needed to clarify unresolved issues were mentioned. Firstly, in Chapter 4, no associations between an elevated resting heart rate and risk of fatal or non-fatal stroke or sudden death were observed in post-MI patients. Similarly, in Chapters 5 and 6 respectively, no associations were observed between an elevated resting heart rate and risk of stroke in the EUROPA population of patients who had CHD without HF, or risk of

stroke death in the PROSPER population of elderly individuals with, or at an increased risk of, vascular disease. In each case, the number of events was low, and so there may have been insufficient statistical power to detect associations. In addition, none of the studies of subjects with ACS, or with, or at increased risk of, vascular disease, identified in Chapter 2, investigated the relationship between heart rate and risk stroke or sudden death, or stroke death, respectively. Moreover, the studies by Diaz et al. 2005 and Ho et al. 2010, which enrolled patients with CHD, previously examined the relationship between baseline resting heart rate and stroke and observed no association. Thus, further prospective studies or post-hoc analyses of clinical trials with longer follow-up periods and larger sample sizes of such patients, where more of these events would be likely to occur, are needed to elucidate whether a relationship between resting heart rate and risk of these events exists or not.

Additional studies of the association between resting heart rate and risk of MI and unstable angina in patients with CHD both without HF or LVSD, and with HF or LVSD, are also required. Neither the EUROPA analysis of CHD patients without HF presented in Chapter 5, or the previous studies by Diaz et al. 2005 and Ho et al. 2010, observed any associations between resting heart rate and the risk of MI, or unstable angina. Conversely, an elevated resting heart rate was associated with a higher risk of MI and the combined endpoint of MI or unstable angina in the BEAUTIFUL analysis of CHD patients with LVSD, some of whom also had HF, presented in Chapter 8. This suggests that there could be differences in the association between resting heart rate and risk of MI or unstable angina in CHD patients without HF or a reduced EF, and CHD patients with HF or reduced EF, but because these seem to be the only four studies which have examined such associations in such patients, further similar studies are required before conclusions can be drawn.

Likewise, as mentioned in Section 10.2.1, a higher resting heart rate was associated with a decrease in the risk of revascularisation in EUROPA and PROSPER, and an increase in risk in BEAUTIFUL. It was proposed that this may have been because

revascularisation was more likely to be related to angina in the EUROPA and PROSPER trials, which took place in the late 1990s, and emergency events such as acute MI in the BEAUTIFUL trial which took place in the mid-2000s, when revascularisation was more frequently used to treat acute MI[276]. It would appear that these are the only three analyses which have investigated this association in patients with CHD: therefore, further post-hoc analyses of clinical trials which enrolled patients with CHD both without HF or LVSD, and with HF or LVSD, recorded information on revascularisation events, and that took place at different times from the beginning of the 90s to the present day, would need to be performed to test this hypothesis.

In general, as can be seen from Table 10-1, studies of the association between resting heart rate and risk of adverse events in patients with diabetes and kidney disease, and those who have undergone, or are about to undergo, CABG surgery, are still lacking. In addition, future prospective studies should strive to measure subjects' resting heart rates throughout follow-up at regular intervals, and along with post-hoc analyses of clinical trials that measured resting heart rate throughout follow-up, should analyse associations between both baseline and time-updated heart rate and risk.

At the moment, however, the cost-effectiveness of measuring heart rate to assess patients' risk is unknown. While measurement of pulse may be relatively cheap, and could be done by individuals without the assistance of a healthcare professional, measurement using ECG would be more expensive and ECGs are not commonly recorded in primary care. In addition, the optimal frequency of heart rate assessment has yet to be explored. This thesis investigated the prognostic value of time-updated heart rate in six different trial populations. In each trial, heart rate values were obtained at pre-determined visits that took place at different points in time during follow-up. Currently, it is not known if measuring heart rate more frequently throughout follow-up would enhance the predictive value of resting heart rate, or whether measuring heart rate less frequently would be just as useful but more cost-effective.

Furthermore, the role of continuously recording resting heart rate, for example, when individuals are at home, has had little investigation. It could contribute similarly valuable prognostic information to that acquired by measurement of resting heart rate at pre-determined visits. In the study by Hozawa et al. 2004[285], participants were provided with a device that allowed self-measurement of heart rate, and asked to measure their resting heart rate at home, in the morning and evening, over the course of four weeks. Morning and evening home heart rate was then defined as the mean of all morning and evening measurements acquired for each individual, respectively. A 5bpm higher morning home heart rate was associated with a 17% ($p = 0.003$) and 20% ($p = 0.01$) increase in the risk of cardiovascular mortality, and cerebrovascular mortality, respectively. Similar results were observed for a 5bpm higher evening home heart rate. The study was not able to directly compare the prognostic value of home heart rate with that of clinic heart rate, however, as clinic heart rate measurements were not obtained. Thus, further studies comparing the predictive value of self-measured heart rate at home with that of heart rate measured in a clinical setting would provide further insight into the usefulness of home heart rate for assessing cardiovascular risk.

The potential benefit of measuring a risk marker for CV disease, apart from the general information this provides on an individual patient, is to identify patients who would have a high enough risk to justify the cost of implementing a pharmacological or other risk reduction treatment, or to identify those in whom modification of that particular risk marker would confer benefit. Although there is a clear association between an elevation in heart rate and an increase in risk, lowering heart rate, unlike lowering other risk markers such as cholesterol and blood pressure, has only been shown definitively to reduce the risk of adverse outcomes in patients with a resting heart rate greater than or equal to 70bpm, in sinus rhythm, with LVSD and chronic HF[32]. In the SHIFT trial, treatment with ivabradine, the first of a new class of drugs that lowers heart rate without any other direct effects on the CV system, reduced risk of the primary outcome of CV death or hospital admission for worsening HF by 18% (95% CI 10

to 25%, p<0.0001)[32]. Treatment with ivabradine also reduced risk of admission to hospital for MI, admission to hospital for MI or unstable angina, and coronary revascularisation by 36%, 22% and 30%, respectively, in a subgroup of patients with a heart rate greater than or equal to 70bpm in the BEAUTIFUL trial[248]. However, as there was no impact on the primary endpoint in the total trial population, the finding is not considered as definitive. On the other hand, in the recent SIGNIFY trial of patients with CHD without HF, treatment with ivabradine was not associated with a reduction in risk of any of the outcomes evaluated, and there was a suggestion of a possible increase in risk in the subgroup of participants with angina[286]. Further assessment of heart rate reduction with ivabradine in relation to risk of adverse outcomes in individuals with other conditions would be informative. However, given the results of SIGNIFY this is unlikely to happen. Other drugs, such as beta-blockers, diltiazem and verapamil, lower heart rate, as does smoking cessation and increased exercise. However, as they have other effects on the CV system it is not possible to identify the specific impact on outcomes of their heart rate lowering effects.

Finally, at this moment in time, one of the most important questions for future research to address is what defines a high heart rate. As discussed in Section 10.4, there is currently no objective cut-off value for the definition of a high resting heart rate: the textbook definition of tachycardia – a resting heart rate greater than 100bpm – is not appropriate for epidemiological purposes since virtually all of the research on the association between resting heart rate and risk has shown that risk of adverse outcomes increases at resting heart rates much lower than 100bpm. The optimal method for defining the upper normal limit of a clinical variable is to establish the value at which the benefits of treatment outweigh the risks[72]. However, ivabradine is presently the only drug which lowers heart rate without affecting any other part of the CV system, and as discussed in the previous paragraph, it is unlikely that further assessment of heart rate reduction with ivabradine will take place in the foreseeable future. The evidence from the BEAUTIFUL and SHIFT trials, although somewhat inconclusive,

indicated that patients with a baseline resting heart rate greater than or equal to 70bpm benefited from treatment with ivabradine[32,248,287]. However, approximately 87% and 90% of the patients enrolled in BEAUTIFUL and SHIFT, respectively, were taking beta-blockers at randomisation, and thus their natural resting heart rate would probably have been much higher than their heart rate recorded at baseline. The only other available data on the effect of heart rate reduction in humans can be derived from retrospective analyses of post-MI patients or those with congestive HF[288,289]. Carvedilol has demonstrated favourable effects in individuals with congestive HF but the mortality benefit was only clear in patients with a resting heart rate greater than 82bpm[290]. Nonetheless, these results cannot be transferred to individuals from the general population or those with other forms of pre-existing disease. If researchers were somehow able to overcome these issues in the future, and specify a new definition of tachycardia applicable to all individuals, the public could be informed of the risks associated with a resting heart rate greater than this level. Individuals could then choose to monitor their own resting heart rate, and possibly implement lifestyle changes with the aim of lowering their resting heart rate, or seek medical advice, if they identified that it was consistently above the threshold. As a result, they could potentially lower their risk of developing CV disease, or delay any existing CV disease from progressing to a more dangerous stage.

10.6 Limitations

A limitation of the analyses presented in this thesis was that the data analysed in Chapters 4 to 8 were taken from previous clinical trials, and so the findings may not be generalisable to other populations of patients. However, the trial designs ensured independent endpoint adjudication with well-defined criteria, and standardised measurement of resting heart rate.

10.7 Summary

Using meta-analyses techniques and the extended Cox model that allows for assessment of time-dependent covariates, it has been demonstrated that both elevated baseline and time-updated resting heart rates are associated with an increase in the risk of adverse CV events in patients with varying pre-existing diseases and conditions. In some instances, elevated time-updated heart rate predicts risk of events where baseline heart rate does not. Time-updated heart rate also contributes additional information about the risk of certain events despite knowledge of baseline heart rate or previous heart rate measurements. These findings could encourage medical practitioners to use routine assessment of resting heart rate as a means of identifying individuals at higher risk of adverse events.

Appendices

Appendix 1

Supplementary Tables for Chapter 2

Table A1-1: PRISMA 2009 checklist[94] for the systematic review of heart rate as a prognostic risk marker for mortality and adverse cardiovascular outcomes.

Section/Topic	Item No.	Checklist Item	Reported On Page No.
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	21
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	N/A as thesis chapter as opposed to journal article
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	21
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes and study design (PICOS).	21
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as Web address), and, if available, provide registration information including registration number.	No review protocol, noted as limitation in discussion
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria of eligibility, giving rationale.	23-4
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	22-3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	22-3, and Table A1-2 provided in Appendix 1
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	23
Data collection process	10	Describe the method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	24
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made.	24
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at study or outcome level), and how this information is to be used in any data synthesis	25

Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the method of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistics) for each meta-analysis.	N/A
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selecting reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	25-6, Figure 2-1
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations.	26-55, Tables A1-4 to A1-14 and Tables A1-16 and A1-17
Risk of bias within studies	19	Present data on risk bias of each study and, if available, any outcome-level assessment (see item 12).	26 and 49, Tables A1-3 and A1-15
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of inconsistency.	26-55
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16).	N/A
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, uses, and policy makers).	55-61
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias).	61-2
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	63
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	PhD funded by Servier; systematic review not specifically funded

Table A1-2: Search strategy applied using Ovid to simultaneously search MEDLINE (1946-April 2015) and Embase (1947-April 2015) for studies that focused on the prognostic value resting heart rate for mortality and adverse cardiovascular outcomes.

Search	Search Term(s)	Result
#1	"heart rate" OR "pulse rate" OR "pulse"	32,607
#2	"risk" OR "hazard" OR "prognos**" OR "predict**" OR "event**" OR "outcome**" OR "adverse" OR "death" OR "mortality" OR "survival"	1,023,274
#3	#1 AND #2	3,330
#4	#3 de-duplicated with Field Preference "has abstract" with Database Preferences 1. Embase and 2. MEDLINE	1,977
#5	#4 NOT ("paediatric" OR "pediatric" OR "fetal" OR "foetal" OR "fetus" OR "foetus" OR "infant" OR "child" OR "newborn" OR "baby" OR "babies")	1,762
#6	#5 NOT ("pulse pressure" OR "wave**" OR "oxi**" OR "oxy**" OR "energy")	1,201
#7	#6 NOT ("react**" OR "respons**" OR "dynamic**" OR "turbul**")	1,047
#8	#7 NOT ("heart rate varia**" OR "heart rate recovery" OR "maxim**")	569
#9	#8 NOT "ST segment"	556

All searches were Title searches, and specified the following limits: English Language; Full Text; Human; and Humans.

Table A1-3: The quality of each of the 'baseline heart rate' studies, according to the Newcastle Ottawa Scale[96].

Study	Population	Selection	Comparability	Outcome	Total	
Dyer et al. 1980[101]	General	***	**	**	*******	7
Kannel et al. 1987[108]	General	****	**	**	********	8
Gillum et al. 1991[109]	General	***	**	***	********	8
Filipovsky et al. 1992[102]	General	***	**	**	*******	7
Shaper et al. 1993[107]	General	****	**	**	********	8
Greenland et al. 1999[110]	General	****	**	***	*********	9
Palatini et al. 1999[111]	General	***	**	**	*******	7
Benetos et al. 1999[112]	General	***	**	**	*******	7
Reunanen et al. 2000[113]	General	****	**	**	********	8
Kristal-Boneh et al. 2000[103]	General	***	**	***	********	8
Seccareccia et al. 2001[104]	General	***	**	***	********	8
Fujiura et al.2001[105]	General	***	**	**	*******	7
Kado et al. 2002[123]	General	***	**	**	*******	7
Chang et al. 2003[97]	General	***	**	*	******	6
Perk et al. 2003[114]	General	****	**	**	********	8
Okamura et al. 2004[115]	General	****	**	***	*********	9
Theobald and Wandell 2007[116]	General	***	**	**	*******	7
Cacciatore et al. 2007[125]	General	***	**	***	********	8
Kizilbash et al. 2008[117]	General	***	**	***	********	8
Tverdal et al. 2008[100]	General	*****	**	***	*********	9
Hsia et al. 2009[124]	General	****	**	**	********	8
Fagundes and Castro 2010[126]	General	**	**	***	*******	7
Nauman et al. 2010[118]	General	****	**	**	********	8
Cooney et al. 2010[119]	General	****	**	**	********	8
Batty et al. 2010[98]	General	***	**	**	*******	7
Mao et al. 2010[120]	General	****	**	***	*********	9
Jensen et al. 2011[127]	General	****	**	**	********	8
Jensen et al. 2012[128]	General	****	**	**	********	8
Pfister et al. 2012[129]	General	***	**	**	*******	7

O'Hartaigh et al. 2012[130]	General	***	**	**	*******	7
Teodorescu et al.2013[137]	General	****	**	***	*********	9
Pittaras et al. 2013[131]	General	***	**	**	*******	7
Johansen et al. 2013[132]	General	***	**	**	*******	7
Jensen et al. 2013[106]	General	***	**	**	*******	7
Opdahl et al. 2014[66]	General	****	**	**	********	8
Aladin et al. 2014[133]	General	***	**	**	*******	7
Wang et al. 2014[134]	General	****	**	*	*******	7
Carlson et al. 2014[99]	General	***	**	***	********	8
Makita et al. 2014[121]	General	***	**	**	*******	7
Woodward et al. 2014[135]	General	****	**	**	********	8
Vassalle et al. 2014[122]	General	***	**	**	*******	7
Khan et al. 2015[136]	General	***	**	**	*******	7
Stettler et al. 2007[140]	Diabetic	***	**	***	********	8
Hillis et al. 2012[141]	Diabetic	***	**	**	*******	7
Miot et al. 2012[142]	Diabetic	***	**	**	*******	7
Gillman et al. 1993[144]	Hypertensive	****	**	**	********	8
Palatini et al. 2002[147]	Hypertensive	***	**	**	*******	7
King et al. 2006[145]	Hypertensive	***	**	**	*******	7
Salles et al. 2013[146]	Hypertensive	***	**	**	*******	7
Diaz et al. 2005[148]	CHD	***	**	**	*******	7
Ho et al. 2010[149]	CHD	***	**	**	*******	7
Anselmino et al. 2010[150]	CHD	****	**	*	*******	7
Ortiz et al. 2010[151]	CHD	****	**	**	********	8
Hjalmarson et al. 1990[152]	Post-MI/ACS	****	**	*	*******	7
Disegni et al. 1995[153]	Post-MI/ACS	***	**	**	*******	7
Zuanetti et al. 1998[154]	Post-MI/ACS	***	**	**	*******	7
Kovar et al. 2004[155]	Post-MI/ACS	***	**	**	*******	7
Mauss et al. 2005[156]	Post-MI/ACS	****	**	*	*******	7
Honda et al. 2010[157]	Post-MI/ACS	***	**	***	********	8
Parodi et al. 2010[159]	Post-MI/ACS	****	**	*	*******	7

Bangalore et al. 2010[160]	Post-MI/ACS	****	**	**	********	8
Timoteo et al. 2011[161]	Post-MI/ACS	****	**	*	*******	7
Han et al. 2012[162]	Post-MI/ACS	****	**	**	********	8
Facila et al. 2012[163]	Post-MI/ACS	****	**	***	*********	9
Antoni et al. 2012[169]	Post-MI/ACS	****	**	**	********	8
Noman et al. 2013[164]	Post-MI/ACS	****	**	**	********	8
Jensen et al. 2013[170]	Post-MI/ACS	***	**	**	*******	7
Davidovic et al. 2013[165]	Post-MI/ACS	***	*	*	*****	5
Li et al. 2013[166]	Post-MI/ACS	***	**	**	*******	7
Seronde et al. 2014[171]	Post-MI/ACS	****	**	**	********	8
Asaad et al. 2014[167]	Post-MI/ACS	****	**	*	*******	7
Salwa et al. 2015[168]	Post-MI/ACS	***	**	**	*******	7
Kapoor and Heidenreich 2010[172]	Heart Failure	***	**	**	*******	7
Castagno et al. 2012[173]	Heart Failure	***	**	**	*******	7
Maeder and Kaye 2012[174]	Heart Failure	***	**	**	*******	7
Bui et al. 2013[177]	Heart Failure	****	**	**	********	8
Habal et al. 2014[178]	Heart Failure	****	**	**	********	8
Bohm et al. 2014[175]	Heart Failure	***	**	**	*******	7
Kaplon-Cieslicka et al. 2014[179]	Heart Failure	****	**	*	*******	7
Takada et al. 2014[176]	Heart Failure	****	**	*	*******	7
Lancellotti et al. 2015[180]	Heart Failure	***	**	**	*******	7
Laskey et al. 2015[181]	Heart Failure	****	**	*	*******	7
Fox et al. 2008[184]	LV Dysfunction	***	**	**	*******	7
Bohm et al. 2010[182]	LV Dysfunction	***	**	**	*******	7
Fosbol et al. 2010[183]	LV Dysfunction	***	**	**	*******	7
Fillinger et al. 2002[185]	Pre- or Post-CABG	****	**	**	********	8
Aboyans et al. 2008[186]	Pre- or Post-CABG	***	**	**	*******	7
Frank et al. 2010[187]	Pre- or Post-CABG	****	**	**	********	8
Bemelmans et al. 2013[188]	Vascular Disease	***	**	***	********	8
Nanchen et al. 2013[138]	Vascular Disease	***	**	**	*******	7
van Kruijsdijk et al. 2014[189]	Vascular Disease	***	**	***	********	8

Bohm et al. 2012[190]	Post-Stroke	***	**	**	*******	7
Fox et al. 2013[191]	Post-Stroke	***	**	**	*******	7
Sandset et al. 2014[192]	Post-Stroke	***	**	**	*******	7
Erdur et al. 2014[193]	Post-Stroke	***	**	**	*******	7
Beddhu et al. 2009[194]	Kidney Disease	***	**	*	******	6
Iseki et al. 2011[195]	Kidney Disease	****	**	**	********	8
Inoue et al. 2012[196]	Kidney Disease	***	**	**	*******	7

Table A1-4: An overview of studies which have investigated baseline resting heart rate as a risk marker in a general population of subjects.

Authors	Year	Study Name	Study Population	No. of Subjects	Follow-up	Type of Heart Rate	Type of Analysis	Outcomes
Dyer et al.[101]	1980	The Chicago People Gas Company study; the Chicago Western Electric Company study; and the Chicago Heart Association Detection Project in Industry	Three groups of middle-aged white men (between 40 and 64 years) free of definite CHD	1233, 1899 and 5784, respectively	15, 17 and 5 years, respectively	Baseline resting heart rate measured by ECG, pulse, and ECG, respectively for the three different study groups	Cox proportional hazards regression	All-cause death CV death CHD death Sudden death
Kannel et al.[108]	1987	The Framingham Study	White men and women free of CV disease	5070	30 years	Baseline resting heart rate measured by ECG	Logistic regression	All-cause death CV death CHD death Sudden death
Gillum et al.[109]	1991	NHEFS	Black and white men and women without known CV disease	5995	9.9 years for white, and 10.3 years for black subjects	Baseline resting heart rate measured by pulse	Cox proportional hazards regression	All-cause death CV death CHD death (white subjects only) Incidence of CHD (white subjects only)
Filipovsky et al.[102]	1992	The Paris Prospective Study I	Native-born Frenchmen aged 42 to 53 years employed by the Paris Civil Service without known CV disease	4907	17 years	Baseline resting heart rate and difference between baseline and exercise test heart rate	Cox proportional hazards regression	All-cause death CV death

Shaper et al.[107]	1993	British Regional Heart Study	Men aged 40 to 59 years selected from GP age-sex registers in 24 towns across Britain	7735 (7683 with heart rate measurements)	8 years	Baseline resting heart rate measured by ECG	Logistic regression	Major CHD event CHD death Sudden death
Greenland et al.[110]	1999	Chicago Heart Association Detection Project	Men and women aged 18 to 74 years from Chicago, with no evidence of a prior MI	33781	22 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	All-cause death CV death CHD death
Palatini et al.[111]	1999	CASTEL	Men and women from northeast Italy, aged ≥65 years in sinus rhythm	1938	12 years	Baseline resting heart rate measured by palpation of the radial pulse	Logistic regression	All-cause death CV death Sudden death
Benetos et al.[112]	1999	-	Men and women from Paris, aged 40 to 69 years	19386	18.2 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	All-cause death CV death CHD death Stroke death
Reunanen et al.[113]	2000	-	Finnish men and women aged 30 to 59 years	10717	23 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	All-cause death CV death CHD death Stroke death
Kristal-Boneh et al.[103]	2000	The CORDIS Study	Jewish male Israeli industrial employees at least 25 years old without CV disease or on heart medication, with a mean age of 43 years	3527	8 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	All-cause death CV death

Seccareccia et al.[104]	2001	MATISS	Middle-aged men (40 to 69 years) residing in Central Italy	2533	-	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	All-cause death CV death
Fujiura et al.[105]	2001	-	Men aged 40 to 64 years from the rural farming community Tanushimaru in Japan	573	18 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	All-cause death
Kado et al.[123]	2002	Study of Osteoporotic Fractures	Elderly white women (≥65 years old) from America	9702	6 years	Baseline resting heart rate	Cox proportional hazards regression and logistic regression	All-cause death CHD death Stroke death
Chang et al.[97]	2003	WHAS I	American community-dwelling older women (≥65 years old) with a moderate to severe disability	953	3 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	All-cause death
Perk et al.[114]	2003	Jerusalem 70-year-old Longitudinal Survey	Elderly men and women (aged 70 years at entry) living in Jerusalem	422	6 years	Baseline resting heart rate measured by pulse and ECG	Logistic regression	All-cause death
Okamura et al.[115]	2004	National Survey on Circulatory Disorders	Men and women from Japan who were community dwellers aged 30 years or older, with no history of CHD or stroke, any arrhythmias or AF	8088	16.5 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	All-cause death CV death CHD and HF death
Theobald and Wandell[116]	2007	-	Men and women from Stockholm county aged 18 to 64 years	989	26 years	Resting baseline heart rate measured from pulse	Cox proportional hazards regression	All-cause death
Cacciatore et al.[125]	2007	Osservatorio Geriatrico Regione Campania	Elderly Italian men and women (>65 years old)	1163	12 years	Baseline resting heart rate measured by cardiac auscultation	Cox proportional hazards regression	All-cause death

Kizilbash et al.[117]	2008	Chicago Heart Association Detection Project in Industry	Normal-weight men and women aged 18 to 59 years with no history or evidence of MI	14653	32 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	CV death
Tverdal et al.[100]	2008	-	Middle-aged (40 to 45 years) Norwegian men and women with no history of CV disease or diabetes	379843	12.6 years	Baseline resting heart rate measured using an automatic device	Cox proportional hazards regression	All-cause death CV death CHD death Stroke death Sudden death
Hsia et al.[124]	2009	The Women's Health Initiative	Post-menopausal women from the United States with a mean age of approximately 62 years, without a prior MI, stroke or revascularisation, or on heart rate medication	129135	7.8 years	Baseline resting heart rate measured by palpation of the radial pulse	Cox proportional hazards regression	MI or coronary death Stroke
Fagundes and Castro[126]	2010	-	Men and women from Brazil who were dead (case) or alive (control) who had undergone exercise stress testing, with a mean age of 55.43 years	7055	12 years	Seated resting heart rate measured manually before exercise stress testing by a heart monitor	Logistic regression	AC death CV death
Nauman et al.[118]	2010	HUNT	Men and women from Norway, aged 20 years or older, with no signs of CV disease	50088	18.2 years	Baseline resting heart rate measured by radial pulse palpation	Cox proportional hazards regression	CHD death
Cooney et al.[119]	2010	FINRISK	Finnish men and women aged 25 to 74 years drawn from the general population with no history of MI, angina or HF, not on hypertensive medications	28047	12 years	Baseline resting heart rate measured by palpation of the radial artery	Cox proportional hazards regression	All-cause death CV disease death CHD death Fatal and non-fatal CHD events

Batty et al.[98]	2010	The Whitehall Study	Non-industrial, government employed men aged 40 to 69 years from London	1183	40 years	Baseline resting heart rate	Cox proportional hazards regression	All-cause death CHD death Stroke death
Mao et al.[120]	2010	China National Hypertension Survey Epidemiology Follow-Up Study	Chinese men and women aged 40 years or older without prevalent CV disease or hypertension	108534	8.3 years	Baseline resting heart rate obtained manually	Cox proportional hazards regression	CV disease Heart disease CHD Stroke Ischemic stroke Haemorrhagic stroke
Jensen et al.[127]	2011	CCHS	Men and women aged 20 years and older sampled from the Copenhagen Population Register, without CHD, diabetes or AF, who had never had an MI or stroke, not taking any heart medications	16516	21.2 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	All-cause death CV death
Jensen et al.[128]	2012	CCHS	Danish men and women with a mean age of 56.2 years without CHD, diabetes or AF, who had never had an MI or stroke, not taking any heart medications	6518	14 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	All-cause death CV death
Pfister et al.[129]	2012	EPIC-Norfolk	Men and women aged 39 to 79 years from Norfolk in the United Kingdom	22126	12.9 years	Baseline resting heart rate	Cox proportional hazards regression	Incident HF
O'Hartaigh et al.[130]	2012	LURIC	German Caucasian men and women aged 18 to 95 years who were referred for coronary angiography, with stable clinical disease	3316	9.9 years	Baseline resting heart rate	Cox proportional hazards regression	All-cause death CV death

Teodorescu et al.[137]	2013	Oregon Sudden Unexpected Death Study	Men and women from Portland, Oregon, who had died of sudden cardiac death (case) or who were alive with or without CHD (control) aged ≥35 years with a mean age of 67.7 years	756	-	Resting heart rate measured by ECG – the most prior but unrelated to the sudden cardiac death for cases	Logistic regression	Sudden cardiac death
Pittaras et al.[131]	2013	-	Male and female veterans with a mean age of 58 years	18462	10 years	Baseline resting heart rate	Cox proportional hazards regression	All-cause death
Johansen et al.[132]	2013	The Copenhagen Holter Study	Middle-aged and elderly men and women (55 to 75 years) from Copenhagen with no known heart disease	653	6.3 years	Baseline resting heart rate	Cox proportional hazards regression	All-cause death CV event (CV death, acute MI, or revascularisation)
Jensen et al.[106]	2013	The Copenhagen Male Study	Healthy Caucasian middle-aged men employed at 14 large workplaces in Copenhagen in 1970 to 1971	2798	16 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	All-cause death
Opdahl et al.[66]	2014	The MESA Study	Men and women from America aged 45 to 84 years without known CV disease	-	7 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	Incident HF
Aladin et al.[133]	2014	The FIT Project	Men and women ≥18 years without known CHD or AF who underwent a clinically indicated exercise stress test	56634	11.1 years	Baseline resting heart rate	Cox proportional hazards regression	All-cause death MI Revascularisation Major adverse cardiac event (a combination of the three above)

Wang et al.[134]	2014	The Kailuan Study	Men and women aged 18 to 98 years from the Kailuan community in Tangshan of China	92562	4 years	Baseline resting heart rat measured by ECG	Cox proportional hazards regression	All-cause death CV disease MI Any stroke Ischemic stroke Hemorrhagic stroke
Carlson et al.[99]	2014	CCHS	Men and women from Copenhagen >20 years with no known CV disease	131	13.6 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	Composite of non-fatal HF, acute MI, CHD and CV death
Makita et al.[121]	2014	Iwate-Kenpoku Cohort Study	Community-dwelling 40 to 79 year-old men and women from northern Japan without known CV disease or AF	17766	5.6 years	Baseline resting pulse rate	Cox proportional hazards regression	Any CV disease event including CV death
Woodward et al.[135]	2014	APCSC	Men and women within the Asian-Pacific region at least 20 years old, drawn from the general population	112680	7.4 years	Baseline resting heart rate	Cox proportional hazards regression	All-cause death CV disease death HF death Fatal and non-fatal: CV disease CHD All stroke Haemorrhagic stroke Ischemic stroke Unclassified stroke

Vassalle et al.[122]	2014	-	Men and women admitted to the Coronary Care Unit of the CNR-Clinical Physiology Institute in Pisa to undergo a coronary angiography, with a mean age of 66 years	3559	2.9 years	Resting heart rate obtained at admission	Cox proportional hazards regression	All-cause death Cardiac death
Khan et al.[136]	2015	Health ABC; CHD; KIHD	American men and women aged 65 to 100 years, and men from Eastern Finland aged 42 to 61 years, without prevalent HF or major ECG abnormalities; mean age 67 years	7073 Meta-analysis n = 43051	-	Baseline resting heart rate measured by ECG	Cox proportional hazards regression Meta-analysis	Incident HF (non-fatal hospital admission for HF)

If no study name is given it is because the study was not explicitly named in the publication or was not given a name. Follow-up duration for each study is either total, median or mean follow-up depending on what was stated in the publication; if follow-up was given in months or days it was converted to the approximate time in years if appropriate. If no method of heart rate measurement is stated it is because it was not stated in the publication. Note that some studies presented results for other adverse non-CV outcomes, such as cancer, but they are not mentioned in the table since they were not relevant to the review.

NHEFS stands for the first National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-Up Study (NHEFS).

CASTEL stands for the CArdiovasuclar STudy of the ELderly.

CORDIS stands for Cardiovascular Occupational Risk Factors Determination in Israel.

MATISS stands for the Malattie Cardiovasculari Aterosclerotiche, Istituto Superiore di Sanita (MATISS) Project. Seccareccia et al. 2001[104] do not explicitly state the follow-up period.

WHAS I stands for the Women's Health and Aging Study I.

HUNT stands for the Nord-Trondelag Health (HUNT) Study.

FINRISK stands for the Finland Cardiovascular Risk Study.

CCHS stands for the Copenhagen City Heart Study.

EPIC-Norfolk stands for the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk Study.

LURIC stands for the Ludwigshafen Risk and Cardiovascular Health (LURIC) Study.

MESA stands for the Multi-Ethnic Study of Atherosclerosis (MESA). In the Opdahl et al. 2014[66] publication it is not completely clear how many patients were included in the different analyses.

FIT stands for Henry Ford Exercise Testing (FIT).

APCSC stands for the Asia Pacific Cohort Studies Collaboration.

ABC stands for Aging and Body Composition; CHD stands for Cardiovascular Health Study; and KIHD stands for Kuopio Ischemic Heart Disease. Khan et al. 2015[136] only stated follow-up in person-years.

AF = Atrial Fibrillation; CV = Cardiovascular; CHD = Coronary Heart Disease; ECG = Electrocardiography; GP = General Practitioner; HF = Heart Failure; MI = Myocardial Infarction.

Table A1-5: An overview of studies which have investigated baseline resting heart rate as a risk marker in subjects with diabetes.

Authors	Year	Study Name	Study Population	No. of Subjects	Follow-up	Type of Heart Rate	Type of Analysis	Outcomes
Stettler et al.[140]	2007	The WHO Multinational Study of Vascular Disease in Diabetes	Swiss men and women aged between 35 and 54 years with type 1 or 2 diabetes	523	22.6 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	All-cause death CV death Cardiac death CHD death
Hillis et al.[141]	2012	ADVANCE	Men and women at least 55 years old with type 2 diabetes, with a mean age of 66 years	11138	4.4 years	Baseline resting heart rate measured using a digital monitor	Cox proportional hazards regression Proportional sub-distributions hazards regression	All-cause death CV death Major CV event (CV death, non-fatal MI, or stroke)
Miot et al.[142]	2012	SURDIAGENE	Men and women from France, with type 2 diabetes, with a mean age of approximately 65 years	1088	4.2 years	Baseline resting heart rate measured by ECG	Fine and Gray[143]	Primary outcome: CV death, non-fatal MI, non-fatal stroke, hospitalisation from HF, or onset of end-stage renal disease

If no study name is given it is because the study was not explicitly named in the publication. Follow-up duration for each study is either total, median or mean follow-up depending on what was stated in the publication; if follow-up was given in months or days it was converted to the approximate time in years if appropriate. If no method of heart rate measurement is stated it is because it was not stated in the publication. Note that some studies presented results for other adverse non-CV outcomes, such as cancer, but they are not mentioned in the table since they were not relevant to the review.

WHO stands for the World Health Association (WHO).

ADVANCE stands for the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) Study.

SURDIAGENE stands for Survie Diabete de type 2 et Genetique (SURDIAGENE) study.

CV = Cardiovascular; CHD = Coronary Heart Disease; ECG = Electrocardiography; HF = Heart Failure; MI = Myocardial Infarction.

Table A1-6: An overview of studies which have investigated baseline resting heart rate as a risk marker in subjects with hypertension.

Authors	Year	Study Name	Study Population	No. of Subjects	Follow-up	Type of Heart Rate	Type of Analysis	Outcomes
Gillman et al.[144]	1993	The Framingham Study	Men and women with hypertension (SBP >140mmHg or DBP >90mmHg) not taking anti-hypertensive medication, with a mean age of around 55 years	4530	36 years	Baseline resting heart rate measured by ECG	Logistic regression	All-cause death CV death CHD death Sudden death CV disease (fatal and non-fatal) CHD (fatal and non-fatal)
Palatini et al.[147]	2002	Syst-Eur	Men and women ≥60 years with a baseline blood pressure measurement between 160 and 219mmHg systolic, and <95mmHg diastolic, who were randomised to the placebo group	2293	2 years	Baseline resting heart rate, referred to as clinical/conventional heart rate in the paper (the mean of six readings during three visits in the placebo run-in period)	Cox proportional hazards regression	All-cause death CV death
King et al.[145]	2006	ARIC	Men and women aged between 45 and 64 years, with pre-hypertension, free of CHD	3275	10.1 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	All-cause death Incident CHD
Salles et al.[146]	2013	-	Men and women from Brazil, with resistant hypertension and a mean age of 60 to 70 years, who were in sinus rhythm	528	4.8 years	Baseline resting heart rate measured by radial artery palpation (clinic heart rate) Baseline resting heart rate measured by ECG	Cox proportional hazards regression	All-cause death CV death Composite endpoint: all fatal or non-fatal CV events

If no study name is given it is because the study was not explicitly named in the publication. Follow-up duration for each study is either total, median or mean follow-up depending on what was stated in the publication; if follow-up was given in months or days it was converted to the approximate time in years if appropriate. If no method of heart rate measurement is stated it is because it was not stated in the publication. Note that some studies presented results for other adverse non-CV outcomes, such as cancer, but they are not mentioned in the table since they were not relevant to the review.

Sys-Eur stands for the Systolic Hypertension in Europe (Sys-Eur) trial.

ARIC stands for the Atherosclerosis Risk in communities (ARIC) study.

CV = Cardiovascular; CHD = Coronary Heart Disease; DBP = Diastolic Blood Pressure; ECG = Electrocardiography; SBP = Systolic Blood Pressure.

Table A1-7: An overview of studies which have investigated baseline heart rate as a risk marker in subjects with coronary heart disease.

Authors	Year	Study Name	Study Population	No. of Subjects	Follow-up	Type of Heart Rate	Type of Analysis	Outcomes
Diaz et al.[148]	2005	CASS	Men and women who underwent a coronary angiography for suspected or proven CHD, who were shown to have stable CHD if suspected, with a mean age of 53 years	24913	14.7 years	Baseline resting heart rate measured by pulse	Cox proportional hazards regression	All-cause death CV death CV rehospitalisation (hospitalisation for MI, angina, stroke, revascularisation or rhythm disturbance) Rehospitalisation due to acute MI Rehospitalisation due to angina Rehospitalisation due to stroke Rehospitalisation due to congestive HF
Ho et al.[149]	2010	TNT	Men and women aged 35 to 75 years with clinically evident CHD, defined by one or more of the following: previous MI, previous or current angina with evidence of atherosclerotic CHD, or a history of coronary revascularisation	9580	4.9 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	A major CV event defined as CHD death, non-fatal MI, stroke or a resuscitated cardiac arrest All-cause death Non-fatal MI Fatal or non-fatal stroke HF hospitalisation
Anselmino et al.[150]	2010	Euro Heart Survey	Men and women with CHD, with a mean age in the region of 65 to 70 years	2507	1 year	Baseline resting heart rate (the average of two measurements taken)	Cox proportional hazards regression	All-cause death CV event (all-cause death, non-fatal MI or stroke)

Ortiz et al.[151]	2010	-	Men and women with stable CHD with a mean age of 68 years	1264	2.1 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	A major CV event (death, ACS, revascularisation, stroke or hospitalisation for HF) A coronary event (ACS or revascularisation) All-cause death

If no study name is given it is because the study was not explicitly named in the publication. Follow-up duration for each study is either total, median or mean follow-up depending on what was stated in the publication; if follow-up was given in months or days it was converted to the approximate time in years if appropriate. If no method of heart rate measurement is stated it is because it was not stated in the publication. Note that some studies presented results for other adverse non-CV outcomes, such as cancer, but they are not mentioned in the table since they were not relevant to the review.

CASS stands for the Coronary Artery Surgery Study (CASS).

TNT stands for the Treating to New Targets (TNT) study.

ACS = Acute Coronary Syndrome; CHD = Coronary Heart Disease; CV = Cardiovascular; ECG = Electrocardiography; HF = Heart Failure; MI = Myocardial Infarction.

Table A1-8: An overview of studies which have investigated heart rate as a risk marker in patients with acute coronary syndromes, myocardial infarction and unstable angina.

Authors	Year	Study Name	Study Population	No. of Subjects	Follow-up	Type of Heart ate	Type of Analysis	Outcomes
Hjalmarson et al.[152]	1990	-	Men and women with acute-MI admitted to the hospital within 24-hours of onset of symptoms, with a mean age of around 63 years	1807 (1585 discharged from hospital)	1 year	Admission heart rate	Cox proportional hazards regression	In-hospital mortality 1-year post-discharge mortality
Disegni et al.[153]	1995	SPRINT 2	Men and women hospitalised with proven acute MI in Israel, with a mean age of around 64 years	1044	1 year	Admission heart rate	Logistic regression	In-hospital mortality 1-year post-discharge mortality
Zuanetti et al.[154]	1998	GISSI-2	Men and women hospitalised for acute MI, treated with thrombolytic agents within 12-hours of onset of symptoms	8915	0.5 years	Admission heart rate measured by ECG Discharge heart rate measured by ECG	Logistic regression Cox proportional hazards regression	In-hospital mortality 6-month post-discharge mortality
Kovar et al.[155]	2004	OPUS-TIMI-16	Men and women with ACS, with a mean age of around 61 years	10267	0.83 years	Admission heart rate measured by physical exam or ECG	Cox proportional hazards regression	30-day mortality 10-month mortality
Mauss et al.[156]	2005	-	Men and women presenting with acute MI in Germany, with a mean age of 58 years	432	3.42 years	Discharge heart rate measured by ECG	Logistic regression	The combined endpoint of all-cause death and arrhythmic events (i.e. sudden death, resuscitated ventricular fibrillation, sustained ventricular tachycardia)
Honda et al.[157]	2010	-	Men and women admitted to the Department of Cardiology at Kumamoto Medical Center in Japan, within 24 hours of acute MI, who underwent coronary angiography, with a mean age in the region of 67 to 71 years	200	-	Heart rate measured at the time of arrival at the emergent unit of the Center	Logistic regression	Poor LV function (LVEF before discharge <50%) In-hospital death

Parodi et al.[159]	2010	-	Men and women with STEMI undergoing primary PCI in sinus rhythm with a mean age of around 65 years	2477	0.5 years	Presenting/baseline heart rate assessed by a calliper in the patient diagnostic ECG	Cox proportional hazards regression	6-month mortality
Bangalore et al.[160]	2010	CRUSADE	Men and women with NSTE-ACS admitted to an American hospital, with a mean age of around 67 years	135164	-	Admission heart rate	Generalised estimating equations	Primary: the composite of in-hospital all-cause death, non-fatal re-infarction, and stroke All-cause death Non-fatal re-infarction Stroke
Timoteo et al.[161]	2011	-	Men and women admitted to ICU in Portugal, with ACS, with a mean age of 64 years	1126	1 year	Admission heart rate	Cox proportional hazards regression	1-year post-discharge mortality
Han et al.[162]	2012	-	Men and women with STEMI admitted to a hospital in China within 12 hours of onset of symptoms, with a mean age in the region of 60 to 65 years	7294	30 days	Admission heart rate measured by ECG	Cox proportional hazards regression	30-day all-cause mortality 30-day CV events (all-cause death, re-infarction, or stroke)
Facila et al.[163]	2012	PAMISCA	Men and women admitted to a Spanish hospital with ACS, with a mean age of 67 years	1054	1 year	Admission heart rate measured between day 3 and 7 of the ACS event once the patient was stable	Cox proportional hazards regression	1-year post-discharge mortality
Antoni et al.[169]	2012	-	Men and women admitted with STEMI treated with PCI in sinus rhythm, with a mean age of 61 years from the Netherlands	1492	3.3 years	Discharge heart rate measured by ECG	Cox proportional hazards regression	All-cause death at 1- and 4-years post-discharge CV death at 1- and 4-years post-discharge

Noman et al.[164]	2013	-	Men and women who underwent primary PCI for STEMI at Freeman Hospital in Newcastle, United Kingdom with a mean age of around 62 years	2310	1.6 years	Admission heart rate measured by ECG	Logistic regression Cox proportional hazards regression	Long-term post-discharge mortality In-hospital mortality
Jensen et al.[170]	2013	BASKET-PROVE	Men and women with stable or unstable ACS treated with PCI and in need of stenting, from Switzerland, Denmark, Austria and Italy, with a mean age of around 63 years	2029	2 years	Discharge heart rate measured by ECG	Cox proportional hazards regression	All-cause death CV death or non-fatal MI
Davidovic et al.[165]	2013	-	Men and women with anterior wall STEMI treated in the Coronary Unit at the Clinical Center Kragujevac in Serbia, ≥30 years with no history of diabetes	140	-	Admission heart rate measured by ECG	Logistic regression	In-hospital mortality
Li et al.[166]	2013	OMEGA	Post-MI men and women presenting with AF, with a mean age of 72 years	211	1 year	Admission heart rate	Logistic regression	1-year mortality
Seronde et al.[171]	2014	FAST-MI	Male and female patients admitted to coronary care units in France for MI, who survived, with a mean age of around 66 years	3079	5 years	Discharge heart rate	Cox proportional hazards regression	1-year post-discharge mortality 5-year post-discharge mortality 5-year post-discharge mortality excluding patients who died within the first year
Asaad et al.[167]	2014	Gulf RACE-2	Male and female ACS patients (diagnosed with unstable angina and NSTEMI or STEMI/LBBB) from Middle Eastern Gulf countries, with a mean age of 56 years	7939	1 year	Admission heart rate	Logistic regression	In-hospital HF 1-month mortality

Salwa et al.[168]	2015	-	Men and women with STEMI hospitalised in the Clinical Department of Cardiology in Poland, with a mean age of 65 years	927	-	Admission heart rate measured by ECG	Logistic regression	In-hospital CV death

If no study name is given it is because the study was not explicitly named in the publication. Follow-up duration for each study is either total, median or mean follow-up depending on what was stated in the publication; if follow-up was given in months or days it was converted to the approximate time in years if appropriate. If no method of heart rate measurement is stated it is because it was not stated in the publication. Note that some studies presented results for other adverse non-CV outcomes, such as cancer, but they are not mentioned in the table since they were not relevant to the review.

Honda et al. 2010[157], Bangalore et al. 2010[160], Davidovic et al. 2013[165] and Salwa et al. 2015[168] only analysed in-hospital events hence why no follow-up period is stated.

SPRINT 2 stands for the Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT 2).

GISSI-2 stands for the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI) 2 trial. GISSI an influence Italian cardiology research group for the study of the survival of MI.

OPUS-TIMI stands for the Orofiban in Patients with Unstable coronary Syndromes-Thrombolysis In Myocardial Infarction (OPUS-TIMI)-16 trial.

CRUSADE stands for the Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the American College of Cardiology/American Heart Association Guidelines (CRUSADE) National Quality Improvement Initiative database.

PAMISCA stands for the Prevalence of Peripheral Arterial Disease in Patients with Acute Coronary Syndrome (PAMISCA) registry study. The heart rate measurement in Facila et al. 2012[163] was determined between day 3 and 7 of a subject experiencing an ACS event once they were stable.

BASKET-PROVE stands for the BAsel Stent Kosten Effektivitats Trial PROspective Validation Examination.

OMEGA was a randomised trial investigating the effect of omega-3 fatty acid supplementation on the rate of sudden cardiac death in survivors of acute MI.

FAST-MI stands for the French Registry of Acute ST-Elevation or non-ST-elevation Myocardial Infarction (FAST-MI) 2005 registry.

Gulf RACE-2 stands for the Gulf Registry of Acute Coronary Events.

AF = Atrial Fibrillation; ACS = Acute Coronary Syndrome; CV = Cardiovascular; ECG = Electrocardiography; HF = Heart Failure; ICU = Intensive Care Unit; LBBB = Left Bundle Branch Block; LV = Left-Ventricular; LVEF = Left-Ventricular Ejection Fraction; MI = Myocardial Infarction; NSTE-ACS = Non-ST Segment Elevation Acute Coronary Syndrome; NSTEMI = Non-ST Segment Elevation Myocardial Infarction; PCI = Percutaneous Coronary Intervention; STEMI = ST Segment Elevation Myocardial Infarction.

Table A1-9: An overview of studies which have investigated baseline, admission or, in-hospital or discharge heart rate as a risk marker in subjects with heart failure.

Authors	Year	Study Name	Study Population	No. of Subjects	Follow-up	Type of Heart Rate	Type of Analysis	Outcomes
Kapoor and Heidenreich[172]	2010	-	Men and women with HF and LVEF ≥50%, with a mean age of 70 years, in sinus rhythm	685	2.9 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	All-cause death at 1-year post-discharge
Castagno et al.[173]	2012	CHARM	Men and women with chronic HF with a mean age in the region of 65 to 70 years	7597	3.14 years	Baseline resting heart rate measured by ECG, palpation, or auscultation	Cox proportional hazards regression	All-cause death CV death or hospital stay for worsening HF
Maeder and Kaye[174]	2012	DIG (main and ancillary)	Men and women with HF and reduced or preserved ejection fraction, with a mean age of 63 years and 67 years, respectively, in sinus rhythm	7780	Around 3 years (median of 3.15 years in the main trial and 3.21 years in the ancillary trial)	Baseline resting heart rate	Cox proportional hazards regression	All-cause death HF hospitalisation
Bui et al.[177]	2013	GWTG-HF	Men and women hospitalised for HF with a mean age in the region of 70 to 80 years	145221	-	Admission heart rate defined as the first measurement obtained after presentation to the emergency department or admission to the hospital ward	Logistic regression	In-hospital mortality

Habal et al.[178]	2014	EFFECT-HF	Men and women hospitalised for HF in sinus rhythm with a mean age of around 80 years	9097	1 year	Discharge heart rate defined as the last recorded heart rate obtained within 24 hours before or at discharge	Logistic regression Cox proportional hazards regression	All-cause death at 30 days and 1- year post-discharge CV death at 30 days and 1-year post-discharge Re-admission for HF at 30 days and 1-year post-discharge Re-admission for CHD at 30 days and 1-year post-discharge Re-admission for CV disease at 30 days and 1-year post-discharge
Bohm et al.[175]	2014	I-PRESERVE	Men and women >60 years old on irbesartan with HF and preserved ejection fraction (>45%) in sinus rhythm or AF	3967 (3271 in sinus rhythm and 696 in AF)	4.13 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	All-cause death or CV hospitalisation (hospitalisation due to HF, MI, unstable angina, arrhythmia or stroke) All-cause death CV death or HF hospitalisation CV death HF hospitalisation
Kaplon-Cieslicka et al.[179]	2014	Heart Failure Pilot Survey of the European Society of Cardiology	Polish men and women admitted to hospital due to HF with a median age of 69 years	598	-	Admission heart rate	Logistic regression	In-hospital mortality

Takada et al.[176]	2014	CHART-2	Japanese men and women with HF in sinus rhythm, with a mean age of 67.5 years	10219	3.13 years	Baseline resting heart rate	Cox proportional hazards regression	All-cause death CV death HF death HF hospital admission
Lancellotti et al.[180]	2015	-	Men and women presenting with acute HF at Centre Hospitalier Universitaire of Liege, Belgium, in sinus rhythm, who were alive 24 to 36 hours after admission, with a mean age of 72 years	712	-	Resting heart rate at 24-36 hours after admission obtained by ECG or cardiac monitoring	Logistic regression	In-hospital mortality
Laskey et al.[181]	2015	GWTG-HF	Men and women hospitalised for HF with a median age of 80 years	46127 (26020 in sinus rhythm and 20197 in AF)	1 year	Discharge heart rate measured by palpation or telemetry for subjects in sinus rhythm, or by ECG or telemetry for subjects in AF	Cox proportional hazards regression	All-cause death All-cause readmission All-cause readmission or death

If no study name is given it is because the study was not explicitly named in the publication. Follow-up duration for each study is either total, median or mean follow-up depending on what was stated in the publication; if follow-up was given in months or days it was converted to the approximate time in years if appropriate. If no method of heart rate measurement is stated it is because it was not stated in the publication. Note that some studies presented results for other adverse non-CV outcomes, such as cancer, but they are not mentioned in the table since they were not relevant to the review.

Bui et al. 2013[177], Kaplon-Cieslicka et al. 2014[179], and Lancellotti et al. 2015[180] only analysed in-hospital events hence why no follow-up period is stated.

CHARM stands for the Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity (CHARM) Program.

DIG stands for the Digitalis Investigations Group (DIG) trial.

GWTG-HF stands for the American Heart Failure Associations' Get With the Guidelines-Heart Failure (GWTG-HF) program.

EFFECT-HF stands for the Enhanced Feedback for Effective Cardiac Treatment (EFFECT-HF) cohort.

I-PRESERVE stands for the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) study.

CHART-2 stands for the Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2) Study.

AF = Atrial Fibrillation; CHD = Coronary Heart Disease; CV = Cardiovascular; ECG = Electrocardiography; HF = Heart Failure; LVEF = Left-Ventricular Ejection Fraction; MI = Myocardial Infarction.

Table A1-10: An overview of studies which have investigated baseline resting heart rate as a risk marker in subjects with left-ventricular dysfunction.

Authors	Year	Study Name	Study Population	No. of Subjects	Follow-up	Type of Heart Rate	Type of Analysis	Outcomes
Fox et al.[184]	2008	BEAUTIFUL	Men and women ≥55 years old with CHD, LVEF <40% and end-diastolic short-axis internal dimension larger than 56mm, in sinus rhythm with baseline heart rate ≥60bpm	5438	1.58 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	CV death HF hospitalisation (fatal and non-fatal) MI hospitalisation (fatal and non-fatal) Coronary revascularisation
Bohm et al.[182]	2010	SHIFT	Men and women with symptomatic chronic HF with baseline heart rate ≥70bpm and LVEF ≤35% in sinus rhythm, with a mean age of 60.4 years	3264	1.91 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	CV death or hospital admission for worsening HF All-cause death CV death Death from HF All-cause hospital admission Hospital admission for worsening HF Any CV hospital admission CV death, or hospital admission for worsening HF or non-fatal MI
Fosbol et al.[183]	2010	DIAMOND	Men and women with a mean age of around 70 years who were hospitalised with LVEF ≤35% with either HF or who were post-MI	3013 (1518 with HF and 1510 who were post-MI)	10 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	All-cause death

If no study name is given it is because the study was not explicitly named in the publication. Follow-up duration for each study is either total, median or mean follow-up depending on what was stated in the publication; if follow-up was given in months or days it was converted to the approximate time in years if appropriate. If no method of heart rate measurement is stated it is because it was not stated in the publication. Note that some studies presented results for other adverse non-CV outcomes, such as cancer, but they are not mentioned in the table since they were not relevant to the review.

BEAUTIFUL stands for the morBidity-mortality EvAlUaTion of the I(f) inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction (BEAUTIFUL) study. Fox et al. 2008[184] did not explicitly state the follow-up period of the placebo group.

SHIFT stands for the Systolic Heart failure treatment with the I(f) inhibitor ivabradine Trial (SHIFT). Bohm et al. 2010[182] also evaluated heart rate achieved at 28 days in the ivabradine group, but since ivabradine can affect heart rate, only the number of patients in the placebo group is stated.

DIAMOND stands for the Danish Investigations and Arrhythmia ON Dofetilide (DIAMOND) study.

CHD = Coronary Heart Disease; CV = Cardiovascular; ECG = Electrocardiography; HF = Heart Failure; LVEF = Left-Ventricular Ejection Fraction; MI = Myocardial Infarction.

Table A1-11: An overview of studies which have investigated pre-induction, admission, or post-operative heart rate as a risk marker in CABG patient populations.

Authors	Year	Study Name	Study Population	No. of Subjects	Follow-up	Type of Heart Rate	Type of Analysis	Outcomes
Fillinger et al.[185]	2002	NNECDSG	Men and women having isolated CABG procedures, with a mean age of around 65 years	5934	-	Pre-induction heart rate measured by ECG upon arrival to the operating room	Logistic regression used to calculate predicted risk of adverse outcomes for each patient Cuzik extension of the Wilcoxon's ranked sum non-parametric test for trend	In-hospital mortality Intra- or post-operative stroke
Aboyans et al.[186]	2008	-	Men and women with a mean age of 67 years referred for non-urgent CABG	1022	30 days post-CABG	Pre-operative admission heart rate measured by ECG	Logistic regression	Primary: All-cause death, non-fatal MI or non-fatal stroke or TIA Secondary: All-cause death or stroke or TIA
Frank et al.[187]	2010	-	Men and women with a mean age of 66 years referred for non-urgent CABG	794	3.2 years	Post-operative heart rate measured by ECG at the first outpatient visit	Cox proportional hazards regression	Primary: All-cause death Secondary: All-cause death, secondary coronary revascularisation, non-fatal ACS, non-fatal stroke or TIA, or vascular surgery

If no study name is given it is because the study was not explicitly named in the publication. Follow-up duration for each study is either total, median or mean follow-up depending on what was stated in the publication; if follow-up was given in months or days it was converted to the approximate time in years if appropriate. If no method of heart rate measurement is stated it is because it was not stated in the publication. Note that some studies presented results for other adverse non-CV outcomes, such as cancer, but they are not mentioned in the table since they were not relevant to the review.

NNECDSG stands for the Northern New England Cardiovascular Disease Study Group. Follow-up is not stated for Fillinger et al. 2002[185] since only in-hospital outcomes were evaluated.

Note that Aboyans et al. 2008[186] and Frank et al. 2010[187] analysed the same population of patients.

ACS = Acute Coronary Syndrome; CABG = Coronary Artery Bypass Graft; ECG = Electrocardiography; MI = Myocardial Infarction; TIA = Transient Ischemic Attack.

Table A1-12: An overview of studies which have investigated baseline resting heart rate as a risk marker in mixed groups of subjects with some form of vascular disease.

Authors	Year	Study Name	Study Population	No. of Subjects	Follow-up	Type of Heart Rate	Type of Analysis	Outcomes
Bemelmans et al.[188]	2013	SMART	Men and women aged 18 to 80 years from the Netherlands with manifest atherosclerotic vascular disease: CHD; cerebrovascular disease; PAD; or abdominal aortic aneurysm	4272	4.4 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	MI Ischemic stroke All vascular events Vascular death All-cause death
Nanchen et al.[138]	2013	PROSPER	Men and women aged 70 to 82 years from the Netherlands, Scotland and Ireland, with a history of vascular disease defined as coronary, cerebral or PAD, or those with known CV risk factors, such as smoking, hypertension, or diabetes, in sinus rhythm, with a mean age of 75 years	4084	3.2 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	HF hospitalisation CV mortality
van Kruijsdijk et al.[189]	2014	SMART	Men and women aged 18 to 80 years from the Netherlands with manifest atherosclerotic vascular disease: CHD; cerebrovascular disease; PAD; or abdominal aortic aneurysm	6007	6 years	Baseline resting heart rate measured by ECG	Fine and Gray[143]	All-cause death

If no study name is given it is because the study was not explicitly named in the publication. Follow-up duration for each study is either total, median or mean follow-up depending on what was stated in the publication; if follow-up was given in months or days it was converted to the approximate time in years if appropriate. If no method of heart rate measurement is stated it is because it was not stated in the publication. Note that some studies presented results for other adverse non-CV outcomes, such as cancer, but they are not mentioned in the table since they were not relevant to the review.

SMART stands for the Second Manifestations of ARTerial disease study.

PROSPER stands for the PROspective study of pravastatin in the elderly at risk (PROSPER) study.

CHD = Coronary Heart Disease; CV = Cardiovascular; ECG = Electrocardiography; HF = Heart Failure; MI = Myocardial Infarction; PAD = Peripheral Artery Disease.

Table A1-13: An overview of studies which have investigated baseline resting heart rate as a risk marker in post-stroke subjects.

Authors	Year	Study Name	Study Population	No. of Subjects	Follow-up	Type of Heart Rate	Type of analysis	Outcomes
Bohm et al.[190]	2012	PRoFESS	Post-ischemic stroke patients (male and female) aged 55 years or older, or aged 50 to 54 years with two additional CV risk factors, with a mean age of 66 years	20165	2.4 years	Baseline resting heart rate	Cox proportional hazards regression	Recurrent stroke of any type MI Chronic HF All-cause death Vascular death
Fox et al.[191]	2013	PERFORM	Post ischemic stroke or TIA men and women aged 55 years or older	18980	2.4 yeas	Baseline resting heart rate measured by palpitation, auscultation, or 12-lead ECG	Cox proportional hazards regression	All fatal or non-fatal MI Non-fatal MI All fatal or non-fatal ischemic stroke Non-fatal ischemic stroke All fatal or non-fatal stroke Vascular death All-cause death Fatal or non-fatal ischemic stroke, MI, and other vascular death
Sandset et al.[192]	2014	VALUE	Male and female post-stroke or TIA patients with hypertension aged 50 years or older, with a mean age of 67.3 years	3014	4.5 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	Recurrent stroke

Erdur et al.[193]	2014	-	Acute ischemic stroke patients admitted to hospital within 72 hours after onset of symptoms with a median age of 73 years, in sinus rhythm	1335	-	Admission to the emergency department heart rate measured by ECG	Logistic regression	In-hospital mortality

If no study name is given it is because the study was not explicitly named in the publication. Follow-up duration for each study is either total, median or mean follow-up depending on what was stated in the publication; if follow-up was given in months or days it was converted to the approximate time in years if appropriate. If no method of heart rate measurement is stated it is because it was not stated in the publication. Note that some studies presented results for other adverse non-CV outcomes, such as cancer, but they are not mentioned in the table since they were not relevant to the review.

Erdur et al. 2014[193] only analysed in-hospital events hence why no follow-up period is stated.

PRoFESS stands for the Prevention Regimen for Effectively Avoiding Second Stroke (PRoFESS) trial.

PERFORM stands for the Prevention of cerebrovascular and cardiovascular Events of ischemic origin with teRutroban in patients with a history oF ischemic stroke or tRansientischemic attack (PERFORM) trial.

VALUE stands for the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial.

CV = Cardiovascular; ECG = Electrocardiography; HF = Heart Failure; MI = Myocardial Infarction; TIA = Transient Ischemic Attack.

Table A1-14: An overview of studies which have investigated baseline resting heart rate as a risk marker in subjects with kidney disease.

Authors	Year	Study Name	Study Population	No. of Subjects	Follow-up	Type of Heart Rate	Type of Analysis	Outcomes
Beddhu et al.[194]	2009	ARIC	American men and women aged 45 to 64 years with chronic kidney disease, with a mean age of 57 years	460	From 1987-1989 until 1998 (approximately 9 to 11 years)	Resting heart rate measured by ECG after a 12-hour fast followed by a light snack and ≥1 hour after smoking or caffeine intake	Cox proportional hazards regression	CV event (MI, fatal CHD event, incident stroke or coronary revascularisation) All-cause death
Iseki et al.[195]	2011	JSDT	Japanese men and women with a mean age of 64 years receiving haemodialysis three times a week from the database of the Committee of Renal Data Registry for the JSDT	147702	1 year	Pre-haemodialysis resting heart rate measured by pulse, generally in the supine position	Logistic regression	All-cause death
Inoue et al.[196]	2012	-	Japanese men and women with a mean age of 62 years receiving haemodialysis three times a week, recruited from two clinics in Okinawa, Japan	229	1.4 years	Baseline resting heart rate measured by ECG	Cox proportional hazards regression	Primary: All-cause death, ACS, or stroke Secondary: the primary outcome or any other CV event

If no study name is given it is because the study was not explicitly named in the publication. Follow-up duration for each study is either total, median or mean follow-up depending on what was stated in the publication; if follow-up was given in months or days it was converted to the approximate time in years if appropriate. If no method of heart rate measurement is stated it is because it was not stated in the publication. Note that some studies presented results for other adverse non-CV outcomes, such as cancer, but they are not mentioned in the table since they were not relevant to the review.

ARIC stands for the Atherosclerosis Risk in Communities (ARIC) study. Beddhu et al. 2009[194] did not explicitly state the period of follow-up.

JSDT stands for the Japanese Society for Dialysis Therapy.

ACS = Acute Coronary Syndrome; CHD = Coronary Heart Disease; CV = Cardiovascular; ECG = Electrocardiography; MI = Myocardial Infarction.

Table A1-15: The quality of each of the 'multiple heart rate measurement' studies according to the Newcastle-Ottawa scale[96].

Study	Population	Selection	Comparability	Outcome	Total	
Mensink and Hoffmeister 1999[197]	General	**	**	***	*******	7
Jouven et al. 2001[202]	General	***	**	***	********	8
Jouven et al. 2009[198]	General	***	**	***	********	8
Nauman et al. 2011[199]	General	****	**	***	*********	9
Legeai et al. 2011[206]	General	***	**	**	*******	7
Leistner et al. 2012[200]	General	****	**	**	********	8
Nanchen et al. 2013[139]	General	****	**	**	********	8
Ho et al. 2014[204]	General	****	**	**	********	8
O'Hartaigh et al. 2014[201]	General	***	**	**	*******	7
O'Hartaigh et al. 2015[207]	General	***	**	***	********	8
Floyd et al. 2015[203]	General	***	**	**	*******	7
Paul et al. 2010[209]	Hypertensive	****	**	**	********	8
Okin et al. 2010[210]	Hypertensive	***	**	**	*******	7
Okin et al. 2012[211]	Hypertensive	***	**	**	*******	7
Julius et al. 2012[212]	Hypertensive	***	**	**	*******	7
Kolloch et al. 2008[208]	Stable CHD and Hypertensive	***	**	***	********	8
Jabre et al. 2014[213]	Post-MI	****	**	***	*********	9
Greene et al. 2013[214]	Heart Failure	***	**	**	*******	7
Vazir et al. 2014[215]	Heart Failure	***	**	**	*******	7
Lonn et al. 2014[216]	Vascular Disease	***	**	**	*******	7

Table A1-16: An overview of studies which have investigated one or more heart rate measurements updated post-baseline as a risk marker in subjects from the general population.

Authors	Year	Study Name	Study Population	No. of Subjects	Follow-up	Type of Heart Rate	Type of Analysis	Outcomes
Mensink and Hoffmeister[197]	1997	Spandau Health Test	Men and women who were citizens of Berlin-Spandau aged 40 to 80 years	4756	12 years	Baseline and change in resting heart over the following 2 years	Cox proportional hazards regression	All-cause death CV disease death
Jouven et al.[202]	2001	Paris Prospective Study 1	Native French men employed by the Paris Civil Service aged 42 to 53 years who were free of clinically detectable CV disease	7079	23 years	Baseline and average of resting heart rate over the first 5 years of follow-up measured by radial pulse (although the paper states that subjects underwent an ECG also)	Cox proportional hazards regression	Sudden death Fatal MI
Jouven et al.[198]	2009	Paris Prospective Study 1	Native French men employed by the Paris Civil Service aged 42 to 53 years who were free of clinically detectable CV disease	5139	23 years	Baseline and change in resting heart rate over the following 5 years, measured by radial pulse (although the paper states that subjects underwent an ECG also)	Cox proportional hazards regression	All-cause death
Nauman et al.[199]	2011	HUNT-1 and HUNT-2	Men and women from Norway aged 20 years or older without known CV disease	29325	12 years	Change in resting heart rate from HUNT-1 to HUNT-2, measured by palpation of the radial pulse in HUNT-1, and by Dinamap in HUNT-2	Cox proportional hazards regression	CHD death All-cause death
Legeai et al.[206]	2011	Three-City Study	Men and women aged 65 years or older, who were French community dwellers, selected from the electoral roll of three large cities	7147	6 years	Baseline resting heart rate, as well as heart rate updated at each examination, measured using a validated digital electronic tensiometer	Time-fixed and time-dependent Cox proportional hazards regression	All-cause death CV death CHD

Leistner et al.[200]	2012	DETECT	Unselected male and female primary care subjects from Germany, free from any known CV disease, with a mean age of 55.9 years	5320 (4472 with 1-year heart rate measurements)	5 years	Baseline resting heart rate measured in the standard way the primary care physician measured it in their daily routine Change in heart rate from baseline to the 1-year follow-up assessment	Cox proportional hazards regression	All-cause death CV death Major CV event (MI, revascularisation or CV death) CV event (non-fatal MI or revascularisation)
Nanchen et al.[139]	2013	Rotterdam Study	Men and women from Rotterdam in the Netherlands, aged 55 years or older, not using beta-blockers or CCBs, free of heart disease and in sinus rhythm	4768	14.6 years	Baseline rate and time-updated resting heart rate measured at 3 follow-up visits post-baseline, measured by radial artery palpation, as well as by ECG	Time-fixed and time-dependent Cox proportional hazards regression	The development of HF
Ho et al.[204]	2014	Framingham Heart Study	Men and women with a mean age of 55 years, from Framingham, Massachusetts, United States, with no evidence of a prior MI, HF or AF, not taking any heart rate-affecting medications	4058	19 years	Baseline resting heart rate, and time-updated heart rate updated over 8 years post-baseline measured using an ECG, analysed as an average of the measurements, and as a time-dependent variable	Time-fixed and time-dependent Cox proportional hazards regression	CV disease HF CHD Stroke All-cause death CV death
O'Hartaigh et al.[201]	2014	The MRC NSHD	Men and women born in Britain during one week in 1946, still alive and living in Britain in 1971	4638	-	Resting heart rate at age 6, 7, 11, 36 and 43, and change in resting heart rate from age 36 to 43, measured using the radial artery	Cox proportional hazards regression	All-cause death
O'Hartaigh et al.[207]	2015	CHS	Men and women from America ≥65 years old, identified from the Medicare eligibility lists of the Health Care Financing Administration	5691	7.9 years	Time-updated resting heart rate measured at 6 annual assessments post-baseline	Time-dependent Cox proportional hazards regression	All-cause death

Floyd et al.[203]	2015	CHS	Men and women from the United States, aged over 65 years, with no prevalent CV disease, not using any medications that directly affect heart rate	1991	12.4 years	Mean, trend and variation of five annual resting heart rate measurements, estimated using linear regression, measured by ECG	Cox proportional hazards regression	Incident MI All-cause death

If no study name is given it is because the study was not explicitly named in the publication. Follow-up duration for each study is either total, median or mean follow-up depending on what was stated in the publication; if follow-up was given in months or days it was converted to the approximate time in years if appropriate. If no method of heart rate measurement is stated it is because it was not stated in the publication. Note that some studies presented results for other adverse non-CV outcomes, such as cancer, but they are not mentioned in the table since they were not relevant to the review.

HUNT stands for the Nord-Trondelag Health (HUNT) Study.

DETECT stands for the Diabetes Cardiovascular Risk Evaluation Targets and Essential Data for Commitment of Treatment (DETECT) trial.

MRC NSHD stands for the Medical Research Council (MRC) National Survey of Health and Development (NSHD). In the O'Hartaigh et al. 2014 study, subjects were followed-up until the age of 66.

CHS stands for the Cardiovascular Health Study.

AF = Atrial Fibrillation; CCB = Calcium Channel Blocker; CHD = Coronary Heart Disease; CV = Cardiovascular; ECG = Electrocardiography; HF = Heart Failure; MI = Myocardial Infarction.

Table A1-17: An overview of studies which have investigated heart rate updated over time in disease-specific populations.

Type of Population	Authors	Year	Study Name	Study Population	No. of Subjects	Follow-up	Type of Heart Rate	Type of Analysis	Outcomes
Hypertensive	Paul et al.[209]	2010	Glasgow Blood Pressure Clinic	Men and women from the west of Scotland, with hypertension, with a mean age of around 50 to 55 years, in sinus rhythm	4065	2.5 yeas	Baseline, final and change in resting heart rate from baseline to final, analysed in a number of different ways	Cox proportional hazards regression	All-cause death CV death CHD death
	Okin et al.[210]	2010	LIFE	Men and women with hypertension and ECG LV hypertrophy, with a mean age of around 67 years	9190	4.8 years	Baseline and time-updated heart rate measured throughout follow-up, measured by ECG	Time-dependent Cox proportional hazards regression	All-cause death CV death
	Okin et al.[211]	2012	LIFE	Men and women with hypertension and ECG LV hypertrophy, without HF, with a mean age of around 67 years	9024	4.7 years	Baseline and time-updated resting heart rate measured throughout follow-up, measured by ECG	Time-dependent Cox proportional hazards regression	The development of HF
	Julius et al.[212]	2012	VALUE	Men and women with hypertension at high CV risk, with a mean age of around 67 years	15193	5 years	Baseline and 1-year post-baseline resting heart rate measured by ECG	Cox proportional hazards regression	Cardiac event (primary endpoint) HF Sudden cardiac death MI Stroke All-cause death
Stable CHD and Hypertensive	Kolloch et al.[208]	2008	INVEST	Men and women with stable CHD and hypertension, with a mean age of 67 years	22192	2.7 years	Baseline and average of resting heart rate updated throughout follow-up	Cox proportional hazards regression	All-cause death, non-fatal MI, or non-fatal stroke

Post-MI	Jabre et al.[213]	2014	-	Men and women ≥18 years hospitalised for an incident MI in Olmsted County (Minnesota, United States)	1571	7 years	Admission heart rate and heart rate obtained around 6 months post-MI, measured by ECG	Cox proportional hazards regression	All-cause death CV death
Heart Failure	Greene et al.[214]	2013	EVEREST	Men and women ≥18 years who were hospitalised with worsening HF, with LVEF ≤40%, and signs of fluid overload, in sinus rhythm	1947	0.83 years	Resting heart rate measured at baseline, discharge (or day 7), 1-week post-discharge and 4-weeks post-discharge The change between heart rate measured at baseline and measured at discharge (or day 7)	Cox proportional hazards regression	All-cause death
	Vazir et al.[215]	2014	CHARM	Men and women with symptomatic chronic HF in sinus rhythm or in AF, on standard therapy, with a mean age of 65 years	7599	3.17 years	Baseline, time-updated heart rate measured throughout follow-up, and changes in time-updated heart rate between measurements recorded by palpation, or from auscultation of the heart, or from ECG	Time-fixed and time-dependent Cox proportional hazards regression	All-cause death CV death or hospitalisation for HF CV death Hospitalisation for HF Fatal and non-fatal MI Fatal and non-fatal stroke

Vascular Disease	Lonn et al.[216]	2014	ONTARGET and TRANSCEND	Men and women aged 55 years or older with coronary, peripheral or cerebrovascular disease, or diabetes with end organ damage	31531	4.7 years	Baseline and average of resting heart rate at baseline, and updated throughout follow-up, measured using an automated validated device	Cox proportional hazards regression	Major vascular event (CV death, MI, stroke or hospitalisation for HF) CV death MI Stroke Hospitalisation for HF All-cause death

If no study name is given it is because the study was not explicitly named in the publication. Follow-up duration for each study is either total, median or mean follow-up depending on what was stated in the publication; if follow-up was given in months or days it was converted to the approximate time in years if appropriate. If no method of heart rate measurement is stated it is because it was not stated in the publication. Note that some studies presented results for other adverse non-CV outcomes, such as cancer, but they are not mentioned in the table since they were not relevant to the review.

LIFE stands for the Losartan Intervention for Endpoint (LIFE) in hypertension study.

VALUE stands for the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial.

INVEST stands for the International Verapamil-SR/trandolapril Study (INVEST).

EVEREST stands for the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (VEREST) study.

CHARM stands for the Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity (CHARM) Program.

ONTARGET stands for the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET). TRANSCEND stands for the Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) trials.

AF = Atrial Fibrillation; CHD = Coronary Heart Disease; CV = Cardiovascular; ECG = Electrocardiography; HF = Heart Failure; LV = Left-Ventricular; LVEF = Left-Ventricular Ejection Fraction; MI = Myocardial Infarction.

Appendix 2

Supplementary Tables for Chapter 4

Table A2-1: Results of fitting Cox proportional hazards models. Hazard ratios, 95% confidence intervals, and p-values for each of the five baseline heart rate groups greater than or equal to 65bpm, relative to a baseline heart rate <65bpm, in the pooled population of patients included in the High Risk MI Database.

	Group 2 65-69bpm	Group 3 70-74bpm	Group 4 75-79bpm	Group 5 80-84bpm	Group 6 ≥85bpm	P-value for Interaction*
	Hazard Ratio (95% Confidence Interval), p-value					
Mortality-Related Endpoints						
All-cause death, n = 5108	1.12 (1.15 to 1.25) 0.061	1.15 (1.04-1.27), 0.0073	1.28 (1.15 to 1.42), <0.001	1.35 (1.22 to 1.49), <0.001	1.67 (1.52 to 1.83), <0.001	0.076
Cardiovascular death, n = 4387	1.13 (1.00 to 1.28), 0.052	1.13 (1.01 to 1.26), 0.027	1.30 (1.16 to 1.46), <0.001	1.37 (1.24 to 1.54), <0.001	1.71 (1.55 to 1.89), <0.001	0.040
Hospitalisation-related endpoints						
Cardiovascular hospitalisation, n = 13111	1.01 (0.95 to 1.08), 0.75	0.98 (0.92 to 1.03), 0.39	1.02 (0.96 to 1.08), 0.55	0.99 (0.94 to 1.05), 0.83	1.09 (1.03 to 1.15), 0.0016	0.0025
Heart failure hospitalisation, n = 3375	1.24 (1.08 to 1.43), 0.0025	1.23 (1.08 to 1.39), 0.0013	1.37 (1.20 to 1.57), <0.001	1.49 (1.32 to 1.69), <0.001	1.82 (1.62 to 2.04), <0.001	0.071
Other Individual Endpoints						
Subsequent MI (fatal or non-fatal), n = 3116	1.06 (0.93 to 1.21), 0.36	0.95 (0.84 to 1.07), 0.38	0.98 (0.86 to 1.11), 0.71	1.00 (0.88 to 1.13), 0.99	1.17 (1.04 to 1.31), 0.0069	0.35
Stroke (fatal or non-fatal), n = 937	0.99 (0.77 to 1.27), 0.94	1.03 (0.83 to 1.28), 0.77	1.19 (0.94 to 1.50), 0.14	1.02 (0.82 to 1.28), 0.84	1.13 (0.92 to 1.39), 0.24	0.44
Composite Endpoints						
Cardiovascular death or non-fatal MI, n = 6104	1.07 (0.97 to 1.18), 0.20	1.05 (0.96 to 1.14), 0.30	1.10 (1.00 to 1.21), 0.044	1.18 (1.08 to 1.29), <0.001	1.39 (1.28 to 1.51), <0.001	0.57
Cardiovascular death or non-fatal stroke, n = 4939	1.14 (1.01 to 1.28), 0.031	1.12 (1.01 to 1.24), 0.036	1.31 (1.18 to 1.46), <0.001	1.31 (1.18 to 1.45), <0.001	1.64 (1.50 to 1.80), <0.001	0.12
Cardiovascular death or heart failure hospitalisation, n = 6646	1.16 (1.05 to 1.29), 0.0037	1.18 (1.08 to 1.29), <0.001	1.31 (1.19 to 1.44), <0.001	1.41 (1.29 to 1.54), <0.001	1.76 (1.62 to 1.90), <0.001	0.027
Cardiovascular death, non-fatal MI, or non-fatal stroke, n = 6597	1.07 (0.97 to 1.18), 0.15	1.04 (0.96 to 1.13), 0.34	1.13 (1.03 to 1.23), 0.011	1.15 (1.06 to 1.26), 0.0012	1.37 (1.27 to 1.49), <0.001	0.54
Cardiovascular death, non-fatal MI, non-fatal stroke or heart failure hospitalisation, n = 8457	1.10 (1.01 to 1.20), 0.023	1.10 (1.02 to 1.19), 0.012	1.17 (1.08 to 1.27), <0.001	1.24 (1.15 to 1.34), <0.001	1.48 (1.38 to 1.59), <0.001	0.12

Cardiovascular death or cardiovascular hospitalisation, n = 15017	1.01 (0.95 to 1.08), 0.66	1.00 (0.94 to 1.05), 0.88	1.05 (0.99 to 1.11), 0.099	1.04 (0.98 to 1.10), 0.21	1.18 (1.12 to 1.24), <0.001	0.034

*P-values for the likelihood ratio test comparing the model containing the interaction heart rate group x study, and the model containing only heart rate group and study additively. MI = Myocardial Infarction.

Models were additionally adjusted for: age; sex; race; body mass index (BMI); smoking history; diabetes; hypertension; angina; prior myocardial infarction (MI); atrial fibrillation (AF); dyslipidaemia; heart failure (HF); chronic obstructive pulmonary disease; diastolic blood pressure (DBP); Killip class; intake of certain drugs at randomisation which were aspirin, statins, vitamin K antagonists, diuretics and cardiac glycosides; and study.

Table A2-2: Results of fitting Cox proportional hazards models. Hazard ratios, 95% confidence intervals, and p-values for a 5bpm higher baseline heart rate, in the pooled population of patients included in the High Risk MI Database.

	Hazard Ratio (95% Confidence Interval), p-value	P-value for Interaction*
Mortality-Related Endpoints		
All-cause death, n = 5108	1.07 (1.06 to 1.09), <0.001	0.082
Cardiovascular death, n = 4387	1.08 (1.07 to 1.09), <0.001	0.099
Hospitalisation-Related Endpoints		
Cardiovascular hospitalisation, n = 13111	1.01 (1.00 to 1.02), 0.0059	<0.001
Heart failure hospitalisation, n = 3375	1.08 (1.07 to 1.10), <0.001	0.059
Other Individual Endpoints		
Subsequent MI (fatal or non-fatal), n = 3116	1.02 (1.00 to 1.03), 0.0086	0.0045
Stroke (fatal or non-fatal), n = 937	1.02 (1.00 to 1.05), 0.062	0.36
Composite Endpoints		
Cardiovascular death or non-fatal MI, n = 6104	1.05 (1.04 to 1.06), <0.001	0.65
Cardiovascular death or non-fatal stroke, n = 4939	1.07 (1.06 to 1.09), <0.001	0.43
Cardiovascular death or heart failure hospitalisation, n = 6646	1.08 (1.07 to 1.09), <0.001	0.068
Cardiovascular death, non-fatal MI, or non-fatal stroke, n = 6597	1.05 (1.04 to 1.06), <0.001	0.42
Cardiovascular death, non-fatal MI, non-fatal stroke or heart failure hospitalisation, n = 8457	1.06 (1.05 to 1.07), <0.001	0.079
Cardiovascular death or cardiovascular hospitalisation, n = 15017	1.022 (1.015 to 1.03), <0.001	0.0027

*P-values for the likelihood ratio test comparing the model containing the interaction heart rate x study, and the model containing only heart rate and study additively. MI = Myocardial Infarction.

Models were additionally adjusted for: age; sex; race; body mass index (BMI); smoking history; diabetes; hypertension; angina; prior myocardial infarction (MI); atrial fibrillation (AF); dyslipidaemia; heart failure (HF); chronic obstructive pulmonary disease; diastolic blood pressure (DBP); Killip class; intake of certain drugs at randomisation which were aspirin, statins, vitamin K antagonists, diuretics and cardiac glycosides; and study.

Table A2-3: C-statistics and likelihood ratio tests for the model excluding resting heart rate and the model including the baseline heart rate groups variable, which produced the results shown in Table A2-1 in the pooled population of patients included in the High Risk MI Database.

		C-statistic	Likelihood Ratio Test Statistic, p-value
Mortality-Related Endpoints			
All-cause death, n = 5108	Model	0.712	
	Model + Baseline	0.719	151.83, <0.001
Cardiovascular death, n = 4387	Model	0.715	
	Model + Baseline	0.723	147.40, <0.001
Hospitalisation-Related Endpoints			
Cardiovascular hospitalisation, n = 13111	Model	0.581	
	Model + Baseline	0.582	19.57, 0.0015
Heart failure hospitalisation, n = 3375	Model	0.727	
	Model + Baseline	0.735	126.81, <0.001
Other Individual Endpoints			
Subsequent MI (fatal or non-fatal), n = 3116	Model	0.650	
	Model + Baseline	0.652	16.30, 0.0060
Stroke (fatal or non-fatal), n = 937	Model	0.675	
	Model + Baseline	0.679	3.78, 0.58
Composite Endpoints			
Cardiovascular death or non-fatal MI, n = 6104	Model	0.675	
	Model + Baseline	0.679	82.07, <0.001
Cardiovascular death or non-fatal stroke, n = 4939	Model	0.703	
	Model + Baseline	0.709	140.14, <0.001
Cardiovascular death or heart failure hospitalisation, n = 6646	Model	0.710	
	Model + Baseline	0.717	231.82, <0.001
Cardiovascular death, non-fatal MI, or non-fatal stroke, n = 6597	Model	0.670	
	Model + Baseline	0.674	80.71, <0.001
Cardiovascular death, non-fatal MI, non-fatal stroke or heart failure hospitalisation, n = 8457	Model	0.677	
	Model + Baseline	0.682	145.71, <0.001
Cardiovasuclar death or cardiovascular hospitalisation, n = 15017	Model	0.588	
	Model + Baseline	0.591	55.68, <0.001

'Model' is the multivariate model excluding heart rate which included: age; sex; race; body mass index (BMI); smoking history; diabetes; hypertension; angina; prior myocardial infarction (MI); atrial fibrillation (AF); dyslipidaemia; heart failure (HF); chronic obstructive pulmonary disease; diastolic blood pressure (DBP); Killip class; intake of certain drugs at randomisation which were aspirin, statins, vitamin K antagonists, diuretics and cardiac glycosides; and study.

'Model + Baseline' is the multivariate model described above including the baseline resting heart rate group variable.

The likelihood ratio test statistic and corresponding p-value were computed by comparing the multivariate model including baseline resting heart rate to the multivariate model excluding resting heart rate.

Table A2-4: C-statistics and likelihood ratio tests for the model excluding resting heart rate and the model including the continuous baseline heart rate variable, which produced the results shown in Table A2-2 in the pooled population of patients included in the High Risk MI Database.

		C-statistic	Likelihood Ratio Test Statistic, p-value
Mortality-Related Endpoints			
All-cause death, n = 5108	Model	0.712	
	Model + Baseline	0.720	173.85, <0.001
Cardiovascular death, n = 4387	Model	0.715	
	Model + Baseline	0.724	174.72, <0.001
Hospitalisation-Related Endpoints			
Cardiovascular hospitalisation, n = 13111	Model	0.581	
	Model + Baseline	0.582	7.53, 0.0060
Heart failure hospitalisation, n = 3375	Model	0.727	
	Model + Baseline	0.736	139.77, <0.001
Other Individual Endpoints			
Subsequent MI (fatal or non-fatal), n = 3116	Model	0.650	
	Model + Baseline	0.651	6.83, 0.0089
Stroke (fatal or non-fatal), n = 937	Model	0.675	
	Model + Baseline	0.676	3.44, 0.064
Composite Endpoints			
Cardiovascular death or non-fatal MI, n = 6104	Model	0.675	
	Model + Baseline	0.679	89.39, <0.001
Cardiovascular death or non-fatal stroke, n = 4939	Model	0.703	
	Model + Baseline	0.710	166.24, <0.001
Cardiovascular death or heart failure hospitalisation, n = 6646	Model	0.710	
	Model + Baseline	0.719	271.61, <0.001
Cardiovascular death, non-fatal MI, or non-fatal stroke, n = 6597	Model	0.670	
	Model + Baseline	0.674	88.79, <0.001
Cardiovascular death, non-fatal MI, non-fatal stroke or heart failure hospitalisation, n = 8457	Model	0.677	
	Model + Baseline	0.683	162.43, <0.001
Cardiovasuclar death or cardiovascular hospitalisation, n = 15017	Model	0.588	
	Model + Baseline	0.591	44.93, <0.001

'Model' is the multivariate model excluding heart rate which included: age; sex; race; body mass index (BMI); smoking history; diabetes; hypertension; angina; prior myocardial infarction (MI); atrial fibrillation (AF); dyslipidaemia; heart failure (HF); chronic obstructive pulmonary disease; diastolic blood pressure (DBP); Killip class; intake of certain drugs at randomisation which were aspirin, statins, vitamin K antagonists, diuretics and cardiac glycosides; and study.

'Model + Baseline' is the multivariate model described above including the continuous baseline resting heart rate variable.

The likelihood ratio test statistic and corresponding p-value were computed by comparing the multivariate model including baseline resting heart rate to the multivariate model excluding resting heart rate.

Table A2-5: P-values for the Grambsch and Therneau 1994 test for non-proportionality of hazards for each of the five baseline heart rate groups greater than or equal to 65bpm, relative to a baseline heart rate <65bpm, in the pooled population of patients included in the High Risk MI Database.

	Group 2 65-69bpm n = 3278 P-value	Group 3 70-74bpm n = 5250	Group 4 75-79bpm n = 3740	Group 5 80-84bpm n = 4558	Group 6 ≥85bpm n = 6141
Mortality-Related Endpoints					
All-cause death, n = 5108	0.82	0.94	0.018	<0.001	<0.001
Cardiovascular death, n = 4387	0.89	0.62	0.044	<0.001	<0.001
Hospitalisation-related endpoints					
Cardiovascular hospitalisation, n = 13111	0.69	0.47	0.70	0.30	0.0078
Heart failure hospitalisation, n = 3375	0.35	0.38	0.32	0.043	0.012
Other Individual Endpoints					
Subsequent MI (fatal or non-fatal), n = 3116	0.92	0.61	0.83	0.067	<0.001
Stroke (fatal or non-fatal), n = 937	0.72	0.94	0.44	0.054	0.17
Composite Endpoints					
Cardiovascular death or non-fatal MI, n = 6104	0.58	0.16	0.78	0.014	<0.001
Cardiovascular death or non-fatal stroke, n = 4939	0.94	0.71	0.083	<0.001	<0.001
Cardiovascular death or heart failure hospitalisation, n = 6646	0.64	0.50	0.061	<0.001	<0.001
Cardiovascular death, non-fatal MI, or non-fatal stroke, n = 6597	0.85	0.30	0.64	0.0040	<0.001
Cardiovascular death, non-fatal MI, non-fatal stroke or heart failure hospitalisation, n = 8457	0.66	0.75	0.22	<0.001	<0.001
Cardiovascular death or cardiovascular hospitalisation, n = 15017	0.75	0.44	0.73	0.038	<0.001

MI = Myocardial Infarction.

Table A2-6: P-values for the Grambsch and Therneau 1994 test for non-proportionality of hazards for an elevated continuous baseline heart rate, in the pooled population of patients included in the High Risk MI Database.

Mortality-Related Endpoints	**P-value**
All-cause death, n = 5108	<0.001
Cardiovascular death, n = 4387	<0.001
Hospitalisation-Related Endpoints	
Cardiovascular hospitalisation, n = 13111	<0.001
Heart failure hospitalisation, n = 3375	<0.001
Other Individual Endpoints	
Subsequent MI (fatal or non-fatal), n = 3116	<0.001
Stroke (fatal or non-fatal), n = 937	0.045
Composite Endpoints	
Cardiovascular death or non-fatal MI, n = 6104	<0.001
Cardiovascular death or non-fatal stroke, n = 4939	<0.001
Cardiovascular death or heart failure hospitalisation, n = 6646	<0.001
Cardiovascular death, non-fatal MI, or non-fatal stroke, n = 6597	<0.001
Cardiovascular death, non-fatal MI, non-fatal stroke or heart failure hospitalisation, n = 8457	<0.001
Cardiovascular death or cardiovascular hospitalisation, n = 15017	<0.001

MI = Myocardial Infarction.

Table A2-7: Results of fitting Cox proportional hazards models. Hazard ratios, 95% confidence intervals, and p-values for each of the five baseline heart rate groups greater than or equal to 65bpm, relative to a baseline heart rate <65bpm, in the CAPRICORN, EPHESUS, OPTIMAAL and VALIANT populations, for the outcomes that showed a significant interaction between heart rate and study.

		Group 2 65-69bpm	Group 3 70-74bpm	Group 4 75-79bpm	Group 5 80-84bpm	Group 6 ≥85bpm
		Hazard Ratio (95% Confidence Interval), p-value				
Mortality-Related Endpoints						
Cardiovascular death, n = 4387	CAPRICORN	1.09 (0.57 to 2.11), 0.79	1.67 (0.98 to 2.85), 0.60	2.01 (1.17 to 3.44), 0.011	1.52 (0.87 to 2.66), 0.14	1.65 (0.98 to 2.79), 0.59
	EPHESUS	1.28 (0.99 to 1.66), 0.60	1.20 (0.95 to 1.51), 0.13	1.30 (1.01 to 1.68), 0.040	1.36 (1.07 to 1.73), 0.011	1.83 (1.46 to 2.29), <0.001
	OPTIMAAL	1.25 (0.93 to 1.69), 0.14	1.40 (1.08 to 1.83), 0.013	1.30 (0.96 to 1.76), 0.092	1.80 (1.40 to 2.32), <0.001	2.06 (1.64 to 2.59), <0.001
	VALIANT	1.02 (0.86 to 1.21), 0.78	0.98 (0.85 to 1.14), 0.82	1.22 (1.05 to 1.42), 0.0099	1.21 (1.05 to 1.40), 0.0088	1.54 (1.35 to 1.75), <0.001
Hospitalisation-Related Endpoints						
Cardiovascular hospitalisation, n = 13111	CAPRICORN	1.04 (0.72 to 1.50), 0.84	1.12 (0.82 to 1.55), 0.47	1.42 (1.03 to 1.96), 0.032	1.07 (0.77 to 1.49), 0.68	1.40 (1.03 to 1.89), 0.032
	EPHESUS	0.95 (0.83 to 1.09), 0.49	1.01 (0.90 to 1.14), 0.83	1.05 (0.92 to 1.19), 0.50	1.11 (0.98 to 1.25), 0.11	1.25 (1.11 to 1.41), <0.001
	OPTIMAAL	1.04 (0.91 to 1.19), 0.53	1.02 (0.91 to 1.15), 0.70	1.04 (0.91 to 1.19), 0.54	0.94 (0.83 to 1.06), 0.31	0.98 (0.88 to 1.10), 0.73
	VALIANT	1.02 (0.93 to 1.11), 0.74	0.93 (0.86 to 1.01), 0.071	0.97 (0.88 to 1.05), 0.44	0.96 (0.88 to 1.04), 0.30	1.06 (0.98 to 1.14), 0.14
Composite Endpoints						
Cardiovascular death or heart failure hospitalisation, n = 6646	CAPRICORN	1.27 (0.79 to 2.03), 0.33	1.57 (1.05 to 2.35), 0.029	1.96 (1.30 to 2.94), 0.0012	1.38 (0.91 to 2.11), 0.13	1.81 (1.23 to 2.67), 0.0028
	EPHESUS	1.21 (0.99 to 1.49), 0.065	1.22 (1.02 to 1.47), 0.028	1.31 (1.07 to 1.59), 0.0075	1.44 (1.20 to 1.73), <0.001	1.89 (1.59 to 2.25), <0.001
	OPTIMAAL	1.23 (0.96 to 1.56), 0.10	1.46 (1.18 to 1.81), <0.001	1.34 (1.05 to 1.71), 0.018	1.76 (1.43 to 2.17), <0.001	1.97 (1.63 to 2.38), <0.001
	VALIANT	1.10 (0.96 to 1.26), 0.19	1.04 (0.92 to 1.17), 0.56	1.22 (1.07 to 1.38), 0.0025	1.26 (1.12 to 1.42), <0.001	1.59 (1.43 to 1.77), <0.001
Cardiovascular death or cardiovascular hospitalisation, n = 15017	CAPRICORN	1.10 (0.79 to 1.55), 0.57	1.21 (0.90 to 1.63), 0.20	1.50 (1.11 to 2.02), 0.0078	1.19 (0.87 to 1.61), 0.27	1.48 (1.11 to 1.96), 0.0067
	EPHESUS	0.99 (0.86 to 1.12), 0.82	1.05 (0.93 to 1.18), 0.42	1.07 (0.95 to 1.22), 0.27	1.13 (1.00 to 1.27), 0.049	1.29 (1.15 to 1.45), <0.001
	OPTIMAAL	1.05 (0.93 to 1.20), 0.43	1.04 (0.93 to 1.17), 0.51	1.07 (0.94 to 1.22), 0.31	1.01 (0.89 to 1.13), 0.91	1.08 (0.97 to 1.20), 0.18
	VALIANT	1.00 (0.92 to 1.09), 0.96	0.94 (0.87 to 1.02), 0.12	1.00 (0.92 to 1.09), 0.997	0.99 (0.92 to 1.09), 0.88	1.15 (1.07 to 1.24), <0.001

MI = Myocardial Infarction.

Models were additionally adjusted for: age; sex; race; body mass index (BMI); smoking history; diabetes; hypertension; angina; prior myocardial infarction (MI); atrial fibrillation (AF); dyslipidaemia; heart failure (HF); chronic obstructive pulmonary disease; diastolic blood pressure (DBP); Killip class; and intake of certain drugs at randomisation which were aspirin, statins, vitamin K antagonists, diuretics and cardiac glycosides.

Table A2-8: Results of fitting Cox proportional hazards models. Hazard ratios, 95% confidence intervals, and p-values for a 5bpm higher baseline heart rate, in CAPRICORN, EPHESUS, OPTIMAAL and VALIANT populations, for the outcomes that showed a significant interaction between heart rate and study.

	CAPRICORN	EPHESUS	OPTIMAAL	VALIANT
	Hazard Ratio (95% Confidence Interval), p-value			
Hospitalisation-Related Endpoints				
Cardiovascular hospitalisation, n = 13111	1.05 (1.01 to 1.09), 0.0086	1.03 (1.02 to 1.05), <0.001	0.99 (0.98 to 1.01), 0.28	1.01 (1.00 to 1.02), 0.18
Other Individual Endpoints				
Subsequent MI (fatal or non-fatal), n = 3116	1.06 (0.98 to 1.15), 0.14	1.04 (1.00 to 1.07), 0.039	0.97 (0.95 to 1.00), 0.077	1.03 (1.01 to 1.05), <0.001
Composite Endpoints				
Cardiovascular death or cardiovascular hospitalisation, n = 15017	1.05 (1.02 to 1.09), 0.0022	1.04 (1.02 to 1.05), <0.001	1.01 (0.99 to 1.02), 0.30	1.02 (1.01 to 1.03), <0.001

MI = Myocardial Infarction.

Models were additionally adjusted for: age; sex; race; body mass index (BMI); smoking history; diabetes; hypertension; angina; prior myocardial infarction (MI); atrial fibrillation (AF); dyslipidaemia; heart failure (HF); chronic obstructive pulmonary disease; diastolic blood pressure (DBP); Killip class; and intake of certain drugs at randomisation which were aspirin, statins, vitamin K antagonists, diuretics and cardiac glycosides.

Table A2-9: Results of fitting Cox proportional hazards models. Hazard ratios, 95% confidence intervals, and p-values for a heart rate ≥75bpm compared to a heart rate <75bpm in the CAPRICORN placebo population.

	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Heart Rate Adjusted for Previous
	HR (95% CI), p-value			
Primary Endpoints				
All-cause mortality, n = 150	1.24 (0.88 to 1.75), 0.21	1.62 (1.15 to 2.28), 0.0058	1.58 (1.11 to 2.25), 0.012	1.54 (1.06 to 2.22), 0.023
All-cause mortality or cardiovascular cause hospital admission, n = 366	1.30 (1.05 to 1.61), 0.017	1.30 (1.06 to 1.61), 0.014	1.23 (0.99 to 1.53), 0.067	1.27 (1.01 to 1.60), 0.043
Secondary Endpoints				
Sudden death, n = 68	1.28 (0.77 to 2.12), 0.34	1.44 (0.87 to 2.36), 0.15	1.37 (0.82 to 2.31), 0.23	1.27 (0.74 to 2.18), 0.38
Hospital admission for heart failure, n = 138	1.65 (1.14 to 2.38), 0.0075	1.91 (1.33 to 2.74), <0.001	1.74 (1.20 to 2.53), 0.0037	1.78 (1.20 to 2.62), 0.0039
Other Endpoints				
Cardiovascular-cause mortality, n = 138	1.20 (0.84 to 1.70), 0.32	1.57 (1.10 to 2.23), 0.013	1.54 (1.07 to 2.23), 0.021	1.51 (1.03 to 2.21), 0.036
Death due to heart failure, n = 30	1.88 (0.79 to 4.45), 0.15	1.76 (0.80 to 3.89), 0.16	1.59 (0.71 to 3.56), 0.26	1.68 (0.72 to 3.93), 0.23
Non-fatal myocardial infarction, n = 57	1.78 (1.02 to 3.11), 0.042	1.19 (0.70 to 2.00), 0.52	1.01 (0.58 to 1.73), 0.98	1.10 (0.62 to 1.94), 0.76
All-cause mortality or non-fatal myocardial infarction, n = 191	1.34 (0.93 to 1.81), 0.056	1.43 (1.06 to 1.92), 0.019	1.35 (0.99 to 1.83), 0.058	1.33 (0.96 to 1.84), 0.082

Models were additionally adjusted for: sex; previous diabetes; left-ventricular ejection fraction (LVEF); site of MI; and in-hospital treatment with intravenous diuretics.

Table A2-10: Results of fitting Cox proportional hazards models. Hazard ratios, 95% confidence intervals, and p-values for a 5bpm higher heart rate in the CAPRICORN placebo population.

	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Heart Rate Adjusted for Previous
	Hazard Ratio (95% Confidence Interval), p-value			
Primary Endpoints				
All-cause mortality, n = 150	1.05 (0.98 to 1.12), 0.15	1.12 (1.06 to 1.18), 0.012	1.12 (1.06 to 1.18), <0.001	1.11 (1.04 to 1.18), 0.0014
All-cause mortality or cardiovascular cause hospital admission, n = 366	1.05 (1.01 to 1.10), 0.020	1.08 (1.04 o 1.13), <0.001	1.08 (1.03 to 1.12), <0.001	1.08 (1.03 to 1.13), 0.0010
Secondary Endpoints				
Sudden death, n = 68	1.02 (0.92 to 1.13), 0.68	1.08 (0.99 to 1.19), 0.087	1.09 (0.99 to 1.20), 0.094	1.04 (0.93 to 1.16), 0.47
Hospital admission for heart failure, n = 138	1.09 (1.02 to 1.17), 0.012	1.12 (1.06 to 1.18), <0.001	1.11 (1.05 to 1.17), <0.001	1.10 (1.04 to 1.17), 0.0018
Other Endpoints				
Cardiovascular-cause mortality, n = 138	1.05 (0.98 to 1.12), 0.19	1.10 (1.04 to 1.17), <0.001	1.10 (1.03 to 1.17), 0.0031	1.09 (1.02 to 1.17), 0.015
Death due to heart failure, n = 30	1.17 (1.03 to 1.33), 0.018	1.12 (1.00 to 1.25), 0.060	1.07 (0.95 to 1.22), 0.27	1.12 (0.97 to 1.28), 0.11
Non-fatal myocardial infarction, n = 57	1.08 (0.96 to 1.20), 0.19	1.09 (0.99 to 1.20), 0.089	1.07 (0.96 to 1.19), 0.20	1.08 (0.96 to 1.21), 0.20
All-cause mortality or non-fatal myocardial infarction, n = 191	1.06 (1.00 to 1.12), 0.060	1.10 (1.05 to 1.16), <0.001	1.09 (1.04 to 1.15), <0.001	1.09 (1.02 to 1.15), 0.0057

Models were additionally adjusted for: sex; previous diabetes; left-ventricular ejection fraction (LVEF); site of MI; and in-hospital treatment with intravenous diuretics.

Table A2-11: Results of fitting Cox proportional hazards models. Hazard ratios, 95% confidence intervals and p-values for the time-updated categorical heart rate patterns 'high-low', 'low-high' and 'high-high' relative to the category 'low-low' in the CAPRICORN placebo population.

	Heart Rate Category	Hazard Ratio (95% Confidence Interval), p-value
Primary Endpoints		
All-cause mortality, n = 150	high-low	0.85 (0.47 to 1.55), 0.60
	low-high	1.20 (0.69 to 2.07), 0.52
	high-high	1.67 (1.12 to 2.49), 0.012
All-cause mortality or cardiovascular-cause hospital admission, n = 366	high-low	1.14 (0.81 to 1.59), 0.46
	low-high	1.34 (0.97 to 1.86), 0.075
	high-high	1.36 (1.06 to 1.76), 0.017
Secondary Endpoints		
Sudden death, n = 68	high-low	1.17 (0.52 to 2.63), 0.71
	low-high	1.08 (0.46 to 2.50), 0.87
	high-high	1.69 (0.93 to 3.06), 0.086
Hospital admission for heart failure, n = 138	high-low	1.22 (0.66 to 2.26), 0.52
	low-high	1.80 (1.03 to 3.13), 0.038
	high-high	2.14 (1.38 to 3.33), <0.001
Other Endpoints		
Cardiovascular-cause mortality, n = 138	high-low	0.85 (0.45 to 1.58), 0.60
	low-high	1.21 (0.69 to 2.13), 0.50
	high-high	1.59 (1.05 to 2.42), 0.028
Death due to heart failure, n = 30	high-low	0.87 (0.22 to 3.50), 0.84
	low-high	1.34 (0.38 to 4.77), 0.65
	high-high	1.79 (0.69 to 4.64), 0.23
Non-fatal myocardial infarction, n = 57	high-low	1.24 (0.55 to 2.80), 0.60
	low-high	1.12 (0.48 to 2.61), 0.79
	high-high	1.33 (0.71 to 2.50), 0.37
All-cause mortality or non-fatal myocardial infarction, n = 191	high-low	1.01 (0.61 to 1.65), 0.61
	low-high	1.13 (0.70 to 1.84), 0.61
	high-high	1.54 (1.09 to 2.19), 0.015

Patients were classified as being in the low-low category if their heart rate measurement at both the current and previous visit was below 75bpm. Similarly, patients were classified as being in the high-high category if their heart rate measurement at both the current and previous visit was greater than or equal to 75bpm, and so on.

Models were additionally adjusted for: sex; previous diabetes; left-ventricular ejection fraction (LVEF); site of MI; and in-hospital treatment with intravenous diuretics.

Table A2-12: C-statistics and likelihood ratio tests for the model excluding resting heart rate and the models including the heart rate variables that categorised subjects according to whether they had a heart rate less than, or greater than or equal to, 75bpm, which produced the results shown in Table A2-9 in the CAPRICORN placebo population.

		C-statistic	Likelihood Ratio Test Statistic, p-value
Primary Endpoints			
All-cause mortality, n = 150	Model	0.632	
	Model + Baseline	0.640	1.60, 0.021
	Model + Time-Updated	0.645	7.90, 0.0049
	Model + Time-Updated + Baseline	0.646	8.17, 0.017
	Model + Time-Updated + Previous	0.644	8.42, 0.015
All-cause mortality or cardiovascular-cause hospital admission, n = 366	Model	0.604	
	Model + Baseline	0.609	5.82, 0.016
	Model + Time-Updated	0.609	6.14, 0.013
	Model + Time-Updated + Baseline	0.613	9.22, 0.010
	Model + Time-Updated + Previous	0.610	6.45, 0.040
Secondary Endpoints			
Sudden death, n = 68	Model	0.622	
	Model + Baseline	0.636	0.94, 0.33
	Model + Time-Updated	0.630	2.07, 0.15
	Model + Time-Updated + Baseline	0.638	2.38, 0.30
	Model + Time-Updated + Previous	0.640	3.33, 0.19
Hospital admission for heart failure, n = 138	Model	0.682	
	Model + Baseline	0.692	7.53, 0.0061
	Model + Time-Updated	0.699	13.09, <0.001
	Model + Time-Updated + Baseline	0.703	16.41, <0.001
	Model + Time-Updated + Previous	0.699	14.02, <0.001
Other Endpoints			
Cardiovascular-cause mortality, n = 138	Model	0.630	
	Model + Baseline	0.636	0.99, 0.32
	Model + Time-Updated	0.641	6.38, 0.012
	Model + Time-Updated + Baseline	0.642	6.48, 0.039
	Model + Time-Updated + Previous	0.642	6.63, 0.0036
Death due to heart failure, n = 30	Model	0.733	
	Model + Baseline	0.759	2.23, 0.14
	Model + Time-Updated	0.752	2.08, 0.15
	Model + Time-Updated + Baseline	0.768	3.55, 0.17
	Model + Time-Updated + Previous	0.756	2.17, 0.34
Non-fatal myocardial infarction, n = 57	Model	0.632	
	Model + Baseline	0.657	4.35, 0.037

	Model + Time-Updated	0.636	0.409, 0.52
	Model + Time-Updated + Baseline	0.656	4.35, 0.11
	Model + Time-Updated + Previous	0.638	0.86, 0.65
All-cause mortality or non-fatal myocardial infarction, n = 191	Model	0.607	
	Model + Baseline	0.618	3.74, 0.053
	Model + Time-Updated	0.614	5.67, 0.017
	Model + Time-Updated + Baseline	0.619	7.38, 0.025
	Model + Time-Updated + Previous	0.616	6.80, 0.035

'Model' is the multivariate model excluding heart rate which included: sex; previous diabetes; left-ventricular ejection fraction (LVEF); site of MI; and in-hospital treatment with intravenous diuretics.

'Model + Baseline' is the multivariate model described above including the baseline heart rate group variable.

'Model + Time-Updated' is the multivariate model described above including the time-updated heart rate group variable.

'Model + Time-Updated + Baseline' is the multivariable model described above including both the baseline and the time-updated heart rate group variables.

'Model + Time-Updated + Previous' is the multivariate model described above including both the time-updated heart rate group variable and the previous time-updated heart rate group variable.

The likelihood ratio test statistics and corresponding p-values were computed by comparing the multivariate models including the different heart rate variables to the multivariate model excluding resting heart rate.

Table A2-13: C-statistics and likelihood ratio tests for the model excluding resting heart rate and the models including the continuous heart rate variables, which produced the results shown in Table A2-10 in the CAPRICORN placebo population.

		C-statistic	Likelihood Ratio Test Statistic, p-value
Primary Endpoints			
All-cause mortality, n = 150	Model	0.632	
	Model + Baseline	0.638	2.01, 0.157
	Model + Time-Updated	0.657	14.80, <0.001
	Model + Time-Updated + Baseline	0.657	14.80, <0.001
	Model + Time-Updated + Previous	0.658	15.12, <0.001
All-cause mortality or cardiovascular-cause hospital admission, n = 366	Model	0.604	
	Model + Baseline	0.610	5.24, 0.022
	Model + Time-Updated	0.622	15.58, <0.001
	Model + Time-Updated + Baseline	0.622	16.38, <0.001
	Model + Time-Updated + Previous	0.622	15.68, <0.001
Secondary Endpoints			
Sudden death, n = 68	Model	0.622	
	Model + Baseline	0.625	0.17, 0.68
	Model + Time-Updated	0.632	2.64, 0.10
	Model + Time-Updated + Baseline	0.631	2.69, 0.26
	Model + Time-Updated + Previous	0.640	4.21, 0.12
Hospital admission for heart failure, n = 138	Model	0.682	
	Model + Baseline	0.691	6.02, 0.014
	Model + Time-Updated	0.711	14.94, <0.001
	Model + Time-Updated + Baseline	0.711	16.33, <0.001
	Model + Time-Updated + Previous	0.710	15.58, <0.001
Other Endpoints			
Cardiovascular-cause mortality, n = 138	Model	0.630	
	Model + Baseline	0.635	1.65, 0.20
	Model + Time-Updated	0.647	9.15, 0.0025
	Model + Time-Updated + Baseline	0.647	9.19, 0.010
	Model + Time-Updated + Previous	0.647	9.37, 0.0092
Death due to heart failure, n = 30	Model	0.733	
	Model + Baseline	0.773	4.97, 0.026
	Model + Time-Updated	0.758	2.89, 0.089
	Model + Time-Updated + Baseline	0.775	6.07, 0.048
	Model + Time-Updated + Previous	0.758	2.90, 0.24
Non-fatal myocardial infarction, n = 57	Model	0.632	
	Model + Baseline	0.651	1.66, 0.20
	Model + Time-Updated	0.648	2.56, 0.11

	Model + Time-Updated + Baseline	0.652	3.13, 0.21
	Model + Time-Updated + Previous	0.649	2.60, 0.27
All-cause mortality or non-fatal myocardial infarction, n = 191	Model	0.607	
	Model + Baseline	0.618	3.42, 0.064
	Model + Time-Updated	0.629	12.68, <0.001
	Model + Time-Updated + Baseline	0.631	13.04, 0.0015
	Model + Time-Updated + Previous	0.630	13.24, 0.0013

'Model' is the multivariate model excluding heart rate which included: sex; previous diabetes; left-ventricular ejection fraction (LVEF); site of MI; and in-hospital treatment with intravenous diuretics.

'Model + Baseline' is the multivariate model described above including the continuous baseline heart rate variable.

'Model + Time-Updated' is the multivariate model described above including the continuous time-updated heart rate variable.

'Model + Time-Updated + Baseline' is the multivariable model described above including both the continuous baseline and time-updated heart rate variables.

'Model + Time-Updated + Previous' is the multivariate model described above including both the continuous time-updated heart rate variable and the previous time-updated heart rate variable.

The likelihood ratio test statistics and corresponding p-values were computed by comparing the multivariate models including the different heart rate variables to the multivariate model excluding resting heart rate.

Table A2-14: C-statistics and likelihood ratio tests for the model excluding resting heart rate and the models including the time-updated categorical heart rate patterns variable, which produced the results shown in Table A2-11 in the CAPRICORN placebo population.

		C-statistic	Likelihood Ratio Test Statistic, p-value
Primary Endpoints			
All-cause mortality, n = 150	Model	0.632	
	Model + Pattern	0.646	10.03, 0.018
All-cause mortality or cardiovascular-cause hospital admission, n = 366	Model	0.604	
	Model + Pattern	0.611	6.69, 0.083
Secondary Endpoints			
Sudden death, n = 68	Model	0.622	
	Model + Pattern	0.640	3.60, 0.31
Hospital admission for heart failure, n = 138	Model	0.682	
	Model + Pattern	0.699	14.02, 0.0029
Other Endpoints			
Cardiovascular-cause mortality, n = 138	Model	0.630	
	Model + Pattern	0.642	7.80, 0.050
Death due to heart failure, n = 30	Model	0.733	
	Model + Pattern	0.752	2.40, 0.49
Non-fatal myocardial infarction, n = 57	Model	0.632	
	Model + Pattern	0.638	0.86, 0.83
All-cause mortality or non-fatal myocardial infarction, n = 191	Model	0.607	
	Model + Pattern	0.617	7.61, 0.055

'Model' is the multivariate model excluding heart rate which included: sex; previous diabetes; left-ventricular ejection fraction (LVEF); site of MI; and in-hospital treatment with intravenous diuretics.

'Model + Pattern' is the multivariate model described above including the time-updated categorical heart rate patterns variable.

The likelihood ratio test statistic and corresponding p-value were computed by comparing the multivariate model including the time-updated categorical heart rate patterns variable to the multivariate model excluding resting heart rate.

Table A2-15: P-values for the Grambsch and Therneau 1994 test for non-proportionality of hazards for a heart rate ≥75bpm compared to a heart rate <75bpm in the CAPRICORN placebo population.

	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Heart Rate Adjusted for Previous
	P-value			
Primary Endpoints				
All-cause mortality, n = 150	0.50	0.13	0.076	0.063
All-cause mortality or cardiovascular cause hospital admission, n = 366	0.16	0.27	0.41	0.080
Secondary Endpoints				
Sudden death, n = 68	0.25	0.48	0.26	0.37
Hospital admission for heart failure, n = 138	0.49	0.74	0.65	0.68
Other Endpoints				
Cardiovascular-cause mortality, n = 138	0.28	0.19	0.097	0.11
Death due to heart failure, n = 30	0.84	0.077	0.071	0.036
Non-fatal myocardial infarction, n = 57	0.87	0.18	0.11	0.17
All-cause mortality or non-fatal myocardial infarction, n = 191	0.37	0.41	0.014	0.032

Table A2-16: P-values for the Grambsch and Therneau 1994 test for non-proportionality of hazards for an elevated continuous heart rate in the CAPRICORN placebo population.

	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Heart Rate Adjusted for Previous
	P-value			
Primary Endpoints				
All-cause mortality, n = 150	0.70	0.18	0.15	0.17
All-cause mortality or cardiovascular cause hospital admission, n = 366	0.41	0.85	0.65	0.55
Secondary Endpoints				
Sudden death, n = 68	0.55	0.997	0.89	0.87
Hospital admission for heart failure, n = 138	0.25	0.45	0.68	0.90
Other Endpoints				
Cardiovascular-cause mortality, n = 138	0.58	0.38	0.28	0.38
Death due to heart failure, n = 30	0.97	0.055	0.029	0.018
Non-fatal myocardial infarction, n = 57	0.20	0.52	0.21	0.27
All-cause mortality or non-fatal myocardial infarction, n = 191	0.46	0.14	0.069	0.20

Table A2-17: P-values for the Grambsch and Therneau 1994 test for non-proportionality of hazards for the time-updated categorical heart rate patterns 'high-low', 'low-high' and 'high-high' relative to the category 'low-low' in the CAPRICORN placebo population.

	Heart Rate Category	P-value
Primary Endpoints		
All-cause mortality, n = 150	high-low	0.64
	low-high	0.076
	high-high	0.42
All-cause mortality or cardiovascular-cause hospital admission, n = 366	high-low	0.28
	low-high	0.22
	high-high	0.99
Secondary Endpoints		
Sudden death, n = 68	high-low	0.57
	low-high	0.12
	high-high	0.55
Hospital admission for heart failure, n = 138	high-low	0.081
	low-high	0.76
	high-high	0.17
Other Endpoints		
Cardiovascular-cause mortality, n = 138	high-low	0.52
	low-high	0.20
	high-high	0.52
Death due to heart failure, n = 30	high-low	0.060
	low-high	0.50
	high-high	0.64
Non-fatal myocardial infarction, n = 57	high-low	0.72
	low-high	0.47
	high-high	0.31
All-cause mortality or non-fatal myocardial infarction, n = 191	high-low	0.69
	low-high	0.11
	high-high	0.15

Patients were classified as being in the low-low category if their heart rate measurement at both the current and previous visit was below 75bpm. Similarly, patients were classified as being in the high-high category if their heart rate measurement at both the current and previous visit was greater than or equal to 75bpm, and so on.

Appendix 3

Supplementary Tables for Chapter 5

Table A3-1: Results of fitting Cox proportional hazards models. Hazard ratios, 95% confidence intervals, and p-values for a heart rate ≥70bpm compared to a heart rate <70bpm in the EUROPA population.

	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Heart Rate Adjusted for Previous
	Hazard Ratio (95% Confidence Interval), p-value			
Primary Composite Endpoint				
Cardiovascular mortality, MI or cardiac arrest, n = 1091	1.02 (0.90 to 1.16), 0.71	1.07 (0.95 to 1.21), 0.25	1.07 (0.94 to 1.23), 0.28	1.05 (0.92 to 1.21), 0.49
Individual Components of the Primary Composite Endpoint				
Cardiovascular mortality, n = 464	1.15 (0.95 to 1.39), 0.16	1.30 (1.08 to 1.57), 0.0059	1.28 (1.05 to 1.56), 0.015	1.24 (1.01 to 1.53), 0.042
Fatal or non-fatal MI, n = 738	0.95 (0.81 to 1.11), 0.53	0.99 (0.85 to 1.15), 0.85	1.00 (0.85 to 1.18), 0.97	0.99 (0.84 to 1.17), 0.90
Cardiac arrest, n = 17	0.98 (0.35 to 2.69), 0.96	2.56 (0.92 to 7.12), 0.071	3.20 (1.05 to 9.78), 0.041	4.19 (1.35 to 13.04), 0.013
Other Composite Endpoints				
Total mortality, MI, unstable angina or cardiac arrest, n = 1946	1.03 (0.93 to 1.13), 0.57	1.16 (1.06 to 1.27), 0.0017	1.17 (1.06 to 1.29), 0.0016	1.13 (1.02 to 1.26), 0.017
Other Mortality Endpoints				
Total mortality, n = 795	1.23 (1.06 to 1.42), 0.0061	1.62 (1.40 to 1.86), <0.001	1.59 (1.37 to 1.85), <0.001	1.52 (1.30 to 1.78), <0.001
Other Individual Endpoints				
Unstable angina, n = 708	0.91 (0.78 to 1.07), 0.27	0.92 (0.79 to 1.07), 0.29	0.94 (0.80 to 1.12), 0.49	0.92 (0.77 to 1.09), 0.33
Stroke, n = 199	0.90 (0.66 to 1.21), 0.47	1.18 (0.89 to 1.57), 0.25	1.26 (0.93 to 1.71), 0.13	1.17 (0.85 to 1.61), 0.35
Revascularisation, n = 1177	0.86 (0.76 to 0.98), 0.020	0.89 (0.79 to 1.00), 0.052	0.92 (0.81 to 1.05), 0.22	0.96 (0.84 to 1.10), 0.59
Heart failure requiring hospital admission, n = 166	1.28 (0.93 to 1.76), 0.14	1.47 (1.08 to 2.02), 0.015	1.41 (1.01 to 1.97), 0.042	1.14 (0.81 to 1.62), 0.46

MI = Myocardial Infarction.

Models were additionally adjusted for: age; sex; history of percutaneous coronary intervention (PCI); history of coronary artery bypass graft (CABG); peripheral artery disease (PAD); diabetes mellitus; hypercholesterolemia; treatment with platelet inhibitors; lipid-lowering therapies; beta-blockers; calcium channel blockers (CCBs); and diuretics (potassium sparing and other); and systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Table A3-2: Results of fitting Cox proportional hazards models. Hazard ratios, 95% confidence intervals, and p-values for a 5bpm higher heart rate in the EUROPA population.

	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Heart Rate Adjusted for Previous
	Hazard Ratio (95% Confidence Interval), p-value			
Primary Composite Endpoint				
Cardiovascular mortality, MI or cardiac arrest, n = 1091	1.03 (1.00 to 1.06), 0.098	1.03 (1.01 to 1.06), 0.019	1.03 (1.00 to 1.06), 0.076	1.03 (1.00 to 1.06), 0.16
Individual Components of the Primary Composite Endpoint				
Cardiovascular mortality, n = 464	1.06 (1.02 to 1.11), 00058	1.11 (1.07 to 1.16), <0.001	1.10 (1.06 to 1.15), <0.001	1.10 (1.05 to 1.15), <0.001
Fatal or non-fatal MI, n = 738	1.00 (0.96 to 1.04), 0.999	1.02 (0.98 to 1.05), 0.38	1.02 (0.98 to 1.06), 0.32	1.02 (0.98 to 1.06), 0.41
Cardiac arrest, n = 17	0.95 (0.75 to 1.21), 0.67	1.15 (0.94 to 1.41), 0.17	1.25 (1.01 to 1.56), 0.045	1.27 (1.02 to 1.59), 0.035
Other Composite Endpoints				
Total mortality, MI, unstable angina or cardiac arrest, n = 1946	1.03 (1.01 to 1.05), 0.0072	1.06 (1.04 to 1.09), <0.001	1.06 (1.04 to 1.09), <0.001	1.06 (1.04 to 1.09), <0.001
Other Mortality Endpoints				
Total mortality, n = 795	1.09 (1.05 to 1.13), <0.001	1.17 (1.13 to 1.20), <0.001	1.16 (1.13 to 1.20), <0.001	1.16 (1.12 to 1.20), <0.001
Other Individual Endpoints				
Unstable angina, n = 708	0.99 (0.95 to 1.02), 0.45	1.00 (0.96 to 1.03), 0.84	1.00 (0.96 to 1.05), 0.87	1.00 (0.96 to 1.05), 0.92
Stroke, n = 199	0.99 (0.92 to 1.06), 0.72	1.05 (0.99 to 1.12), 0.12	1.07 (1.00 to 1.16), 0.051	1.07 (0.99 to 1.15), 0.10
Revascularisation, n = 1177	0.96 (0.93 to 0.99), 0.0070	0.96 (0.94 to 0.99), 0.011	0.98 (0.94 to 1.10), 0.15	0.98 (0.95 to 1.02), 0.29
Heart failure requiring hospital admission, n = 166	1.08 (1.00 to 1.16), 0.052	1.17 (1.10 to 1.25), <0.001	1.18 (1.10 to 1.26), <0.001	1.10 (1.01 to 1.19), 0.021

MI = Myocardial Infarction.

Models were additionally adjusted for: age; sex; history of percutaneous coronary intervention (PCI); history of coronary artery bypass graft (CABG); peripheral artery disease (PAD); diabetes mellitus; hypercholesterolemia; treatment with platelet inhibitors; lipid-lowering therapies; beta-blockers; calcium channel blockers (CCBs); and diuretics (potassium sparing and other); and systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Table A3-3: Results of fitting Cox proportional hazards models. Hazard ratios, 95% confidence intervals, and p-values for the time-updated categorical heart rate patterns 'high-low', 'low-high' and 'high-high' relative to the category 'low-low' in the EUROPA population.

	Heart Rate Category	Hazard Ratio (95% Confidence Interval), p-value
Primary Composite Endpoint		
Cardiovascular mortality, MI or cardiac arrest, n = 1091	high-low	1.05 (0.86 to 1.27), 0.64
	low-high	1.04 (0.86 to 1.26), 0.65
	high-high	1.11 (0.96 to 1.28), 0.18
Individual Components of the Primary Composite Endpoint		
Cardiovascular mortality, n = 464	high-low	1.08 (0.79 to 1.45), 0.64
	low-high	1.20 (0.90 to 1.61), 0.21
	high-high	1.38 (1.11 to 1.72), 0.0040
Fatal or non-fatal MI, n = 738	high-low	1.00 (0.80 to 1.26), 0.98
	low-high	1.00 (0.79 to 1.26), 0.99
	high-high	0.98 (0.82 to 1.17), 0.83
Cardiac Arrest, n = 17	high-low	-
	low-high	-
	high-high	-
Other Composite Endpoints		
Total mortality, MI, unstable angina or cardiac arrest, n = 1946	high-low	1.08 (0.93 to 1.24), 0.31
	low-high	1.16 (1.01 to 1.34), 0.035
	high-high	1.19 (1.07 to 1.32), 0.0020
Other Mortality Endpoints		
Total mortality, n = 795	high-low	1.12 (0.88 to 1.42), 0.35
	low-high	1.48 (1.19 to 1.84), <0.001
	high-high	1.75 (1.48 to 2.07), <0.001
Other Individual Endpoints		
Unstable Angina, n = 708	high-low	1.16 (0.92 to 1.45), 0.21
	low-high	1.06 (0.84 to 1.34), 0.62
	high-high	0.90 (0.75 to 1.09), 0.27
Stroke, n = 199	high-low	1.15 (0.73 to 1.79), 0.55
	low-high	1.29 (0.84 to 1.98), 0.24
	high-high	1.19 (0.85 to 1.67), 0.32
Revascularisation, n = 1177	high-low	0.88 (0.73 to 1.05), 0.16
	low-high	1.02 (0.86 to 1.21), 0.81
	high-high	0.78 (0.67 to 0.90), 0.0010
Heart failure requiring hospital admission, n = 166	high-low	1.32 (0.80 to 2.17), 0.28
	low-high	0.74 (0.39 to 1.38), 0.34
	high-high	1.98 (1.38 to 2.84), <0.001

Patients were classified as being in the low-low category if their heart rate measurement at both the current and previous visit was below 70bpm. Similarly, patients were classified as being in the high-high category if their heart rate measurement at both the current and previous visit was greater than or equal to 70bpm, and so on.

There were not enough Cardiac Arrest events to allow analysis to be done in this case. MI = Myocardial Infarction.

Models were additionally adjusted for: age; sex; history of percutaneous coronary intervention (PCI); history of coronary artery bypass graft (CABG); peripheral artery disease (PAD); diabetes mellitus; hypercholesterolemia; treatment with platelet inhibitors; lipid-lowering therapies; beta-blockers; calcium channel blockers (CCBs); and diuretics (potassium sparing and other); and systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Table A3-4: C-statistics and likelihood ratio tests for the model excluding resting heart rate and the models including the heart rate variables that categorised subjects according to whether they had a heart rate less than, or greater than or equal to, 70bpm, which produced the results shown in Table A3-1 in the EUROPA population.

		C-statistic	Likelihood Ratio Test Statistics, p-value
Primary Composite Endpoint			
Cardiovascular mortality, MI or cardiac arrest, n = 1091	Model	0.631	
	Model + Baseline	0.631	0.14, 0.71
	Model + Time-Updated	0.632	1.29, 0.26
	Model + Time-Updated + Baseline	0.632	1.29, 0.052
	Model + Time-Updated + Previous	0.632	1.82, 0.40
Individual Components of the Primary Composite Endpoint			
Cardiovascular mortality, n = 464	Model	0.716	
	Model + Baseline	0.717	1.98, 0.16
	Model + Time-Updated	0.720	7.56, 0.0060
	Model + Time-Updated + Baseline	0.720	7.82, 0.020
	Model + Time-Updated + Previous	0.721	8.52, 0.014
Fatal or non-fatal MI, n = 738	Model	0.602	
	Model + Baseline	0.602	0.40, 0.53
	Model + Time-Updated	0.602	0.035, 0.85
	Model + Time-Updated + Baseline	0.602	0.40, 0.82
	Model + Time-Updated + Previous	0.602	0.042, 0.98
Cardiac Arrest, n = 17	Model	0.808	
	Model + Baseline	0.808	0.0023, 0.96
	Model + Time-Updated	0.835	3.44, 0.064
	Model + Time-Updated + Baseline	0.837	4.34, 0.11
	Model + Time-Updated + Previous	0.850	6.88, 0.032
Other Composite Endpoints			
Total mortality, MI, unstable angina or cardiac arrest, n = 1946	Model	0.605	
	Model + Baseline	0.605	0.329, 0.57
	Model + Time-Updated	0.607	9.85, 0.0017
	Model + Time-Updated + Baseline	0.607	10.21, 0.0061
	Model + Time-Updated + Previous	0.607	10.68, 0.0048
Other Mortality Endpoints			
Total mortality, n = 795	Model	0.690	
	Model + Baseline	0.692	7.44, 0.0064
	Model + Time-Updated	0.701	43.38, <0.001
	Model + Time-Updated + Baseline	0.702	43.75, <0.001
	Model + Time-Updated + Previous	0.703	46.50, <0.001
Other Individual Endpoints			
Unstable Angina, n = 708	Model	0.585	

	Model + Baseline	0.587	1.25, 0.26
	Model + Time-Updated	0.587	1.13, 0.29
	Model + Time-Updated + Baseline	0.587	1.72, 0.42
	Model + Time-Updated + Previous	0.587	1.14, 0.57
Stroke, n = 199	Model	0.705	
	Model + Baseline	0.705	0.52, 0.47
	Model + Time-Updated	0.706	1.29, 0.26
	Model + Time-Updated + Baseline	0.706	2.76, 0.25
	Model + Time-Updated + Previous	0.706	1.32, 0.52
Revascularisation, n = 1177	Model	0.615	
	Model + Baseline	0.617	5.53, 0.0019
	Model + Time-Updated	0.616	3.82, 0.051
	Model + Time-Updated + Baseline	0.617	7.02, 0.030
	Model + Time-Updated + Previous	0.617	12.08, 0.0024
Heart failure requiring hospital admission, n = 166	Model	0.754	
	Model + Baseline	0.757	2.22, 0.14
	Model + Time-Updated	0.756	5.88, 0.015
	Model + Time-Updated + Baseline	0.757	6.37, 0.041
	Model + Time-Updated + Previous	0.768	16.11, <0.001

'Model' is the multivariate model excluding heart rate which included: age; sex; history of percutaneous coronary intervention (PCI); history of coronary artery bypass graft (CABG); peripheral artery disease (PAD); diabetes mellitus; hypercholesterolemia; treatment with platelet inhibitors; lipid-lowering therapies; beta-blockers; calcium channel blockers (CCBs); and diuretics (potassium sparing and other); and systolic blood pressure (SBP) and diastolic blood pressure (DBP).

'Model + Baseline' is the multivariate model described above including the baseline heart rate group variable.

'Model + Time-Updated' is the multivariate model described above including the time-updated heart rate group variable.

'Model + Time-Updated + Baseline' is the multivariable model described above including both the baseline and the time-updated heart rate group variables.

'Model + Time-Updated + Previous' is the multivariate model described above including both the time-updated heart rate group variable and the previous time-updated heart rate group variable.

The likelihood ratio test statistics and corresponding p-values were computed by comparing the multivariate models including the different heart rate variables to the multivariate model excluding resting heart rate.

Table A3-5: C-statistics and likelihood ratio tests for the model excluding resting heart rate and the models including the continuous heart rate variables, which produced the results shown in Table A3-2 in the EUROPA population.

		C-statistic	Likelihood Ratio Test Statistics, p-value
Primary Composite Endpoint			
Cardiovascular mortality, MI or cardiac arrest, n = 1091	Model	0.631	
	Model + Baseline	0.632	2.72, 0.099
	Model + Time-Updated	0.633	5.44, 0.020
	Model + Time-Updated + Baseline	0.633	5.83, 0.054
	Model + Time-Updated + Previous	0.633	6.31, 0.043
Individual Components of the Primary Composite Endpoint			
Cardiovascular mortality, n = 464	Model	0.716	
	Model + Baseline	0.719	7.43, 0.0064
	Model + Time-Updated	0.724	24.33, <0.001
	Model + Time-Updated + Baseline	0.724	24.71, <0.001
	Model + Time-Updated + Previous	0.724	25.05, <0.001
Fatal or non-fatal MI, n = 738	Model	0.602	
	Model + Baseline	0.602	0.0000034, 0.999
	Model + Time-Updated	0.603	0.75, 0.39
	Model + Time-Updated + Baseline	0.603	0.97, 0.61
	Model + Time-Updated + Previous	0.603	0.79, 0.68
Cardiac Arrest, n = 17	Model	0.808	
	Model + Baseline	0.806	0.19, 0.66
	Model + Time-Updated	0.821	1.68, 0.19
	Model + Time-Updated + Baseline	0.820	3.46, 0.18
	Model + Time-Updated + Previous	0.823	3.67, 0.16
Other Composite Endpoints			
Total mortality, MI, unstable angina or cardiac arrest, n = 1946	Model	0.605	
	Model + Baseline	0.607	7.14, 0.0075
	Model + Time-Updated	0.611	32.68, <0.001
	Model + Time-Updated + Baseline	0.611	32.68, <0.001
	Model + Time-Updated + Previous	0.611	32.76, <0.001
Other Mortality Endpoints			
Total mortality, n = 795	Model	0.690	
	Model + Baseline	0.695	24.46, <0.001
	Model + Time-Updated	0.712	99.35, <0.001
	Model + Time-Updated + Baseline	0.712	100.04, <0.001
	Model + Time-Updated + Previous	0.712	100.34, <0.001
Other Individual Endpoints			
Unstable Angina, n = 708	Model	0.585	
	Model + Baseline	0.586	0.48, 0.49

	Model + Time-Updated	0.586	0.042, 0.84
	Model + Time-Updated + Baseline	0.586	0.51, 0.78
	Model + Time-Updated + Previous	0.586	0.25, 0.88
Stroke, n = 199	Model	0.705	
	Model + Baseline	0.705	0.13, 0.72
	Model + Time-Updated	0.705	2.29, 0.13
	Model + Time-Updated + Baseline	0.704	3.76, 0.15
	Model + Time-Updated + Previous	0.706	2.71, 0.26
Revascularisation, n = 1177	Model	0.615	
	Model + Baseline	0.617	7.36, 0.0067
	Model + Time-Updated	0.617	6.52, 0.011
	Model + Time-Updated + Baseline	0.617	9.41, 0.0091
	Model + Time-Updated + Previous	0.618	10.12, 0.0063
Heart failure requiring hospital admission, n = 166	Model	0.754	
	Model + Baseline	0.759	3.68, 0.055
	Model + Time-Updated	0.766	22.25, <0.001
	Model + Time-Updated + Baseline	0.766	22.28, <0.001
	Model + Time-Updated + Previous	0.777	31.35, <0.001

'Model' is the multivariate model excluding heart rate which included: age; sex; history of percutaneous coronary intervention (PCI); history of coronary artery bypass graft (CABG); peripheral artery disease (PAD); diabetes mellitus; hypercholesterolemia; treatment with platelet inhibitors; lipid-lowering therapies; beta-blockers; calcium channel blockers (CCBs); and diuretics (potassium sparing and other); and systolic blood pressure (SBP) and diastolic blood pressure (DBP).

'Model + Baseline' is the multivariate model described above including the continuous baseline heart rate variable.

'Model + Time-Updated' is the multivariate model described above including the continuous time-updated heart rate variable.

'Model + Time-Updated + Baseline' is the multivariable model described above including both the continuous baseline and time-updated heart rate variables.

'Model + Time-Updated + Previous' is the multivariate model described above including both the continuous time-updated heart rate variable and the previous time-updated heart rate variable.

The likelihood ratio test statistics and corresponding p-values were computed by comparing the multivariate models including the different heart rate variables to the multivariate model excluding resting heart rate.

Table A3-6: C-statistics and likelihood ratio tests for the model excluding resting heart rate and the models including the time-updated categorical heart rate patterns variable, which produced the results shown in Table A3-3 in the EUROPA population.

		C-statistic	Likelihood Ratio Test Statistic, p-value
Primary Composite Endpoint			
Cardiovascular mortality, MI or cardiac arrest, n = 1091	Model	0.631	
	Model + Pattern	0.632	1.82, 0.61
Individual Components of the Primary Composite Endpoint			
Cardiovascular mortality, n = 464	Model	0.716	
	Model + Pattern	0.721	8.61, 0.035
Fatal or non-fatal MI, n = 738	Model	0.602	
	Model + Pattern	0.602	0.055, 0.997
Cardiac Arrest, n = 17	Model	-	-
	Model + Pattern	-	-
Other Composite Endpoints			
Total mortality, MI, unstable angina or cardiac arrest, n = 1946	Model	0.605	
	Model + Pattern	0.607	10.94, 0.012
Other Mortality Endpoints			
Total mortality, n = 795	Model	0.690	
	Model + Pattern	0.703	46.61, <0.001
Other Individual Endpoints			
Unstable Angina, n = 708	Model	0.585	
	Model + Pattern	0.587	4.21, 0.24
Stroke, n = 199	Model	0.705	
	Model + Pattern	0.706	1.77, 0.62
Revascularisation, n = 1177	Model	0.615	
	Model + Pattern	0.617	13.09, 0.0044
Heart failure requiring hospital admission, n = 166	Model	0.754	
	Model + Pattern	0.772	19.51, <0.001

'Model' is the multivariate model excluding heart rate which included: age; sex; history of percutaneous coronary intervention (PCI); history of coronary artery bypass graft (CABG); peripheral artery disease (PAD); diabetes mellitus; hypercholesterolemia; treatment with platelet inhibitors; lipid-lowering therapies; beta-blockers; calcium channel blockers (CCBs); and diuretics (potassium sparing and other); and systolic blood pressure (SBP) and diastolic blood pressure (DBP).

'Model + Pattern' is the multivariate model described above including the time-updated categorical heart rate patterns variable.

The likelihood ratio test statistic and corresponding p-value were computed by comparing the multivariate model including the time-updated categorical heart rate patterns variable to the multivariate model excluding resting heart rate.

Table A3-7: P-values for the Grambsch and Therneau 1994 test for non-proportionality of hazards for a heart rate ≥70bpm compared to a heart rate <70bpm in the EUROPA population.

	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Heart Rate Adjusted for Previous
	P-value			
Primary Composite Endpoint				
Cardiovascular mortality, MI or cardiac arrest, n = 1091	0.72	0.49	0.36	0.82
Individual Components of the Primary Composite Endpoint				
Cardiovascular mortality, n = 464	0.53	0.82	0.99	0.44
Fatal or non-fatal MI, n = 738	0.58	0.48	0.30	0.51
Cardiac arrest, n = 17	0.98	0.33	0.49	0.32
Other Composite Endpoints				
Total mortality, MI, unstable angina or cardiac arrest, n = 1946	0.77	0.68	0.89	0.35
Other Mortality Endpoints				
Total mortality, n = 795	0.72	0.73	0.88	0.30
Other Individual Endpoints				
Unstable angina, n = 708	0.91	0.56	0.51	0.62
Stroke, n = 199	0.68	0.066	0.055	0.077
Revascularisation, n = 1177	0.89	0.14	0.079	0.34
Heart failure requiring hospital admission, n = 166	0.13	0.14	0.30	0.47

MI = Myocardial Infarction.

Table A3-8: P-values for the Grambsch and Therneau 1994 test for non-proportionality of hazards for an elevated continuous heart rate in the EUROPA population.

	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Change in Heart Rate Adjusted for Previous
	P-value			
Primary Composite Endpoint				
Cardiovascular mortality, MI or cardiac arrest, n = 1091	0.72	0.81	0.63	0.89
Individual Components of the Primary Composite Endpoint				
Cardiovascular mortality, n = 464	0.95	0.068	0.051	0.088
Fatal or non-fatal MI, n = 738	0.62	0.48	0.52	0.52
Cardiac arrest, n = 17	0.40	0.27	0.84	0.14
Other Composite Endpoints				
Total mortality, MI, unstable angina or cardiac arrest, n = 1946	0.90	0.39	0.43	0.36
Other Mortality Endpoints				
Total mortality, n = 795	0.63	0.29	0.20	0.13
Other Individual Endpoints				
Unstable angina, n = 708	0.97	0.38	0.27	0.40
Stroke, n = 199	0.39	0.48	0.34	0.51
Revascularisation, n = 1177	0.34	0.10	0.15	0.56
Heart failure requiring hospital admission, n = 166	0.057	0.24	0.57	0.93

MI = Myocardial Infarction.

Table A3-9: P-values for the Grambsch and Therneau 1994 test for non-proportionality of hazards for the time-updated categorical heart rate patterns 'high-low', 'low-high' and 'high-high' relative to the category 'low-low' in the EUROPA population.

	Heart Rate Category	P-value
Primary Composite Endpoint		
Cardiovascular mortality, MI or cardiac arrest, n = 1091	high-low	0.96
	low-high	0.71
	high-high	0.30
Individual Components of the Primary Composite Endpoint		
Cardiovascular mortality, n = 464	high-low	0.49
	low-high	0.47
	high-high	0.67
Fatal or non-fatal MI, n = 738	high-low	0.80
	low-high	0.78
	high-high	0.54
Cardiac Arrest, n = 17	high-low	-
	low-high	-
	high-high	-
Other Composite Endpoints		
Total mortality, MI, unstable angina or cardiac arrest, n = 1946	high-low	0.88
	low-high	0.10
	high-high	0.73
Other Mortality Endpoints		
Total mortality, n = 795	high-low	0.39
	low-high	0.33
	high-high	0.61
Other Individual Endpoints		
Unstable Angina, n = 708	high-low	0.52
	low-high	0.70
	high-high	0.41
Stroke, n = 199	high-low	0.61
	low-high	0.056
	high-high	0.17
Revascularisation, n = 1177	high-low	0.66
	low-high	0.72
	high-high	0.39
Heart failure requiring hospital admission, n = 166	high-low	0.53
	low-high	0.93
	high-high	0.083

Patients were classified as being in the low-low category if their heart rate measurement at both the current and previous visit was below 70bpm. Similarly, patients were classified as being in the high-high category if their heart rate measurement at both the current and previous visit was greater than or equal to 70bpm, and so on.

There were not enough Cardiac Arrest events to allow analysis to be done in this case. MI = Myocardial Infarction.

Appendix 4
Supplementary Tables for Chapter 6

Table A4-1: Results of fitting Cox proportional hazards models. Hazard ratios, 95% confidence intervals, and p-values for gender-specific heart rate thirds, relative to the low heart rate third in the PROSPER population.

	Heart Rate Third	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Heart Rate Adjusted for Previous
		Hazard Ratio (95% Confidence Interval), p-value			
Primary Endpoint					
CHD death, non-fatal MI or fatal or non-fatal stroke, n = 868	Middle	0.92 (0.78 to 1.09), 0.32	1.00 (0.84 to 1.19), 0.99	1.12 (0.92 to 1.37), 0.26	1.13 (0.92 to 1.39), 0.24
	High	1.09 (0.92 to 1.28), 0.31	1.36 (1.16 to 1.60), <0.001	1.61 (1.29 to 2.01), <0.001	1.54 (1.22 to 1.95), <0.001
Secondary Endpoints					
CHD death or non-fatal MI, n = 639	Middle	0.94 (0.78 to 1.14), 0.55	0.94 (0.77 to 1.15), 0.58	1.04 (0.82 to 1.32), 0.74	1.05 (0.82 to 1.33), 0.72
	High	1.10 (0.91 to 1.33), 0.33	1.42 (1.18 to 1.71), <0.001	1.72 (1.33 to 2.22), <0.001	1.62 (1.24 to 2.12), <0.001
Fatal or non-fatal stroke, n = 261	Middle	0.78 (0.58 to 1.07), 0.12	0.98 (0.73 to 1.34), 0.92	1.13 (0.71 to 1.62), 0.49	1.16 (0.80 to 1.67), 0.44
	High	1.02 (0.76 to 1.37), 0.90	1.06 (0.79 to 1.44), 0.68	1.09 (0.72 to 1.65), 0.67	1.20 (0.78 to 1.85), 0.41
Other Outcomes					
Non-fatal MI, n = 471	Middle	0.92 (0.73 to 1.15), 0.46	0.98 (0.78 to 1.24), 0.88	1.10 (0.84 to 1.45), 0.47	1.12 (0.85 to 1.48), 0.43
	High	1.04 (0.83to 1.30), 0.72	1.31 (1.05 to 1.64), 0.015	1.59 (1.17 to 2.16), 0.0027	1.53 (1.11 to 2.10), 0.0095
Non-fatal stroke, n = 231	Middle	0.78 (0.56 to 1.08), 0.14	0.98 (0.71 to 1.35), 0.89	1.14 (0.78 to 1.66), 0.51	1.19 (0.81 to 1.75), 0.38
	High	1.00 (0.73 to 1.37), 0.997	1.07 (0.78 to 1.48), 0.66	1.14 (0.74 to 1.77), 0.55	1.30 (0.82 to 2.05), 0.26
TIA, n = 177	Middle	0.69 (0.48 to 1.00), 0.051	0.70 (0.49 to 1.00), 0.050	0.75 (0.49 to 1.13), 0.17	0.59 (0.38 to 0.90), 0.015
	High	0.82 (0.57 to 1.17), 0.26	0.68 (0.47 to 0.98), 0.038	0.63 (0.38 to 1.03), 0.066	0.57 (0.34 to 0.95), 0.031
PTCA or CABG, n = 87	Middle	0.85 (0.53 to 1.38), 0.52	0.73 (0.44 to 1.19), 0.20	0.75 (0.41 to 1.34), 0.33	0.65 (0.35 to 1.20), 0.17
	High	0.56 (0.31 to 1.01), 0.055	0.58 (0.33 to 1.02), 0.060	0.73 (0.35 to 1.55), 0.41	0.60 (0.28 to 1.32), 0.21
Peripheral arterial surgery/angioplasty, n = 79	Middle	0.77 (0.45 to 1.34), 0.36	0.74 (0.42 to 1.29), 0.29	0.81 (0.42 to 1.58), 0.54	0.70 (0.35 to 1.39), 0.30
	High	0.91 (0.53 to 1.57), 0.74	0.98 (0.58 to 1.69), 0.95	1.09 (0.52 to 2.30), 0.82	0.85 (0.39 to 1.86), 0.68
All cardiovascular events, n = 963	Middle	0.91 (0.78 to 1.07), 0.24	0.96 (0.82 to 1.13), 0.64	1.07 (0.89 to 1.30), 0.48	1.07 (0.88 to 1.30), 0.50
	High	1.05 (0.90 to 1.22), 0.57	1.28 (1.10 to 1.49), 0.0018	1.51 (1.22 to 1.87), <0.001	1.42 (1.13 to 1.78), 0.0023
Fatal or non-fatal stroke or TIA, n = 409	Middle	0.73 (0.57 to 0.93), 0.011	0.85 (0.67 to 1.08), 0.19	0.96 (0.73 to 1.28), 0.80	0.87 (0.65 to 1.16), 0.35
	High	0.93 (0.73 to 1.17), 0.52	0.88 (0.69 to 1.12), 0.30	0.87 (0.62 to 1.20), 0.39	0.87 (0.62 to 1.23), 0.43
HF hospitalisation, n = 232	Middle	1.49 (1.06 to 2.09), 0.020	1.26 (0.90 to 1.79), 0.19	1.10 (0.73 to 1.66), 0.65	1.08 (0.71 to 1.66), 0.72

	High	1.77 (1.27 to 2.46), <0.001	2.10 (1.52 to 2.92, <0.001	1.94 (1.27 to 2.98), 0.0024	1.78 (1.14 to 2.80), 0.011
Deaths					
CHD, n = 212	Middle	1.10 (0.78 to 1.56), 0.58	0.89 (0.61 to 1.29), 0.54	0.89 (0.58 to 1.36), 0.58	0.4 (0.54 to 1.31), 0.45
	High	1.43 (1.03 to 1.99), 0.035	1.84 (1.33 to 2.54), <0.001	1.97 (1.28 to 3.02), 0.0020	1.90 (1.21 to 2.97), 0.0051
Stroke, n = 35	Middle	0.73 (0.30 to 1.76), 0.49	0.97 (0.43 to 2.19), 0.94	1.06 (0.39 to 2.89), 0.91	0.87 (0.31 to 2.44), 0.79
	High	1.04 (0.47 to 2.32), 0.92	0.82 (0.35 to 1.92), 0.65	0.62 (0.19 to 2.07), 0.44	0.50 (0.14 to 1.71), 0.27
Vascular, n = 287	Middle	1.03 (0.76 to 1.39), 0.87	0.90 (0.66 to 1.23), 0.51	0.90 (0.62 to 1.29), 0.55	0.84 (0.58 to 1.22), 0.35
	High	1.45 (1.09 to 1.93), 0.0099	1.68 (1.27 to 2.22), <0.001	1.64 (1.13 to 2.39), 0.0095	1.59 (1.08 to 2.36), 0.020
Non-vascular, n = 303	Middle	0.95 (0.70 to 1.28), 0.73	0.87 (0.64 to 1.20), 0.40	0.90 (0.63 to 1.29), 0.57	0.86 (0.60 to 1.23), 0.41
	High	1.46 (1.10 to 1.92), 0.0080	1.71 (1.30 to 2.25), <0.001	1.69 (1.17 to 2.42), 0.0046	1.67 (1.14 to 2.43), 0.0079
Cancer, n = 199	Middle	1.04 (0.73 to 1.49), 0.82	0.83 (0.56 to 1.22), 0.33	0.83 (0.54 to 1.28), 0.41	0.81 (0.52 to 1.25), 0.34
	High	1.28 (0.91 to 1.81), 0.16	1.60 (1.15 to 2.23), 0.0057	1.71 (1.11 to 2.62), 0.015	1.75 (1.12 to 2.73), 0.014
All-causes, n = 590	Middle	0.99 (0.80 to 1.22), 0.91	0.89 (0.71 to 1.11), 0.28	0.90 (0.70 to 1.16), 0.41	0.85 (0.65 to 1.11), 0.22
	High	1.46 (1.20 to 1.78), <0.001	1.70 (1.40 to 2.07), <0.001	1.67 (1.29 to 2.16), <0.001	1.64 (1.25 to 2.15), <0.001

Male participants with a baseline heart rate less than or equal to 59bpm, between 60 and 68bpm, and greater than 68bpm, were classed as being in the 'low', 'medium' and 'high' heart rate thirds, respectively. Similarly, female participants with a baseline heart rate less than or equal to 62bpm, between 63 and 72bpm, and greater than 72bpm were classed as being in the 'low', 'medium' and 'high' heart rate thirds.

CABG = Coronary Artery Bypass Graft; CHD = Coronary Heart Disease; HF = Heart Failure; MI = Myocardial Infarction; PTCA = Percutaneous Transluminal Coronary Angioplasty; TIA = Transient Ischemic Attack.

Models were additionally adjusted for: age; smoking status; diabetes; history of vascular disease; hypertension; body mass index (BMI); high-density lipoprotein (HDL) cholesterol; thyroid stimulating hormones; estimated Glomerular Filtration Rate (eGFR); treatment group (pravastatin or placebo); and intake of aspirin, nitrates, diuretics, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs).

Table A4-2: Results of fitting Cox proportional hazards models. Hazard ratios, 95% confidence intervals, and p-values for a 5bpm higher heart rate in the PROSPER population.

	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Heart Rate Adjusted for Previous
	Hazard Ratio (95% Confidence Interval), p-value			
Primary Endpoint				
CHD death, non-fatal MI or fatal or non-fatal stroke, n = 868	1.00 (0.97 to 1.03), 0.92	1.05 (1.02 to 1.08), <0.001	1.10 (1.06 to 1.14), <0.001	1.09 (1.04 to 1.13), <0.001
Secondary Endpoints				
CHD death or non-fatal MI, n = 639	1.01 (0.98 to 1.04), 0.57	1.06 (1.03 to 1.10), <0.001	1.11 (1.07 to 1.16), <0.001	1.10 (1.05 to 1.15), <0.001
Fatal or non-fatal stroke, n = 261	0.97 (0.92 to 1.03), 0.29	1.01 (0.95 to 1.06), 0.85	1.05 (0.98 to 1.13), 0.16	1.04 (0.97 to 1.13), 0.27
Other Outcomes				
Non-fatal MI, n = 471	0.99 (0.95 to 1.03), 0.55	1.04 (1.00 to 1.08), 0.050	1.09 (1.04 to 1.15), <0.001	1.07 (1.02 to 1.13), 0.0097
Non-fatal stroke, n = 231	0.97 (0.92 to 1.03), 0.39	1.01 (0.95 to 1.06), 0.81	1.05 (0.97 to 1.13), 0.22	1.04 (0.96 to 1.13), 0.30
TIA, n = 177	0.97 (0.90 to 1.03), 0.32	0.96 (0.90 to 1.02), 0.19	0.96 (0.87 to 1.05), 0.39	0.94 (0.85 to 1.04), 0.23
PTCA or CABG, n = 87	0.86 (0.78 to 0.96), 0.0052	0.86 (0.78 to 0.96), 0.0054	0.92 (0.79 to 1.07), 0.30	0.87 (0.74 to 1.02), 0.088
Peripheral arterial surgery/angioplasty, n = 79	1.00 (0.90 to 1.10) 0.97	1.03 (0.94 to 1.13), 0.57	1.06 (0.93 to 1.21), 0.38	1.02 (0.89 to 1.18), 0.75
All CV events, n = 963	1.00 (0.97 to 1.02), 0.79	1.04 (1.01 to 1.07), 0.0024	1.09 (1.05 to 1.13), <0.001	1.07 (1.03 to 1.11), <0.001
Fatal or non-fatal stroke or TIA, n = 409	0.97 (0.92 to 1.01), 0.13	0.98 (0.94 to 1.02), 0.38	1.01 (0.95 to 1.07), 0.75	0.99 (0.93 to 1.06), 0.81
HF hospitalisation, n = 232	1.10 (1.05 to 1.16), <0.001	1.17 (1.12 to 1.22), <0.001	1.18 (1.12 to 1.25), <0.001	1.17 (1.11 to 1.24), <0.001
Deaths				
CHD, n = 212	1.08 (1.02 to 1.14), 0.0046	1.13 (1.07 to 1.21), <0.001	1.13 (1.06 to 1.20), <0.001	1.14 (1.07 to 1.22), <0.001
Stroke, n = 35	0.92 (0.79 to 1.07), 0.29	0.95 (0.82 to 1.10), 0.52	1.02 (0.83 to 1.26), 0.82	1.00 (0.79 to 1.25), 0.97
Vascular, n = 287	1.07 (1.02 to 1.13), 0.0046	1.11 (1.06 to 1.16), <0.001	1.11 (1.05 to 1.18), <0.001	1.12 (1.06 to 1.19), <0.001
Non-vascular, n = 303	1.09 (1.04 to 1.15), <0.001	1.13 (1.08 to 1.18), <0.001	1.13 (1.07 to 1.19), <0.001	1.14 (1.08 to 1.20), <0.001
Cancer, n = 199	1.05 (0.99 to 1.12), 0.087	1.12 (1.06 to 1.18), <0.001	1.14 (1.07 to 1.22), <0.001	1.15 (1.08 to 1.23), <0.001
All-causes, n = 590	1.08 (1.05 to 1.12), <0.001	1.12 (1.09 to 1.15), <0.001	1.12 (1.08 to 1.17), <0.001	1.13 (1.09 to 1.18), <0.001

CABG = Coronary Artery Bypass Graft; CHD = Coronary Heart Disease; HF = Heart Failure; MI = Myocardial Infarction; PTCA = Percutaneous Transluminal Coronary Angioplasty; TIA = Transient Ischemic Attack.

Models were additionally adjusted for: age; smoking status; diabetes; history of vascular disease; hypertension; body mass index (BMI); high-density lipoprotein (HDL) cholesterol; thyroid stimulating hormones; estimated Glomerular Filtration Rate (eGFR); treatment group (pravastatin or placebo); and intake of aspirin, nitrates, diuretics, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs).

Table A4-3: Results of fitting Cox proportional hazards models. Hazard ratios, 95% confidence intervals, and p-values for the time-updated categorical heart rate patterns 'high-low', 'low-high' and 'high-high' relative to the category 'low-low' in the PROSPER population.

	Heart Rate Category	Hazard Ratio (95% Confidence Interval), p-value
Primary Composite Endpoint		
CHD death or non-fatal MI or fatal or non-fatal stroke, n = 868	high-low	0.93 (0.70 o 1.23), 0.61
	low-high	1.33 (1.04 to 1.69), 0.022
	high-high	1.19 (1.02 to 1.40), 0.025
Secondary Endpoints		
CHD death or non-fatal MI, n = 639	high-low	0.88 (0.63 to 1.23), 0.45
	low-high	1.37 (1.03 to 1.81), 0.028
	high-high	1.27 (1.06 to 1.52), 0.0098
Fatal or non-fatal stroke, n = 261	high-low	0.95 (0.58 to 1.55), 0.83
	low-high	1.20 (0.77 to 1.87), 0.41
	high-high	0.96 (0.72 to 1.29), 0.80
Other Outcomes		
Non-fatal MI, n = 471	high-low	0.95 (0.66 to 1.39), 0.81
	low-high	1.33 (0.96 to 1.85), 0.090
	high-high	1.15 (0.93 to 1.42), 0.20
Non-fatal stroke, n = 231	high-low	1.00 (0.60 to 1.65), 0.99
	low-high	1.22 (0.77 to 1.94), 0.39
	high-high	0.92 (0.67 to 1.26), 0.60
TIA, n = 177	high-low	0.63 (0.33 to 1.21), 0.17
	low-high	0.90 (0.51 to 1.58), 0.71
	high-high	0.71 (0.49 to 1.03), 0.068
PTCA or CABG, n = 87	high-low	0.72 (0.29 to 1.83), 0.49
	low-high	0.88 (0.37 to 2.06), 0.71
	high-high	0.65 (0.36 to 1.17), 0.15
Peripheral arterial surgery/angioplasty, n = 79	high-low	0.90 (0.35 to 2.30), 0.82
	low-high	0.83 (0.32 to 2.12), 0.70
	high-high	1.01 (0.60 to 1.69), 0.97
All CV events, n = 963	high-low	0.92 (0.70 to 1.19), 0.51
	low-high	1.29 (1.02 to 1.63), 0.033
	high-high	1.15 (1.00 to 1.34), 0.057
Fatal or non-fatal stroke or TIA, n = 409	high-low	0.81 (0.54 to 1.21), 0.30
	low-high	1.06 (0.74 to 1.52), 0.77
	high-high	0.84 (0.67 to 1.07), 0.16
HF hospitalisation, n = 232	high-low	0.97 (0.55 to 1.21), 0.92
	low-high	1.88 (1.21 to 2.92), 0.0050
	high-high	1.84 (1.37 to 2.46), <0.001
Deaths		
CHD, n = 212	high-low	0.69 (0.36 to 1.34), 0.27
	low-high	1.94 (1.26 to 2.98), 0.0025
	high-high	1.65 (1.21 to 2.24), 0.0014
Stroke, n = 35	high-low	0.74 (0.17 to 3.28), 0.69
	low-high	0.72 (0.16 to 3.18), 0.66
	high-high	0.98 (0.46 to 2.09), 0.96
Vascular, n = 287	high-low	0.75 (0.44 to 1.29), 0.30
	low-high	1.73 (1.17 to 2.53), 0.0054
	high-high	1.58 (1.22 to 2.06), <0.001

Non-vascular, n = 303	high-low	0.88 (0.54 to 1.46), 0.63
	low-high	2.24 (1.58 to 3.16), <0.001
	high-high	1.71 (1.31 to 2.21), <0.001
Cancer, n = 199	high-low	0.75 (0.40 to 1.41), 0.37
	low-high	2.51 (1.70 to 3.72), <0.001
	high-high	1.41 (1.01 to 1.96), 0.043
All-causes, n = 590	high-low	0.83 (0.57 to 1.18), 0.29
	low-high	1.99 (1.54 to 2.57), <0.001
	high-high	1.65 (1.37 to 1.98), <0.001

Patients were classified as being in the low-low category if their heart rate measurement at both the current and previous visit was below 70bpm. Similarly, patients were classified as being in the high-high category if their heart rate measurement at both the current and previous visit was greater than or equal to 70bpm, and so on.

CABG = Coronary Artery Bypass Graft; CHD = Coronary Heart Disease; HF = Heart Failure; MI = Myocardial Infarction; PTCA = Percutaneous Transluminal Coronary Angioplasty; TIA = Transient Ischemic Attack.

Models were additionally adjusted for: age; smoking status; diabetes; history of vascular disease; hypertension; body mass index (BMI); high-density lipoprotein (HDL) cholesterol; thyroid stimulating hormones; estimated Glomerular Filtration Rate (eGFR); treatment group (pravastatin or placebo); and intake of aspirin, nitrates, diuretics, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs).

Table A4-4: C-statistics and likelihood ratio tests for the model excluding resting heart rate and the models including the gender-specific heart rate thirds variables, which produced the results shown in Table A4-1 in the PROSPER population.

		C-statistic	Likelihood Ratio Test Statistic, p-value
Primary Composite Endpoint			
CHD death or non-fatal MI or fatal or non-fatal stroke, n = 868	Model	0.619	
	Model + Baseline	0.621	3.92, 0.14
	Model + Time-Updated	0.627	18.26, <0.001
	Model + Time-Updated + Baseline	0.629	23.41, <0.001
	Model + Time-Updated + Previous	0.628	22.35, <0.001
Secondary Endpoints			
CHD death or non-fatal MI, n = 639	Model	0.633	
	Model + Baseline	0.635	2.43, 0.30
	Model + Time-Updated	0.641	20.66, <0.001
	Model + Time-Updated + Baseline	0.643	25.05, <0.001
	Model + Time-Updated + Previous	0.642	22.90, <0.001
Fatal or non-fatal stroke, n = 261	Model	0.614	
	Model + Baseline	0.619	3.48, 0.018
	Model + Time-Updated	0.614	0.29, 0.86
	Model + Time-Updated + Baseline	0.620	3.96, 0.41
	Model + Time-Updated + Previous	0.619	2.83, 0.59
Other Outcomes			
Non-fatal MI, n = 471	Model	0.627	
	Model + Baseline	0.627	1.21, 0.55
	Model + Time-Updated	0.632	8.14, 0.017
	Model + Time-Updated + Baseline	0.634	11.50, 0.021
	Model + Time-Updated + Previous	0.632	10.66, 0.031
Non-fatal stroke, n = 231	Model	0.595	
	Model + Baseline	0.601	2.90, 0.23
	Model + Time-Updated	0.596	0.36, 0.83
	Model + Time-Updated + Baseline	0.602	3.41, 0.49
	Model + Time-Updated + Previous	0.603	3.45, 0.48
TIA, n = 177	Model	0.660	
	Model + Baseline	0.665	3.94, 0.14
	Model + Time-Updated	0.668	5.76, 0.056
	Model + Time-Updated + Baseline	0.671	7.57, 0.11
	Model + Time-Updated + Previous	0.670	7.82, 0.099
PTCA or CABG, n = 87	Model	0.769	
	Model + Baseline	0.773	3.96, 0.14
	Model + Time-Updated	0.772	4.10, 0.13
	Model + Time-Updated + Baseline	0.773	5.11, 0.28

	Model + Time-Updated + Previous	0.774	5.00, 0.29
Peripheral arterial surgery/angioplasty, n = 79	Model	0.755	
	Model + Baseline	0.755	0.86, 0.65
	Model + Time-Updated	0.756	1.42, 0.49
	Model + Time-Updated + Baseline	0.757	1.70, 0.79
	Model + Time-Updated + Previous	0.757	1.67, 0.80
All CV events, n = 963	Model	0.621	
	Model + Baseline	0.623	3.03, 0.22
	Model + Time-Updated	0.626	14.95, <0.001
	Model + Time-Updated + Baseline	0.628	20.17, <0.001
	Model + Time-Updated + Previous	0.628	18.36, 0.0010
Fatal or non-fatal stroke or TIA, n = 409	Model	0.620	
	Model + Baseline	0.625	7.03, 0.030
	Model + Time-Updated	0.621	1.97, 0.37
	Model + Time-Updated + Baseline	0.625	7.83, 0.098
	Model + Time-Updated + Previous	0.621	2.16, 0.71
HF hospitalisation, n = 232	Model	0.699	
	Model + Baseline	0.706	12.17, 0.0023
	Model + Time-Updated	0.712	22.74, <0.001
	Model + Time-Updated + Baseline	0.714	22.77, <0.001
	Model + Time-Updated + Previous	0.712	24.43, <0.001
Deaths			
CHD, n = 212	Model	0.702	
	Model + Baseline	0.703	4.82, 0.90
	Model + Time-Updated	0.721	22.33, <0.001
	Model + Time-Updated + Baseline	0.721	22.89, <0.001
	Model + Time-Updated + Previous	0.721	23.31, <0.001
Stroke, n = 35	Model	0.795	
	Model + Baseline	0.799	0.78, 0.68
	Model + Time-Updated	0.794	0.24, 0.89
	Model + Time-Updated + Baseline	0.799	1.90, 0.75
	Model + Time-Updated + Previous	0.795	1.94, 0.75
Vascular, n = 287	Model	0.701	
	Model + Baseline	0.708	8.48, 0.014
	Model + Time-Updated	0.720	22.15, <0.001
	Model + Time-Updated + Baseline	0.720	22.20, <0.001
	Model + Time-Updated + Previous	0.719	22.70, <0.001
Non-vascular, n = 303	Model	0.667	
	Model + Baseline	0.673	11.52, 0.0031
	Model + Time-Updated	0.679	26.94, <0.001

	Model + Time-Updated + Baseline	0.679	27.65, <0.001
	Model + Time-Updated + Previous	0.679	26.99, <0.001
Cancer, n = 199	Model	0.661	
	Model + Baseline	0.666	2.35, 0.31
	Model + Time-Updated	0.676	15.61, <0.001
	Model + Time-Updated + Baseline	0.675	16.02, 0.0030
	Model + Time-Updated + Previous	0.675	17.24, 0.0017
All-causes, n = 590	Model	0.663	
	Model + Baseline	0.669	20.08, <0.001
	Model + Time-Updated	0.679	49.58, <0.001
	Model + Time-Updated + Baseline	0.679	50.13, <0.001
	Model + Time-Updated + Previous	0.679	49.96, <0.001

'Model' is the multivariate model excluding heart rate which included: age; smoking status; diabetes; history of vascular disease; hypertension; body mass index (BMI); high-density lipoprotein (HDL) cholesterol; thyroid stimulating hormones; estimated Glomerular Filtration Rate (eGFR); treatment group (pravastatin or placebo); and intake of aspirin, nitrates, diuretics, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs).

'Model + Baseline' is the multivariate model described above including the baseline heart rate thirds variable.

'Model + Time-Updated' is the multivariate model described above including the time-updated heart rate thirds variable.

'Model + Time-Updated + Baseline' is the multivariable model described above including both the baseline and the time-updated heart rate thirds variables.

'Model + Time-Updated + Previous' is the multivariate model described above including both the time-updated heart rate thirds variable and the previous time-updated heart rate thirds variable.

The likelihood ratio test statistics and corresponding p-values were computed by comparing the multivariate models including the different heart rate variables to the multivariate model excluding resting heart rate.

Table A4-5: C-statistics and likelihood ratio tests for the model excluding resting heart rate and the models including the continuous heart rate variables, which produced the results shown in Table A4-2 in the PROSPER population.

		C-statistic	Likelihood Ratio Test Statistic, p-value
Primary Composite Endpoint			
CHD death or non-fatal MI or fatal or non-fatal stroke, n = 868	Model	0.619	
	Model + Baseline	0.619	0.0090, 0.92
	Model + Time-Updated	0.624	12.94, <0.001
	Model + Time-Updated + Baseline	0.628	25.26, <0.001
	Model + Time-Updated + Previous	0.625	17.32, <0.001
Secondary Endpoints			
CHD death or non-fatal MI, n = 639	Model	0.633	
	Model + Baseline	0.633	0.31, 0.58
	Model + Time-Updated	0.639	13.95, <0.001
	Model + Time-Updated + Baseline	0.644	22.56, <0.001
	Model + Time-Updated + Previous	0.641	17.12, <0.001
Fatal or non-fatal stroke, n = 261	Model	0.614	
	Model + Baseline	0.615	1.14, 0.029
	Model + Time-Updated	0.614	0.037, 0.85
	Model + Time-Updated + Baseline	0.617	2.99, 0.22
	Model + Time-Updated + Previous	0.617	1.68, 0.43
Other Outcomes			
Non-fatal MI, n = 471	Model	0.627	
	Model + Baseline	0.627	0.37, 0.55
	Model + Time-Updated	0.631	3.75, 0.053
	Model + Time-Updated + Baseline	0.636	11.83, 0.0027
	Model + Time-Updated + Previous	0.632	6.40, 0.50
Non-fatal stroke, n = 231	Model	0.595	
	Model + Baseline	0.597	0.75, 0.39
	Model + Time-Updated	0.595	0.058, 0.81
	Model + Time-Updated + Baseline	0.599	2.21, 0.33
	Model + Time-Updated + Previous	0.599	1.37, 0.50
TIA, n = 177	Model	0.660	
	Model + Baseline	0.662	0.995, 0.32
	Model + Time-Updated	0.664	1.73, 0.19
	Model + Time-Updated + Baseline	0.664	1.74, 0.42
	Model + Time-Updated + Previous	0.665	1.92, 0.38
PTCA or CABG, n = 87	Model	0.769	
	Model + Baseline	0.777	8.35, 0.0039
	Model + Time-Updated	0.778	8.27, 0.0040
	Model + Time-Updated + Baseline	0.779	9.49, 0.0087

	Model + Time-Updated + Previous	0.778	8.28, 0.016
Peripheral arterial surgery/angioplasty, n = 79	Model	0.755	
	Model + Baseline	0.755	0.0016, 0.97
	Model + Time-Updated	0.757	0.31, 0.58
	Model + Time-Updated + Baseline	0.757	0.73, 0.69
	Model + Time-Updated + Previous	0.756	0.31, 0.85
All CV events, n = 963	Model	0.621	
	Model + Baseline	0.621	0.070, 0.79
	Model + Time-Updated	0.624	8.99, 0.0027
	Model + Time-Updated + Baseline	0.628	21.29, <0.001
	Model + Time-Updated + Previous	0.625	12.01, 0.0025
Fatal or non-fatal stroke or TIA, n = 409	Model	0.620	
	Model + Baseline	0.621	2.27, 0.13
	Model + Time-Updated	0.621	0.75, 0.39
	Model + Time-Updated + Baseline	0.621	2.37, 0.31
	Model + Time-Updated + Previous	0.621	0.95, 0.62
HF hospitalisation, n = 232	Model	0.699	
	Model + Baseline	0.705	12.69, <0.001
	Model + Time-Updated	0.718	39.97, <0.001
	Model + Time-Updated + Baseline	0.719	40.52, <0.001
	Model + Time-Updated + Previous	0.718	40.07, <0.001
Deaths			
CHD, n = 212	Model	0.702	
	Model + Baseline	0.705	7.70, 0.0055
	Model + Time-Updated	0.717	20.06, <0.001
	Model + Time-Updated + Baseline	0.717	20.12, <0.001
	Model + Time-Updated + Previous	0.718	20.37, <0.001
Stroke, n = 35	Model	0.795	
	Model + Baseline	0.797	1.15, 0.28
	Model + Time-Updated	0.795	0.43, 0.51
	Model + Time-Updated + Baseline	0.797	1.20, 0.55
	Model + Time-Updated + Previous	0.796	0.65, 0.72
Vascular, n = 287	Model	0.701	
	Model + Baseline	0.706	7.77, 0.0053
	Model + Time-Updated	0.716	19.76, <0.001
	Model + Time-Updated + Baseline	0.716	19.83, <0.001
	Model + Time-Updated + Previous	0.716	20.05, <0.001
Non-vascular, n = 303	Model	0.667	
	Model + Baseline	0.674	13.07, <0.001
	Model + Time-Updated	0.680	30.35, <0.001

	Model + Time-Updated + Baseline	0.680	30.36, <0.001
	Model + Time-Updated + Previous	0.680	30.44, <0.001
Cancer, n = 199	Model	0.661	
	Model + Baseline	0.667	2.88, 0.090
	Model + Time-Updated	0.676	16.07, <0.001
	Model + Time-Updated + Baseline	0.676	17.26, <0.001
	Model + Time-Updated + Previous	0.677	17.92, <0.001
All-causes, n = 590	Model	0.663	
	Model + Baseline	0.669	20.72, <0.001
	Model + Time-Updated	0.677	50.13, <0.001
	Model + Time-Updated + Baseline	0.677	50.15, <0.001
	Model + Time-Updated + Previous	0.677	50.51, <0.001

'Model' is the multivariate model excluding heart rate which included: age; smoking status; diabetes; history of vascular disease; hypertension; body mass index (BMI); high-density lipoprotein (HDL) cholesterol; thyroid stimulating hormones; estimated Glomerular Filtration Rate (eGFR); treatment group (pravastatin or placebo); and intake of aspirin, nitrates, diuretics, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs).

'Model + Baseline' is the multivariate model described above including the continuous baseline heart rate variable.

'Model + Time-Updated' is the multivariate model described above including the continuous time-updated heart rate variable.

'Model + Time-Updated + Baseline' is the multivariable model described above including both the continuous baseline and time-updated heart rate variables.

'Model + Time-Updated + Previous' is the multivariate model described above including both the continuous time-updated heart rate variable and the previous time-updated heart rate variable.

The likelihood ratio test statistics and corresponding p-values were computed by comparing the multivariate models including the different heart rate variables to the multivariate model excluding resting heart rate.

Table A4-6: C-statistics and likelihood ratio tests for the model excluding resting heart rate and the models including the time-updated categorical heart rate patterns variable, which produced the results shown in Table A4-3 in the PROSPER population.

		C-statistic	Likelihood Ratio Test Statistic, p-value
Primary Composite Endpoint			
CHD death or non-fatal MI or fatal or non-fatal stroke, n = 868	Model	0.619	
	Model + Pattern	0.623	9.62, 0.022
Secondary Endpoints			
CHD death or non-fatal MI, n = 639	Model	0.633	
	Model + Pattern	0.638	11.47, 0.0095
Fatal or non-fatal stroke, n = 261	Model	0.614	
	Model + Pattern	0.614	0.89, 0.83
Other Outcomes			
Non-fatal MI, n = 471	Model	0.627	
	Model + Pattern	0.629	4.06, 0.25
Non-fatal stroke, n = 231	Model	0.595	
	Model + Pattern	0.596	1.20, 0.75
TIA, n = 177	Model	0.660	
	Model + Pattern	0.668	4.86, 0.18
PTCA or CABG, n = 87	Model	0.769	
	Model + Pattern	0.771	2.50, 0.48
Peripheral arterial surgery/angioplasty, n = 79	Model	0.755	
	Model + Pattern	0.755	0.21, 0.98
All CV events, n = 963	Model	0.621	
	Model + Pattern	0.624	8.15, 0.043
Fatal or non-fatal stroke or TIA, n = 409	Model	0.620	
	Model + Pattern	0.622	3.15, 0.37
HF hospitalisation, n = 232	Model	0.699	
	Model + Pattern	0.709	20.94, <0.001
Deaths			
CHD, n = 212	Model	0.702	
	Model + Pattern	0.722	18.96, <0.001
Stroke, n = 35	Model	0.795	
	Model + Pattern	0.795	0.33, 0.95
Vascular, n = 287	Model	0.701	
	Model + Pattern	0.719	19.20, <0.001
Non-vascular, n = 303	Model	0.667	
	Model + Pattern	0.681	30.74, <0.001
Cancer, n = 199	Model	0.661	
	Model + Pattern	0.677	23.05, <0.001
All-causes, n = 590	Model	0.663	
	Model + Pattern	0.680	49.27, <0.001

'Model' is the multivariate model excluding heart rate which included: age; smoking status; diabetes; history of vascular disease; hypertension; body mass index (BMI); high-density lipoprotein (HDL) cholesterol; thyroid stimulating hormones; estimated Glomerular Filtration Rate (eGFR); treatment group (pravastatin or placebo); and intake of aspirin, nitrates, diuretics, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs).

'Model + Pattern' is the multivariate model described above including the time-updated categorical heart rate patterns variable.

The likelihood ratio test statistic and corresponding p-value were computed by comparing the multivariate model including the time-updated categorical heart rate patterns variable to the multivariate model excluding resting heart rate.

Table A4-7: P-values for the Grambsch and Therneau 1994 test for non-proportionality of hazards for gender-specific heart rate thirds, relative to the low heart rate third in the PROSPER population.

		Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Heart Rate Adjusted for Previous
	Heart Rate Third	P-value			
Primary Endpoint					
CHD death, non-fatal MI or fatal or non-fatal stroke, n = 868	Middle	0.57	0.32	0.83	0.57
	High	0.56	0.45	0.99	0.88
Secondary Endpoints					
CHD death or non-fatal MI, n = 639	Middle	0.88	0.76	0.55	0.95
	High	0.38	0.67	0.91	0.88
Fatal or non-fatal stroke, n = 261	Middle	0.42	0.069	0.46	0.52
	High	0.55	0.81	0.70	0.95
Other Outcomes					
Non-fatal MI, n = 471	Middle	0.81	0.82	0.68	0.89
	High	0.33	0.81	0.99	0.71
Non-fatal stroke, n = 231	Middle	0.48	0.14	0.64	0.68
	High	0.69	0.97	0.50	0.77
TIA, n = 177	Middle	0.31	0.054	0.054	0.039
	High	0.76	0.12	0.16	0.15
PTCA or CABG, n = 87	Middle	0.31	0.37	0.80	0.96
	High	0.41	0.23	0.35	0.52
Peripheral arterial surgery/angioplasty, n = 79	Middle	0.79	0.82	0.77	0.76
	High	0.28	0.40	0.93	0.79
All cardiovascular events, n = 963	Middle	0.88	0.47	0.84	0.53
	High	0.61	0.45	0.97	0.92
Fatal or non-fatal stroke or TIA, n = 409	Middle	0.81	0.90	0.53	0.43
	High	0.89	0.38	0.26	0.34
HF hospitalisation, n = 232	Middle	0.91	0.078	0.099	0.10
	High	0.86	0.43	0.21	0.12
Deaths					
CHD, n = 212	Middle	0.46	0.98	0.74	0.93
	High	0.74	0.83	0.51	0.76
Stroke, n = 35	Middle	0.62	0.28	0.64	0.69
	High	0.37	0.77	0.97	0.96
Vascular, n = 287	Middle	0.64	0.998	0.74	0.89
	High	0.62	0.91	0.47	0.53
Non-vascular, n = 303	Middle	0.76	0.71	0.45	0.59
	High	0.39	0.45	0.17	0.22
Cancer, n = 199	Middle	0.44	0.79	0.39	0.57
	High	0.25	0.89	0.48	0.61
All-causes, n = 590	Middle	0.90	0.78	0.76	0.79
	High	0.81	0.55	0.66	0.70

Male participants with a baseline heart rate less than or equal to 59bpm, between 60 and 68bpm, and greater than 68bpm, were classed as being in the ‘low’, ‘medium’ and ‘high’ heart rate thirds, respectively. Similarly, female participants with a baseline heart rate less than or equal to 62bpm, between 63 and 72bpm, and greater than 72bpm were classed as being in the ‘low’, ‘medium’ and ‘high’ heart rate thirds.

CABG = Coronary Artery Bypass Graft; CHD = Coronary Heart Disease; HF = Heart Failure; MI = Myocardial Infarction; PTCA = Percutaneous Transluminal Coronary Angioplasty; TIA = Transient Ischemic Attack.

Table A4-8: P-values for the Grambsch and Therneau 1994 test for non-proportionality of hazards for an elevated continuous heart rate in the PROSPER population.

	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Heart Rate Adjusted for Previous
	P-value			
Primary Endpoint				
CHD death, non-fatal MI or fatal or non-fatal stroke, n = 868	0.26	0.32	0.79	0.72
Secondary Endpoints				
CHD death or non-fatal MI, n = 639	0.30	0.44	0.90	0.74
Fatal or non-fatal stroke, n = 261	0.83	0.71	0.90	0.89
Other Outcomes				
Non-fatal MI, n = 471	0.23	0.70	0.98	0.82
Non-fatal stroke, n = 231	0.63	0.90	0.93	0.93
TIA, n = 177	0.66	0.96	0.81	0.58
PTCA or CABG, n = 87	0.34	0.36	0.67	0.61
Peripheral arterial surgery/angioplasty, n = 79	0.32	0.33	0.94	0.86
All CV events, n = 963	0.27	0.35	0.84	0.88
Fatal or non-fatal stroke or TIA, n = 409	0.88	0.79	0.97	0.75
HF hospitalisation, n = 232	0.41	0.80	0.51	0.54
Deaths				
CHD, n = 212	0.71	0.66	0.73	0.78
Stroke, n = 35	0.52	0.58	0.74	0.78
Vascular, n = 287	0.41	0.63	0.50	0.80
Non-vascular, n = 303	0.37	0.27	0.089	0.067
Cancer, n = 199	0.087	0.76	0.31	0.27
All-causes, n = 590	0.99	0.24	0.44	0.24

CABG = Coronary Artery Bypass Graft; CHD = Coronary Heart Disease; HF = Heart Failure; MI = Myocardial Infarction; PTCA = Percutaneous Transluminal Coronary Angioplasty; TIA = Transient Ischemic Attack.

Table A4-9: P-values for the Grambsch and Therneau 1994 test for non-proportionality of hazards for the time-updated categorical heart rate patterns 'high-low', 'low-high' and 'high-high' relative to the category 'low-low' in the PROSPER population.

	Heart Rate Category	P-value
Primary Composite Endpoint		
CHD death or non-fatal MI or fatal or non-fatal stroke, n = 868	high-low	0.77
	low-high	0.91
	high-high	0.49
Secondary Endpoints		
CHD death or non-fatal MI, n = 639	high-low	0.56
	low-high	0.91
	high-high	0.45
Fatal or non-fatal stroke, n = 261	high-low	0.76
	low-high	0.83
	high-high	0.71
Other Outcomes		
Non-fatal MI, n = 471	high-low	0.76
	low-high	0.91
	high-high	0.92
Non-fatal stroke, n = 231	high-low	0.52
	low-high	0.78
	high-high	0.49
TIA, n = 177	high-low	0.47
	low-high	0.72
	high-high	0.68
PTCA or CABG, n = 87	high-low	0.87
	low-high	0.61
	high-high	0.37
Peripheral arterial surgery/angioplasty, n = 79	high-low	0.69
	low-high	0.40
	high-high	0.22
All CV events, n = 963	high-low	0.75
	low-high	0.79
	high-high	0.34
Fatal or non-fatal stroke or TIA, n = 409	high-low	0.50
	low-high	0.73
	high-high	0.57
HF hospitalisation, n = 232	high-low	0.30
	low-high	0.56
	high-high	0.29
Deaths		
CHD, n = 212	high-low	0.31
	low-high	0.71
	high-high	0.72
Stroke, n = 35	high-low	0.26
	low-high	0.27
	high-high	0.34
Vascular, n = 287	high-low	0.077
	low-high	0.40
	high-high	0.42
Non-vascular, n = 303	high-low	0.97

	low-high	0.10
	high-high	0.29
Cancer, n = 199	high-low	0.84
	low-high	0.60
	high-high	0.91
All-causes, n = 590	high-low	0.20
	low-high	0.083
	high-high	0.18

Patients were classified as being in the low-low category if their heart rate measurement at both the current and previous visit was below 70bpm. Similarly, patients were classified as being in the high-high category if their heart rate measurement at both the current and previous visit was greater than or equal to 70bpm, and so on.

CABG = Coronary Artery Bypass Graft; CHD = Coronary Heart Disease; HF = Heart Failure; MI = Myocardial Infarction; PTCA = Percutaneous Transluminal Coronary Angioplasty; TIA = Transient Ischemic Attack.

Table A4-10: Results of fitting the time-updated heart rate Cox proportional hazards models. Hazard ratios, 95% confidence intervals, and p-values for a 5bpm higher time-updated heart rate adjusted for baseline heart rate, in PROSPER subjects who were or were not taking anti-arrhyhtmic drugs and/or beta-blockers at randomisaiton.

	Subgroup	Hazard Ratio (95% Confidence Interval), p-value	P-value for Interaction*
Primary Endpoints			
CHD death or non-fatal MI or fatal or non-fatal stroke, n = 868			0.74
	Beta-blockers or anti-arrhythmics, n = 283	1.11 (1.04 to 1.18), 0.0011	
	No beta-blockers or anti-arrhythmics, n = 585	1.10 (1.05 to 1.15), <0.001	
Secondary Endpoints			
CHD death or non-fatal MI, n = 639			0.39
	Beta-blockers or anti-arrhythmics, n = 202	1.08 (1.01 1.16), 0.036	
	No beta-blockers or anti-arrhythmics, n = 437	1.12 (1.07 to 1.18), <0.001	
Fatal or non-fatal stroke, n = 261			0.042
	Beta-blockers or anti-arrhythmics, n = 94	1.13 (1.03 to 1.25), 0.013	
	No beta-blockers or anti-arrhythmics, n = 167	1.00 (0.91 to 1.10), 0.99	
Other Outcomes			
Non-fatal MI, n = 471			0.58
	Beta-blockers or anti-arrhythmics, n = 153	1.07 (0.98 to 1.17), 0.13	
	No beta-blockers or anti-arrhythmics, n = 318	1.11 (1.04 to 1.18), <0.001	
Non-fatal stroke, n = 231			0.041
	Beta -blockers or anti-arrhythmics, n = 83	1.13 (1.02 to 1.25), 0.022	
	No beta-blockers or anti-arrhythmics, n = 148	1.00 (0.90 to 1.10), 0.93	
TIA, n = 177			0.069
	Taking beta-blockers or anti-arrhythmics, n = 58	1.07 (0.93 to 1.23), 0.36	
	Not taking beta-blockers or anti-arrhythmics, n = 119	0.90 (0.80 to 1.01), 0.081	
PTCA or CABG, n = 87			0.28
	Beta-blockers or anti-arrhythmics, n = 41	1.07 (0.88 to 1.30), 0.50	
	No beta-blockers or anti-arrhythmics, n = 46	0.80 (0.65 to 0.98), 0.033	
Peripheral arterial surgery/angioplasty, n = 79			0.56
	Beta-blockers or anti-arrhythmics, n = 23	1.17 (0.97 to 1.42), 0.094	
	No beta-blockers or anti-arrhythmics, n = 56	1.02 (0.86 to 1.20), 0.86	
All CV events, n = 963			0.42
	Beta-blockers or anti-arrhythmics, n = 317	1.12 (1.05 to 1.19), <0.001	

	No beta-blockers or anti-arrhythmics, n = 646	1.08 (1.03 to 1.13), <0.001	
Fatal or non-fatal stroke or TIA, n = 409			0.0078
	Beta-blockers or anti-arrhythmics, n = 141	1.11 (1.02 to 1.20), 0.017	
	No beta-blockers or anti-arrhythmics, n = 268	0.95 (0.88 to 1.03), 0.23	
HF hospitalisation, n = 232			0.43
	Beta-blockers or anti-arrhythmics, n = 65	1.15 (1.02 to 1.29), 0.023	
	No beta-blockers or anti-arrhythmics, n = 167	1.20 (1.13 to 1.28), <0.001	
Deaths			
CHD, n = 212			0.87
	Beta-blockers or anti-arrhythmics, n = 65	1.13 (1.03 to 1.25), 0.013	
	No beta-blockers or anti-arrhythmics, n = 147	1.12 (1.03 to 1.22), 0.0066	
Stroke, n = 35			0.55
	Beta-blockers or anti-arrhythmics, n = 12	1.17 (0.86 to 1.60), 0.32	
	No beta-blockers or anti-arrhythmics, n = 23	0.98 (0.75 to 1.28), 0.87	
Vascular, n = 287			0.54
	Beta-blockers or anti-arrhythmics, n = 87	1.12 (1.02 to 1.23), 0.022	
	No beta-blockers or anti-arrhythmics, n = 200	1.11 (1.03 to 1.19), 0.0045	
Non-vascular, n = 303			0.53
	Beta-blockers or anti-arrhythmics, n = 70	1.10 (0.99 to 1.22), 0.075	
	No beta-blockers or anti-arrhythmics, n = 233	1.14 (1.07 to 1.21), <0.001	
Cancer, n = 199			0.66
	Beta-blockers or anti-arrhythmics, n = 45	1.14 (1.02 to 1.28), 0.024	
	No beta-blockers or anti-arrhythmics, n = 154	1.14 (1.05 to 1.23), <0.001	
All-causes, n = 590			0.35
	Beta-blockers or anti-arrhythmics, n = 157	1.11 (1.03 to 1.19), 0.0034	
	No beta-blockers or anti-arrhythmics, n = 433	1.13 (1.07 to 1.18), <0.001	

*P-values for the likelihood ratio test comparing the model containing the interaction heart rate x use of anti-arrhythmics and/or beta-blockers at randomisation, and the model containing only heart rate and use of such drugs additively.

CABG = Coronary Artery Bypass Graft; CHD = Coronary Heart Disease; HF = Heart Failure; MI = Myocardial Infarction; PTCA = Percutaneous Transluminal Coronary Angioplasty; TIA = Transient Ischemic Attack.

Models were additionally adjusted for: age; smoking status; diabetes; history of vascular disease; hypertension; body mass index (BMI); high-density lipoprotein (HDL) cholesterol; thyroid stimulating hormones; estimated Glomerular Filtration Rate

(eGFR); treatment group (pravastatin or placebo); and intake of aspirin, nitrates, diuretics, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs).

Appendix 5

Supplementary Tables for Chapter 7

Table A5-1: Results of fitting Cox proportional hazards models. Hazard ratios, 95% confidence intervals, and p-values for a heart rate ≥70bpm compared to a heart rate <70bpm in the PERFORM population.

	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Heart Rate Adjusted for Previous
	Hazard Ratio (95% Confidence Interval), p-value			
Primary Composite Endpoint				
Fatal or non-fatal MI, fatal or non-fatal ischemic stroke, or other vascular death, n = 2141	1.19 (1.08 to 1.30), <0.001	1.23 (1.13 to 1.35), <0.001	1.18 (1.08 to 1.30), <0.001	1.15 (1.04 to 1.27), 0.0050
MI-Related Endpoints				
All fatal or non-fatal MI, n = 285	1.29 (1.01 to 1.64), 0.044	1.33 (1.04 to 1.70), 0.025	1.25 (0.96 to 1.62), 0.094	1.21 (0.92 to 1.59), 0.18
Non-fatal MI, n = 251	1.23 (0.95 to 1.60), 0.11	1.27 (0.98 to 1.65), 0.078	1.20 (0.91 to 1.59), 0.19	1.15 (0.86 to 1.54), 0.33
Stroke Related Endpoints				
All fatal or non-fatal ischemic stroke, n = 1541	1.07 (0.97 to 1.19), 0.18	1.16 (1.04 to 1.29), 0.0057	1.15 (1.03 to 1.29), 0.015	1.12 (0.99 to 1.25), 0.069
Non-fatal ischemic stroke, n = 1446	1.05 (0.94 to 1.16), 0.42	1.15 (1.03 to 1.28), 0.013	1.15 (1.02 to 1.29), 0.019	1.11 (0.99 to 1.25), 0.085
All fatal or non-fatal stroke, n = 1667	1.09 (0.99 to 1.20), 0.095	1.16 (1.05 to 1.28), 0.0044	1.14 (1.03 to 1.27), 0.016	1.12 (1.00 to 1.25), 0.054
Mortality Related Endpoints				
Vascular death, n = 436	1.71 (1.39 to 2.10), <0.001	1.71 (1.38 to 2.11), <0.001	1.52 (1.22 to 1.89), <0.001	1.51 (1.20 to 1.89), <0.001
All-cause mortality, n = 1174	1.41 (1.25 to 1.60), <0.001	1.54 (1.36 to 1.74), <0.001	1.44 (1.26 to 1.63), <0.001	1.40 (1.22 to 1.60), <0.001
Cardiac Endpoints				
Cardiac death, n = 103	1.34 (0.88 to 2.02), 0.172	1.30 (0.86 to 1.96), 0.219	1.22 (0.80 to 1.87), 0.362	1.19 (0.76 to 1.85), 0.450
Hospitalisation due to cardiac cause, n = 887	1.02 (0.89 to 1.17), 0.772	1.11 (0.97 to 1.28), 0.127	1.12 (0.97 to 1.29), 0.135	1.11 (0.95 to 1.29), 0.181

MI = Myocardial Infarction.

Models were additionally adjusted for: age; gender; smoking; body mass index (BMI); prior ischemic stroke; prior myocardial infarction (MI); prior transient ischemic attack (TIA); hypertension; diabetes; and the intake of beta-blockers, statins and antiplatelet agents after the qualifying event.

Table A5-2: Results of fitting Cox proportional hazards models. Hazard ratios, 95% confidence intervals, and p-values for a 5bpm higher heart rate in the PERFORM population.

	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Change in Heart Rate Adjusted for Previous
	Hazard Ratio (95% Confidence Interval), p-value			
Primary Composite Endpoint				
Fatal or non-fatal MI, fatal or non-fatal ischemic stroke, or other vascular death, n = 2141	1.04 (1.02 to 1.06), <0.001	1.07 (1.05 to 1.09), <0.001	1.06 (1.04 to 1.09), <0.001	1.05 (1.02 to 1.07), <0.001
MI-Related Endpoints				
All fatal or non-fatal MI, n = 285	1.07 (1.01 to 1.13), 0.013	1.08 (1.02 to 1.14), 0.0074	1.06 (0.99 to 1.12), 0.077	1.06 (0.99 to 1.13), 0.10
Non-fatal MI, n = 251	1.05 (0.99 to 1.11), 0.088	1.07 (1.00 to 1.13), 0.034	1.05 (0.99 to 1.12), 0.13	1.06 (0.99 to 1.14), 0.090
Stroke-Related Endpoints				
All fatal or non-fatal ischemic stroke, n = 1541	1.02 (0.99 to 1.04), 0.21	1.05 (1.02 to 1.07), <0.001	1.05 (1.02 to 1.08), <0.001	1.03 (1.00 to 1.07), 0.026
Non-fatal ischemic stroke, n = 1446	1.01 (0.99 to 1.04), 0.39	1.04 (1.02 to 1.07), 0.011	1.05 (1.02 to 1.08), 0.012	1.03 (1.00 to 1.06), 0.057
All fatal or non-fatal stroke, n = 1667	1.02 (1.00-1.04), 0.073	1.05 (1.02-1.07), <0.001	1.05 (1.02-1.07), <0.001	1.03 (1.01-1.06), 0.021
Mortality-Related Endpoints				
Vascular death, n = 436	1.12 (1.08 to 1.17), <0.001	1.16 (1.11 to 1.21), <0.001	1.13 (1.08 to 1.18), <0.001	1.10 (1.05 to 1.16), <0.001
All-cause mortality, n = 1174	1.08 (1.05 to 1.11), <0.001	1.16 (1.13 to 1.19), <0.001	1.15 (1.11 to 1.18), <0.001	1.13 (1.10 to 1.16), <0.001
Cardiac Endpoints				
Cardiac death, n = 103	1.12 (1.02 to 1.22), 0.013	1.16 (1.07 to 1.26), <0.001	1.14 (1.04 to 1.25), 0.0067	1.06 (0.96 to 1.17), 0.26
Hospitalisation due to a cardiac cause, n = 887	1.02 (0.99 to 1.05), 0.21	1.06 (1.03 to 1.10), <0.001	1.07 (1.03 to 1.10), <0.001	1.06 (1.02 to 1.11), 0.0014

MI = Myocardial Infarction.

Models were additionally adjusted for: age; gender; smoking; body mass index (BMI); prior ischemic stroke; prior myocardial infarction (MI); prior transient ischemic attack (TIA); hypertension; diabetes; and the intake of beta-blockers, statins and antiplatelet agents after the qualifying event.

Table A5-3: Results of fitting Cox proportional hazards models. Hazard ratios 95% confidence intervals, and p-values for the time-updated categorical heart rate patterns 'high-low', 'low-high' and 'high-high' relative to the category 'low-low' in the PERFORM population.

	Heart Rate Category	Hazard Ratio (95% Confidence Interval), p-value
Primary Composite Endpoint		
Fatal or non-fatal MI, fatal or non-fatal ischemic stroke, or other vascular death, n = 2141	high-low	1.21 (1.04 to 1.40), 0.014
	low-high	1.19 (1.02 to 1.38), 0.026
	high-high	1.36 (1.22 to 1.51), <0.001
MI-Related Endpoints		
All fatal or non-fatal MI, n = 285	high-low	1.16 (0.77 to 1.75), 0.49
	low-high	1.07 (0.70 to 1.64), 0.75
	high-high	1.51 (1.12 to 2.03), 0.0074
Non-fatal MI, n = 251	high-low	1.14 (0.74 to 1.76), 0.56
	low-high	1.01 (0.64 to 1.59), 0.97
	high-high	1.43 (1.04 to 1.96), 0.026
Stroke-Related Endpoints		
All fatal or non-fatal ischemic stroke, n = 1541	high-low	1.14 (0.96 to 1.36), 0.13
	low-high	1.17 (0.98 to 1.38), 0.082
	high-high	1.23 (1.08 to 1.39), 0.0015
Non-fatal ischemic stroke, n = 1446	high-low	1.10 (0.92 to 1.32), 0.29
	low-high	1.14 (0.96 to 1.37), 0.14
	high-high	1.20 (1.05 to 1.36), 0.0066
All fatal or non-fatal stroke, n = 1667	high-low	1.15 (0.98 to 1.36), 0.90
	low-high	1.19 (1.01 to 1.40), 0.038
	high-high	1.22 (1.08 to 1.38), 0.0012
Mortality-Related Endpoints		
Vascular death, n = 436	high-low	1.51 (1.06 to 2.16), 0.022
	low-high	1.60 (1.12 to 2.27), 0.0089
	high-high	2.16 (1.65 to 2.83), <0.001
All-cause mortality, n = 1174	high-low	1.44 (1.17 to 1.77), <0.001
	low-high	1.35 (1.27 to 1.90), <0.001
	high-high	1.86 (1.58 to 2.18), <0.001
Cardiac Endpoints		

Cardiac death, n = 103	high-low	1.31 (0.67 to 2.56), 0.42
	low-high	1.23 (0.62 to 2.43), 0.55
	high-high	1.52 (0.90 to 2.56), 0.11
Hospitalisation due to a cardiac cause, n = 887	high-low	1.14 (0.91 to 1.42), 0.26
	low-high	1.24 (1.00 to 1.54), 0.054
	high-high	1.14 (0.96 to 1.35), 0.12

Patients were classified as being in the low-low category if their heart rate measurement at both the current and previous visit was below 70bpm. Similarly, patients were classified as being in the high-high category if their heart rate measurement at both the current and previous visit was greater than or equal to 70bpm, and so on.

MI = Myocardial Infarction.

Models were additionally adjusted for: age; gender; smoking; body mass index (BMI); prior ischemic stroke; prior myocardial infarction (MI); prior transient ischemic attack (TIA); hypertension; diabetes; and the intake of beta-blockers, statins and antiplatelet agents after the qualifying event.

Table A5-4: C-statistics and likelihood ratio tests for the model excluding resting heart rate and the models including the heart rate variables that categorised subjects according to whether they had a heart rate less than, or greater than or equal to, 70bpm, which produced the results shown in Table A5-1 in the PERFORM population.

		C-statistic	Likelihood Ratio Test Statistic, p-value
Primary Composite Endpoint			
Fatal or non-fatal MI, fatal or non-fatal ischemic stroke, or other vascular death, n = 2141	Model	0.630	
	Model + Baseline	0.633	14.18, <0.001
	Model + Time-Updated	0.634	249.07, <0.001
	Model + Time-Updated + Baseline	0.635	254.63, <0.001
	Model + Time-Updated + Previous	0.636	399.36, <0.001
MI-Related Endpoints			
All fatal or non-fatal MI, n = 285	Model	0.676	
	Model + Baseline	0.679	4.13, 0.042
	Model + Time-Updated	0.677	60.10, <0.001
	Model + Time-Updated + Baseline	0.680	62.32, <0.001
	Model + Time-Updated + Previous	0.680	99.55, <0.001
Non-fatal MI, n = 251	Model	0.673	
	Model + Baseline	0.673	2.55, 0.11
	Model + Time-Updated	0.673	57.59, <0.001
	Model + Time-Updated + Baseline	0.674	58.98, <0.001
	Model + Time-Updated + Previous	0.675	96.57, <0.001
Stroke-Related Endpoints			
All fatal or non-fatal ischemic stroke, n = 1541	Model	0.618	
	Model + Baseline	0.619	1.66, 0.20
	Model + Time-Updated	0.621	139.27, <0.001
	Model + Time-Updated + Baseline	0.621	139.36, <0.001
	Model + Time-Updated + Previous	0.622	227.97, <0.001
Non-fatal ischemic stroke, n = 1446	Model	0.612	
	Model + Baseline	0.613	0.66, 0.42
	Model + Time-Updated	0.615	136.36, <0.001
	Model + Time-Updated + Baseline	0.615	136.37, <0.001
	Model + Time-Updated + Previous	0.616	203.74, <0.001
All fatal or non-fatal stroke, n = 1667	Model	0.614	
	Model + Baseline	0.615	2.80, 0.094
	Model + Time-Updated	0.616	140.92, <0.001
	Model + Time-Updated + Baseline	0.617	141.40, <0.001
	Model + Time-Updated + Previous	0.617	229.80, <0.001
Mortality-Related Endpoints			
Vascular death, n = 436	Model	0.711	
	Model + Baseline	0.723	26.64, <0.001

	Model + Time-Updated	0.723	85.77, <0.001
	Model + Time-Updated + Baseline	0.731	100.72, <0.001
	Model + Time-Updated + Previous	0.727	113.57, <0.001
All-cause mortality, n = 1174	Model	0.678	
	Model + Baseline	0.686	31.32, <0.001
	Model + Time-Updated	0.690	224.39, <0.001
	Model + Time-Updated + Baseline	0.694	239.39, <0.001
	Model + Time-Updated + Previous	0.692	316.53, <0.001
Cardiac Endpoints			
Cardiac death, n = 103	Model	0.748	
	Model + Baseline	0.752	1.90, 0.17
	Model + Time-Updated	0.750	2.66, 0.10
	Model + Time-Updated + Baseline	0.753	3.87, 0.14
	Model + Time-Updated + Previous	0.753	4.40, 0.11
Hospitalisation due to a cardiac cause, n = 887	Model	0.662	
	Model + Baseline	0.662	0.085, 0.77
	Model + Time-Updated	0.662	80.84, <0.001
	Model + Time-Updated + Baseline	0.662	80.87, <0.001
	Model + Time-Updated + Previous	0.661	120.74, <0.001

'Model' is the multivariate model excluding heart rate which included: age; gender; smoking; body mass index (BMI); prior ischemic stroke; prior myocardial infarction (MI); prior transient ischemic attack (TIA); hypertension; diabetes; and the intake of beta-blockers, statins and antiplatelet agents after the qualifying event.

'Model + Baseline' is the multivariate model described above including the baseline heart rate group variable.

'Model + Time-Updated' is the multivariate model described above including the time-updated heart rate group variable.

'Model + Time-Updated + Baseline' is the multivariable model described above including both the baseline and the time-updated heart rate group variables.

'Model + Time-Updated + Previous' is the multivariate model described above including both the time-updated heart rate group variable and the previous time-updated heart rate group variable.

The likelihood ratio test statistics and corresponding p-values were computed by comparing the multivariate models including the different heart rate variables to the multivariate model excluding resting heart rate.

Table A5-5: C-statistics and likelihood ratio tests for the model excluding resting heart rate and the models including the continuous heart rate variables, which produced the results shown in Table A5-2 in the PERFORM population.

		C-statistic	Likelihood Ratio Test Statistic, p-value
Primary Composite Endpoint			
Fatal or non-fatal MI, fatal or non-fatal ischemic stroke, or other vascular death, n = 2141	Model	0.630	
	Model + Baseline	0.633	14.15, <0.001
	Model + Time-Updated	0.636	267.28, <0.001
	Model + Time-Updated + Baseline	0.637	268.52, <0.001
	Model + Time-Updated + Previous	0.638	416.80, <0.001
MI-Related Endpoints			
All fatal or non-fatal MI, n = 285	Model	0.676	
	Model + Baseline	0.681	5.98, 0.014
	Model + Time-Updated	0.678	61.87, <0.001
	Model + Time-Updated + Baseline	0.681	64.36, <0.001
	Model + Time-Updated + Previous	0.679	99.65, <0.001
Non-fatal MI, n = 251	Model	0.673	
	Model + Baseline	0.676	2.84, 0.092
	Model + Time-Updated	0.673	58.75, <0.001
	Model + Time-Updated + Baseline	0.675	59.68, <0.001
	Model + Time-Updated + Previous	0.672	95.38, <0.001
Stroke-Related Endpoints			
All fatal or non-fatal ischemic stroke, n = 1541	Model	0.618	
	Model + Baseline	0.619	1.75, 0.19
	Model + Time-Updated	0.622	143.93, <0.001
	Model + Time-Updated + Baseline	0.621	144.06, <0.001
	Model + Time-Updated + Previous	0.623	233.00, <0.001
Non-fatal ischemic stroke, n = 1446	Model	0.612	
	Model + Baseline	0.613	0.75, 0.39
	Model + Time-Updated	0.615	140.57, <0.001
	Model + Time-Updated + Baseline	0.615	141.10, <0.001
	Model + Time-Updated + Previous	0.617	208.40, <0.001
All fatal or non-fatal stroke, n = 1667	Model	0.614	
	Model + Baseline	0.615	3.18, 0.074
	Model + Time-Updated	0.617	146.94, <0.001
	Model + Time-Updated + Baseline	0.617	146.94, <0.001
	Model + Time-Updated + Previous	0.619	235.42, <0.001
Mortality-Related Endpoints			
Vascular death, n = 436	Model	0.711	
	Model + Baseline	0.725	26.72, <0.001
	Model + Time-Updated	0.732	101.55, <0.001

	Model + Time-Updated + Baseline	0.737	110.73, <0.001
	Model + Time-Updated + Previous	0.737	134.15, <0.001
All-cause mortality, n = 1174	Model	0.678	
	Model + Baseline	0.685	31.22, <0.001
	Model + Time-Updated	0.701	291.30, <0.001
	Model + Time-Updated + Baseline	0.702	295.00, <0.001
	Model + Time-Updated + Previous	0.703	379.04, <0.001
Cardiac Endpoints			
Cardiac death, n = 103	Model	0.748	
	Model + Baseline	0.758	5.90, 0.015
	Model + Time-Updated	0.766	11.84, <0.001
	Model + Time-Updated + Baseline	0.769	13.82, <0.001
	Model + Time-Updated + Previous	0.784	27.09, <0.001
Hospitalisation due to a cardiac cause, n = 887	Model	0.662	
	Model + Baseline	0.662	1.54, 0.21
	Model + Time-Updated	0.663	92.03, <0.001
	Model + Time-Updated + Baseline	0.663	92.11, <0.001
	Model + Time-Updated + Previous	0.663	132.03, <0.001

'Model' is the multivariate model excluding heart rate which included: age; gender; smoking; body mass index (BMI); prior ischemic stroke; prior myocardial infarction (MI); prior transient ischemic attack (TIA); hypertension; diabetes; and the intake of beta-blockers, statins and antiplatelet agents after the qualifying event.

'Model + Baseline' is the multivariate model described above including the continuous baseline heart rate variable.

'Model + Time-Updated' is the multivariate model described above including the continuous time-updated heart rate variable.

'Model + Time-Updated + Baseline' is the multivariable model described above including both the continuous baseline and time-updated heart rate variables.

'Model + Time-Updated + Previous' is the multivariate model described above including both the continuous time-updated heart rate variable and the previous time-updated heart rate variable.

The likelihood ratio test statistics and corresponding p-values were computed by comparing the multivariate models including the different heart rate variables to the multivariate model excluding resting heart rate.

Table A5-6: C-statistics and likelihood ratio tests for the model excluding resting heart rate and the models including the time-updated categorical heart rate patterns variable, which produced the results shown in Table A5-3 in the PERFORM population.

		C-statistic	Likelihood Ratio Test Statistic, p-value
Primary Composite Endpoint			
Fatal or non-fatal MI, fatal or non-fatal ischemic stroke, or other vascular death, n = 2141	Model	0.630	
	Model + Pattern	0.636	259.12, <0.001
MI-Related Endpoints			
All fatal or non-fatal MI, n = 285	Model	0.676	
	Model + Pattern	0.681	63.87, <0.001
Non-fatal MI, n = 251	Model	0.673	
	Model + Pattern	0.677	60.91, <0.001
Stroke-Related Endpoints			
All fatal or non-fatal ischemic stroke, n = 1541	Model	0.618	
	Model + Pattern	0.621	141.95, <0.001
Non-fatal ischemic stroke, n = 1446	Model	0.612	
	Model + Pattern	0.615	137.79, <0.001
All fatal or non-fatal stroke, n = 1667	Model	0.614	
	Model + Pattern	0.617	143.89, <0.001
Mortality-Related Endpoints			
Vascular death, n = 436	Model	0.711	
	Model + Pattern	0.727	95.36, <0.001
All-cause mortality, n = 1174	Model	0.678	
	Model + Pattern	0.693	240.26, <0.001
Cardiac Endpoints			
Cardiac death, n = 103	Model	0.748	
	Model + Pattern	0.753	3.79, 0.28
Hospitalisation due to a cardiac cause, n = 887	Model	0.662	
	Model + Pattern	0.663	82.76, <0.001

'Model' is the multivariate model excluding heart rate which included: age; gender; smoking; body mass index (BMI); prior ischemic stroke; prior myocardial infarction (MI); prior transient ischemic attack (TIA); hypertension; diabetes; and the intake of beta-blockers, statins and antiplatelet agents after the qualifying event.

'Model + Pattern' is the multivariate model described above including the time-updated categorical heart rate patterns variable.

The likelihood ratio test statistic and corresponding p-value were computed by comparing the multivariate model including the time-updated categorical heart rate patterns variable to the multivariate model excluding resting heart rate.

Table A5-7: P-values for the Grambsch and Therneau 1994 test for non-proportionality of hazards for a heart rate ≥70bpm compared to a heart rate <70bpm in the PERFORM population.

	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Heart Rate Adjusted for Previous
	P-value			
Primary Composite Endpoint				
Fatal or non-fatal MI, fatal or non-fatal ischemic stroke, or other vascular death, n = 2141	0.30	0.64	0.93	0.94
MI-Related Endpoints				
All fatal or non-fatal MI, n = 285	0.64	0.089	0.047	0.027
Non-fatal MI, n = 251	0.90	0.080	0.069	0.049
Stroke Related Endpoints				
All fatal or non-fatal ischemic stroke, n = 1541	0.052	0.43	0.86	0.84
Non-fatal ischemic stroke, n = 1446	0.051	0.59	0.97	0.89
All fatal or non-fatal stroke, n = 1667	0.055	0.32	0.74	0.69
Mortality Related Endpoints				
Vascular death, n = 436	0.48	0.54	0.60	0.32
All-cause mortality, n = 1174	0.054	0.15	0.44	0.10
Cardiac Endpoints				
Cardiac death, n = 103	0.98	0.61	0.56	0.48
Hospitalisation due to cardiac cause, n = 887	0.22	0.36	0.68	0.52

MI = Myocardial Infarction.

Table A5-8: P-values for the Grambsch and Therneau 1994 test for non-proportionality of hazards for a 5bpm higher heart rate in the PERFORM population.

	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated in Heart Rate Adjusted for Previous
	P-value			
Primary Composite Endpoint				
Fatal or non-fatal MI, fatal or non-fatal ischemic stroke, or other vascular death, n = 2141	0.074	0.29	0.62	0.56
MI-Related Endpoints				
All fatal or non-fatal MI, n = 285	0.95	0.35	0.30	0.45
Non-fatal MI, n = 251	0.90	0.32	0.31	0.44
Stroke-Related Endpoints				
All fatal or non-fatal ischemic stroke, n = 1541	0.032	0.072	0.21	0.30
Non-fatal ischemic stroke, n = 1446	0.047	0.14	0.31	0.55
All fatal or non-fatal stroke, n = 1667	0.045	0.053	0.16	0.26
Mortality-Related Endpoints				
Vascular death, n = 436	0.32	0.46	0.79	0.25
All-cause mortality, n = 1174	<0.001	0.17	0.76	0.15
Cardiac Endpoints				
Cardiac death, n = 103	0.34	0.70	0.42	0.56
Hospitalisation due to a cardiac cause, n = 887	0.99	0.83	0.61	0.57

MI = Myocardial Infarction.

Table A5-9: P-values for the Grambsch and Therneau 1994 test for non-proportionality of hazards for the time-updated categorical patterns 'high-low', 'low-high' and 'high-high' relative to the category 'low-low' in the PERFORM population.

	Heart Rate Category	P-value
Primary Composite Endpoint		
Fatal or non-fatal MI, fatal or non-fatal ischemic stroke, or other vascular death, n = 2141	high-low	0.43
	low-high	0.38
	high-high	0.94
MI-Related Endpoints		
All fatal or non-fatal MI, n = 285	high-low	0.66
	low-high	0.090
	high-high	0.31
Non-fatal MI, n = 251	high-low	0.65
	low-high	0.049
	high-high	0.12
Stroke-Related Endpoints		
All fatal or non-fatal ischemic stroke, n = 1541	high-low	0.85
	low-high	0.57
	high-high	0.47
Non-fatal ischemic stroke, n = 1446	high-low	0.99
	low-high	0.43
	high-high	0.47
All fatal or non-fatal stroke, n = 1667	high-low	0.80
	low-high	0.62
	high-high	0.38
Mortality-Related Endpoints		
Vascular death, n = 436	high-low	0.040
	low-high	0.91
	high-high	0.29
All-cause mortality, n = 1174	high-low	0.24
	low-high	0.40
	high-high	0.95
Cardiac Endpoints		
Cardiac death, n = 103	high-low	0.33
	low-high	0.89
	high-high	0.94
Hospitalisation due to a cardiac cause, n = 887	high-low	0.76
	low-high	0.82
	high-high	0.32

Patients were classified as being in the low-low category if their heart rate measurement at both the current and previous visit was below 70bpm. Similarly, patients were classified as being in the high-high category if their heart rate measurement at both the current and previous visit was greater than or equal to 70bpm, and so on.

MI = Myocardial Infarction.

Appendix 6

Supplementary Tables for Chapter 8

Table A6-1: Results of fitting Cox proportional hazards models. Hazard ratios, 95% confidence intervals, and p-values for a heart rate ≥70bpm compared to a heart rate <70bpm in the BEAUTIFUL placebo population.

	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Heart Rate Adjusted for Previous
	Hazard Ratio (95% Confidence Interval), p-value			
Primary Composite Endpoint				
Cardiovascular death or admission to hospital for myocardial infarction or new-onset or worsening heart failure, n = 832	1.40 (1.21 to 1.61), <0.001	1.86 (1.61 to 2.15), <0.001	1.78 (1.52 to 2.08), <0.001	1.61 (1.36 to 1.89), <0.001
Mortality Endpoints				
All-cause death, n = 547	1.30 (1.09 to 1.55), 0.0033	1.82 (1.52 to 2.18), <0.001	1.79 (1.48 to 2.17), <0.001	1.70 (1.39 to 2.08), <0.001
Cardiovascular death, n = 435	1.35 (1.10 to 1.64), 0.0032	1.88 (1.53 to 2.30), <0.001	1.83 (1.47 to 2.27), <0.001	1.71 (1.36 to 2.15), <0.001
Cardiac death, n = 151	1.63 (1.16 to 2.31), 0.0054	3.43 (2.33 to 5.10), <0.001	3.35 (2.22 to 5.06), <0.001	3.17 (2.07 to 4.86), <0.001
Heart Failure Endpoints				
Admission to hospital for heart failure, n = 427	1.54 (1.26 to 1.88), <0.001	2.27 (1.84 to 2.81), <0.001	2.15 (1.72 to 2.70), <0.001	1.90 (1.49 to 2.40), <0.001
Cardiovascular death or admission to hospital for new-onset or worsening heart failure, n = 723	1.43 (1.22 to 1.66), <0.001	1.93 (1.65 to 2.26), <0.001	1.84 (1.55 to 2.18), <0.001	1.66 (1.39 to 1.99), <0.001
Coronary Endpoints				
Admission to hospital for myocardial infarction, n = 226	1.47 (1.12 to 1.92), 0.0063	1.62 (1.23 to 2.12), <0.001	1.48 (1.11 to 1.99), 0.0084	1.51 (1.11 to 2.04), 0.0085
Admission to hospital for myocardial infarction or unstable angina, n = 317	1.41 (1.12 to 1.78), 0.0032	1.37 (1.09 to 1.72), 0.0065	1.24 (0.97 to 1.59), 0.084	1.23 (0.95 to 1.58), 0.12
Coronary revascularisation, n = 186	1.38 (1.02-1.86), 0.036	1.37 (1.02 to 1.84), 0.038	1.25 (0.91 to 1.73), 0.17	1.30 (0.93 to 1.82), 0.13

Models were additionally adjusted for: age; smoking; body mass index (BMI); history of diabetes; previous myocardial infarction (MI); previous percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG); peripheral artery disease (PAD); systolic blood pressure (SBP); diastolic blood pressure (DBP); left-ventricular ejection fraction (LVEF); New York Heart Association (NYHA) class; and treatment with aspirin (not including other antithrombotic agents), beta-blockers, statins, diuretics (excluding anti-aldosterone), organic nitrates and anti-aldosterone agents at randomisation.

Table A6-2: Results of fitting Cox proportional hazards models. Hazard ratios, 95% confidence intervals, and p-values for a 5bpm higher heart rate in the BEAUTIFUL placebo population.

	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Heart Rate Adjusted for Previous
	Hazard Ratio (95% Confidence Interval), p-value			
Primary Composite Endpoint				
Cardiovascular death or admission to hospital for myocardial infarction or new-onset or worsening heart failure, n = 832	1.11 (1.08 to 1.15), <0.001	1.16 (1.13 to 1.19), <0.001	1.15 (1.12 to 1.19), <0.001	1.13 (1.09 to 1.17), <0.001
Mortality Endpoints				
All-cause death, n = 547	1.07 (1.03 to 1.11), 0.0010	1.14 (1.10 to 1.17), <0.001	1.14 (1.10 to 1.19), <0.001	1.12 (1.08 to 1.17), <0.001
Cardiovascular death, n = 435	1.08 (1.03 to 1.13), <0.001	1.14 (1.10 to 1.18), <0.001	1.14 (1.09 to 1.19), <0.001	1.12 (1.07 to 1.17), <0.001
Cardiac death, n = 151	1.13 (1.05 to 1.21), 0.0011	1.26 (1.19 to 1.33), <0.001	1.27 (1.20 to 1.35), <0.001	1.26 (1.18 to 1.34), <0.001
Heart Failure Endpoints				
Admission to hospital for heart failure, n = 427	1.16 (1.11 to 1.21), <0.001	1.22 (1.18 to 1.26), <0.001	1.20 (1.16 to 1.25), <0.001	1.18 (1.13 to 1.23), <0.001
Cardiovascular death or admission to hospital for new-onset or worsening heart failure, n = 723	1.12 (1.08 to 1.16), <0.001	1.16 (1.13 to 1.20), <0.001	1.15 (1.11 to 1.19), <0.001	1.13 (1.09 to 1.17), <0.001
Coronary Endpoints				
Admission to hospital for myocardial infarction, n = 226	1.07 (1.00 to 1.14), 0.050	1.14 (1.08 to 1.20), <0.001	1.15 (1.08 to 1.21), <0.001	1.15 (1.08 to 1.23), <0.001
Admission to hospital for myocardial infarction or unstable angina, n = 317	1.07 (1.01 to 1.13), 0.018	1.10 (1.05 to 1.15), <0.001	1.10 (1.04 to 1.15), <0.001	1.09 (1.03 to 1.15), 0.0023
Coronary revascularisation, n = 186	1.08 (1.01 to 1.16), 0.033	1.13 (1.07 to 1.19), <0.001	1.13 (1.05 to 1.20), <0.001	1.13 (1.05 to 1.21), <0.001

Models were additionally adjusted for: age; smoking; body mass index (BMI); history of diabetes; previous myocardial infarction (MI); previous percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG); peripheral artery disease (PAD); systolic blood pressure (SBP); diastolic blood pressure (DBP); left-ventricular ejection fraction (LVEF); New York Heart Association (NYHA) class; and treatment with aspirin (not including other antithrombotic agents), beta-blockers, statins, diuretics (excluding anti-aldosterone), organic nitrates and anti-aldosterone agents at randomisation.

Table A6-3: Results of fitting Cox proportional hazards models. Hazard ratios, 95% confidence intervals, and p-values for the time-updated categorical heart rate patterns 'high-low', 'low-high' and 'high-high' relative to the category 'low-low' in the BEAUTIFUL placebo population.

	Heart Rate Category	Hazard Ratio (95% Confidence Interval), p-value
Primary Composite Endpoint		
Cardiovascular death or admission to hospital for myocardial infarction or new-onset or worsening heart failure, n = 832	high-low	1.29 (1.00 to 1.66), 0.047
	low-high	1.54 (1.22 to 1.94), <0.001
	high-high	2.17 (1.83 to 2.57), <0.001
Mortality Endpoints		
All-cause death, n = 547	high-low	1.29 (0.94 to 1.76), 0.11
	low-high	1.83 (1.40 to 2.41), <0.001
	high-high	2.01 (1.62 to 2.48), <0.001
Cardiovascular death, n = 435	high-low	1.29 (0.91 to 1.84), 0.15
	low-high	1.79 (1.31 to 2.45), <0.001
	high-high	2.10 (1.65 to 2.68), <0.001
Cardiac death, n = 151	high-low	0.81 (0.35 to 1.85), 0.61
	low-high	2.61 (1.50 to 4.53), <0.001
	high-high	3.56 (2.29 to 5.55), <0.001
Heart Failure Endpoints		
Admission to hospital for heart failure, n = 427	high-low	1.43 (0.98 to 2.08), 0.061
	low-high	1.85 (1.32 to 2.59), <0.001
	high-high	2.78 (1.90 to 2.75), <0.001
Cardiovascular death or admission to hospital for new-onset or worsening heart failure, n = 723	high-low	1.39 (1.06 to 1.82), 0.018
	low-high	1.68 (1.31 to 2.16), <0.001
	high-high	2.29 (1.90 to 2.75), <0.001
Coronary Endpoints		
Admission to hospital for myocardial infarction, n = 226	high-low	0.90 (0.55 to 1.48), 0.69
	low-high	1.23 (0.80 to 1.90), 0.34
	high-high	1.73 (1.27 to 2.37), <0.001
Admission to hospital for myocardial infarction or unstable angina, n = 317	high-low	0.96 (0.65 to 1.43), 0.85
	low-high	0.93 (0.63 to 1.38), 0.728
	high-high	1.54 (1.19 to 2.00), <0.001

Coronary revascularisation, n = 186	high-low	0.81 (0.47 to 1.40), 0.45
	low-high	0.99 (0.60 to 1.61), 0.96
	high-high	1.44 (1.03 to 2.02), 0.032

Patients were classified as being in the low-low category if their heart rate measurement at both the current and previous visit was below 70bpm. Similarly, patients were classified as being in the high-high category if their heart rate measurement at both the current and previous visit was greater than or equal to 70bpm, and so on.

Models were additionally adjusted for: age; smoking; body mass index (BMI); history of diabetes; previous myocardial infarction (MI); previous percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG); peripheral artery disease (PAD); systolic blood pressure (SBP); diastolic blood pressure (DBP); left-ventricular ejection fraction (LVEF); New York Heart Association (NYHA) class; and treatment with aspirin (not including other antithrombotic agents), beta-blockers, statins, diuretics (excluding anti-aldosterone), organic nitrates and anti-aldosterone agents at randomisation.

Table A6-4: C-statistics and likelihood ratio tests for the model excluding resting heart rate and the models including the heart rate variables that categorised subjects according to whether they had a heart rate less than, or greater than or equal to, 70bpm, which produced the results shown in Table A6-1 in the BEAUTIFUL placebo population.

		C-statistic	Likelihood Ratio Test Statistic, p-value
Primary Composite Endpoint			
Cardiovascular death or admission to hospital for myocardial infarction or new-onset or worsening heart failure, n = 832	Model	0.689	
	Model + Baseline	0.694	21.54, <0.001
	Model + Time-Updated	0.705	72.37, <0.001
	Model + Time-Updated + Baseline	0.705	74.56, <0.001
	Model + Time-Updated + Previous	0.708	86.36, <0.001
Mortality Endpoints			
All-cause death, n = 547	Model	0.695	
	Model + Baseline	0.698	8.74, 0.0031
	Model + Time-Updated	0.710	44.40, <0.001
	Model + Time-Updated + Baseline	0.710	44.69, <0.001
	Model + Time-Updated + Previous	0.710	46.71, <0.001
Cardiovascular death, n = 435	Model	0.702	
	Model + Baseline	0.706	8.79, 0.003
	Model + Time-Updated	0.716	38.40, <0.001
	Model + Time-Updated + Baseline	0.716	38.88, <0.001
	Model + Time-Updated + Previous	0.716	41.46, <0.001
Cardiac death, n = 151	Model	0.759	
	Model + Baseline	0.773	8.02, 0.0046
	Model + Time-Updated	0.794	45.40, <0.001
	Model + Time-Updated + Baseline	0.795	45.58, <0.001
	Model + Time-Updated + Previous	0.795	46.31, <0.001
Heart Failure Endpoints			
Admission to hospital for heart failure, n = 427	Model	0.753	
	Model + Baseline	0.759	17.80, <0.001
	Model + Time-Updated	0.769	62.40, <0.001
	Model + Time-Updated + Baseline	0.770	64.07, <0.001
	Model + Time-Updated + Previous	0.773	73.36, <0.001
Cardiovascular death or admission to hospital for new-onset or worsening heart failure, n = 723	Model	0.714	
	Model + Baseline	0.719	20.66, <0.001
	Model + Time-Updated	0.729	70.10, <0.001
	Model + Time-Updated + Baseline	0.729	72.16, <0.001
	Model + Time-Updated + Previous	0.731	82.84, <0.001

Coronary Endpoints			
Admission to hospital for myocardial infarction, n = 226	Model	0.661	
	Model + Baseline	0.668	7.56, 0.0060
	Model + Time-Updated	0.673	12.18, <0.001
	Model + Time-Updated + Baseline	0.674	14.59, <0.001
	Model + Time-Updated + Previous	0.674	13.19, 0.0014
Admission to hospital for myocardial infarction or unstable angina, n = 317	Model	0.648	
	Model + Baseline	0.656	8.78, 0.0030
	Model + Time-Updated	0.653	7.42, 0.0064
	Model + Time-Updated + Baseline	0.657	11.78, 0.0028
	Model + Time-Updated + Previous	0.657	10.78, 0.0046
Coronary revascularisation, n = 186	Model	0.651	
	Model + Baseline	0.655	4.44, 0.035
	Model + Time-Updated	0.654	4.34, 0.037
	Model + Time-Updated + Baseline	0.656	6.36, 0.042
	Model + Time-Updated + Previous	0.656	4.80, 0.091

'Model' is the multivariate model excluding heart rate which included: age; smoking; body mass index (BMI); history of diabetes; previous myocardial infarction (MI); previous percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG); peripheral artery disease (PAD); systolic blood pressure (SBP); diastolic blood pressure (DBP); left-ventricular ejection fraction (LVEF); New York Heart Association (NYHA) class; and treatment with aspirin (not including other antithrombotic agents), beta-blockers, statins, diuretics (excluding anti-aldosterone), organic nitrates and anti-aldosterone agents at randomisation.

'Model + Baseline' is the multivariate model described above including the baseline heart rate group variable.

'Model + Time-Updated' is the multivariate model described above including the time-updated heart rate group variable.

'Model + Time-Updated + Baseline' is the multivariable model described above including both the baseline and the time-updated heart rate group variables.

'Model + Time-Updated + Previous' is the multivariate model described above including both the time-updated heart rate group variable and the previous time-updated heart rate group variable.

The likelihood ratio test statistics and corresponding p-values were computed by comparing the multivariate models including the different heart rate variables to the multivariate model excluding resting heart rate.

Table A6-5: C-statistics and likelihood ratio tests for the model excluding resting heart rate and the models including the continuous heart rate variables, which produced the results shown in Table A6-2 in the BEAUTIFUL placebo population.

		C-statistic	Likelihood Ratio Test Statistic, p-value
Primary Composite Endpoint			
Cardiovascular death or admission to hospital for myocardial infarction or new-onset or worsening heart failure, n = 832	Model	0.689	
	Model + Baseline	0.696	40.51, <0.001
	Model + Time-Updated	0.709	111.98, <0.001
	Model + Time-Updated + Baseline	0.709	112.93, <0.001
	Model + Time-Updated + Previous	0.710	117.48, <0.001
Mortality Endpoints			
All-cause death, n = 547	Model	0.695	
	Model + Baseline	0.697	10.32, 0.0013
	Model + Time-Updated	0.707	55.09, <0.001
	Model + Time-Updated + Baseline	0.707	55.49, <0.001
	Model + Time-Updated + Previous	0.708	56.13, <0.001
Cardiovascular death, n = 435	Model	0.702	
	Model + Baseline	0.705	10.83, <0.001
	Model + Time-Updated	0.712	45.13, <0.001
	Model + Time-Updated + Baseline	0.712	45.17, <0.001
	Model + Time-Updated + Previous	0.712	46.36, <0.001
Cardiac death, n = 151	Model	0.759	
	Model + Baseline	0.770	9.82, 0.0017
	Model + Time-Updated	0.790	58.57, <0.001
	Model + Time-Updated + Baseline	0.788	59.04, <0.001
	Model + Time-Updated + Previous	0.790	58.57, <0.001
Heart Failure Endpoints			
Admission to hospital for heart failure, n = 427	Model	0.753	
	Model + Baseline	0.762	44.60, <0.001
	Model + Time-Updated	0.781	113.89, <0.001
	Model + Time-Updated + Baseline	0.781	115.35, <0.001
	Model + Time-Updated + Previous	0.784	120.21, <0.001
Cardiovascular death or admission to hospital for new-onset or worsening heart failure, n = 723	Model	0.714	
	Model + Baseline	0.721	42.36, <0.001
	Model + Time-Updated	0.732	103.58, <0.001
	Model + Time-Updated + Baseline	0.733	105.36, <0.001
	Model + Time-Updated + Previous	0.734	111.41, <0.001

Coronary Endpoints			
Admission to hospital for myocardial infarction, n = 226	Model	0.661	
	Model + Baseline	0.666	3.64, 0.056
	Model + Time-Updated	0.681	22.52, <0.001
	Model + Time-Updated + Baseline	0.680	22.74, <0.001
	Model + Time-Updated + Previous	0.681	22.95, <0.001
Admission to hospital for myocardial infarction or unstable angina, n = 317	Model	0.648	
	Model + Baseline	0.654	5.34, 0.021
	Model + Time-Updated	0.660	16.24, <0.001
	Model + Time-Updated + Baseline	0.660	16.35, <0.001
	Model + Time-Updated + Previous	0.660	16.48, <0.001
Coronary revascularisation, n = 186	Model	0.651	
	Model + Baseline	0.657	4.30, 0.038
	Model + Time-Updated	0.671	15.76, <0.001
	Model + Time-Updated + Baseline	0.671	15.77, <0.001
	Model + Time-Updated + Previous	0.671	15.78, <0.001

'Model' is the multivariate model excluding heart rate which included: age; smoking; body mass index (BMI); history of diabetes; previous myocardial infarction (MI); previous percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG); peripheral artery disease (PAD); systolic blood pressure (SBP); diastolic blood pressure (DBP); left-ventricular ejection fraction (LVEF); New York Heart Association (NYHA) class; and treatment with aspirin (not including other antithrombotic agents), beta-blockers, statins, diuretics (excluding anti-aldosterone), organic nitrates and anti-aldosterone agents at randomisation.

'Model + Baseline' is the multivariate model described above including the continuous baseline heart rate variable.

'Model + Time-Updated' is the multivariate model described above including the continuous time-updated heart rate variable.

'Model + Time-Updated + Baseline' is the multivariable model described above including both the continuous baseline and time-updated heart rate variables.

'Model + Time-Updated + Previous' is the multivariate model described above including both the continuous time-updated heart rate variable and the previous time-updated heart rate variable.

The likelihood ratio test statistics and corresponding p-values were computed by comparing the multivariate models including the different heart rate variables to the multivariate model excluding resting heart rate.

Table A6-6: C-statistics and likelihood ratio tests for the model excluding resting heart rate and the models including the time-updated categorical heart rate patterns variable, which produced the results shown in Table A6-3 in the BEAUTIFUL placebo population.

		C-statistic	Likelihood Ratio Test Statistic, p-value
Primary Composite Endpoint			
Cardiovascular death or admission to hospital for myocardial infarction or new-onset or worsening heart failure, n = 832	Model	0.689	
	Model + Pattern	0.708	86.65, <0.001
Mortality Endpoints			
All-cause death, n = 547	Model	0.695	
	Model + Pattern	0.710	47.46, <0.001
Cardiovascular death, n = 435	Model	0.702	
	Model + Pattern	0.716	41.63, <0.001
Cardiac death, n = 151	Model	0.759	
	Model + Pattern	0.797	47.58, <0.001
Heart Failure Endpoints			
Admission to hospital for heart failure, n = 427	Model	0.753	
	Model + Pattern	0.773	73.40, <0.001
Cardiovascular death or admission to hospital for new-onset or worsening heart failure, n = 723	Model	0.714	
	Model + Pattern	0.731	82.85, <0.001
Coronary Endpoints			
Admission to hospital for myocardial infarction, n = 226	Model	0.661	
	Model + Pattern	0.675	15.07, 0.0018
Admission to hospital for myocardial infarction or unstable angina, n = 317	Model	0.648	
	Model + Pattern	0.658	14.74, 0.0021
Coronary revascularisation, n = 186	Model	0.651	
	Model + Pattern	0.662	7.50, 0.058

'Model' is the multivariate model excluding heart rate which included: age; smoking; body mass index (BMI); history of diabetes; previous myocardial infarction (MI); previous percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG); peripheral artery disease (PAD); systolic blood pressure (SBP); diastolic blood pressure (DBP); left-ventricular ejection fraction (LVEF); New York Heart Association (NYHA) class; and treatment with aspirin (not including other antithrombotic agents), beta-blockers, statins, diuretics (excluding anti-aldosterone), organic nitrates and anti-aldosterone agents at randomisation.

'Model + Pattern' is the multivariate model described above including the time-updated categorical heart rate patterns variable.

The likelihood ratio test statistic and corresponding p-value were computed by comparing the multivariate model including the time-updated categorical heart rate patterns variable to the multivariate model excluding resting heart rate.

Table A6-7: P-values for the Grambsch and Therneau 1994 test for non-proportionality of hazards for a heart rate ≥70bpm compared to a heart rate <70bpm in the BEAUTIFUL placebo population.

	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Heart Rate Adjusted for Previous
	P-value			
Primary Composite Endpoint				
Cardiovascular death or admission to hospital for myocardial infarction or new-onset or worsening heart failure, n = 832	0.014	0.029	0.15	0.39
Mortality Endpoints				
All-cause death, n = 547	0.81	0.15	0.12	0.20
Cardiovascular death, n = 435	0.53	0.12	0.13	0.23
Cardiac death, n = 151	0.096	0.068	0.15	0.31
Heart Failure Endpoints				
Admission to hospital for heart failure, n = 427	0.0047	0.0068	0.060	0.20
Cardiovascular death or admission to hospital for new-onset or worsening heart failure, n = 723	0.023	0.0062	0.033	0.10
Coronary Endpoints				
Admission to hospital for myocardial infarction, n = 226	0.70	0.92	0.94	0.42
Admission to hospital for myocardial infarction or unstable angina, n = 317	0.83	0.90	0.77	0.41
Coronary revascularisation, n = 186	0.72	0.91	0.99	0.92

Table A6-8: P-values for the Grambsch and Therneau 1994 test for non-proportionality of hazards for a 5bpm higher heart rate in the BEAUTIFUL placebo population.

	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Heart Rate Adjusted for Previous
	P-value			
Primary Composite Endpoint				
Cardiovascular death or admission to hospital for myocardial infarction or new-onset or worsening heart failure, n = 832	<0.001	0.015	0.35	0.32
Mortality Endpoints				
All-cause death, n = 547	0.78	0.46	0.70	0.50
Cardiovascular death, n = 435	0.72	0.84	0.82	0.87
Cardiac death, n = 151	0.53	0.68	0.72	0.59
Heart Failure Endpoints				
Admission to hospital for heart failure, n = 427	<0.001	<0.001	0.017	0.021
Cardiovascular death or admission to hospital for new-onset or worsening heart failure, n = 723	0.0019	0.0034	0.11	0.084
Coronary Endpoints				
Admission to hospital for myocardial infarction, n = 226	0.60	0.37	0.25	0.23
Admission to hospital for myocardial infarction or unstable angina, n = 317	0.93	0.37	0.29	0.15
Coronary revascularisation, n = 186	0.77	0.91	0.97	0.81

Table A6-9: P-values for the Grambsch and Therneau 1994 test for non-proportionality of hazards for for the time-updated categorical heart rate patterns 'high-low', 'low-high' and 'high-high' relative to the category 'low-low' in the BEAUTIFUL placebo population.

	Heart Rate Category	P-value
Primary Composite Endpoint		
Cardiovascular death or admission to hospital for myocardial infarction or new-onset or worsening heart failure, n = 832	high-low	0.33
	low-high	0.76
	high-high	0.0086
Mortality Endpoints		
All-cause death, n = 547	high-low	0.54
	low-high	0.68
	high-high	0.32
Cardiovascular death, n = 435	high-low	0.55
	low-high	0.85
	high-high	0.22
Cardiac death, n = 151	high-low	0.27
	low-high	0.33
	high-high	0.21
Heart Failure Endpoints		
Admission to hospital for heart failure, n = 427	high-low	0.38
	low-high	0.64
	high-high	0.0021
Cardiovascular death or admission to hospital for new-onset or worsening heart failure, n = 723	high-low	0.95
	low-high	0.67
	high-high	0.0077
Coronary Endpoints		
Admission to hospital for myocardial infarction, n = 226	high-low	0.064
	low-high	0.81
	high-high	0.29
Admission to hospital for myocardial infarction or unstable angina, n = 317	high-low	0.052
	low-high	0.85
	high-high	0.57
Coronary revascularisation, n = 186	high-low	0.73
	low-high	0.78
	high-high	0.93

Patients were classified as being in the low-low category if their heart rate measurement at both the current and previous visit was below 70bpm. Similarly, patients were classified as being in the high-high category if their heart rate measurement at both the current and previous visit was greater than or equal to 70bpm, and so on.

Table A6-10: Results of fitting Cox proportional hazards models. Hazard ratios, 95% confidence intervals, and p-values for a heart rate ≥80bpm compared to a heart rate <80bpm in the SHIFT placebo population.

	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Heart Rate Adjusted for Previous
	Hazard Ratio (95% Confidence Interval), p-value			
Primary Endpoint				
Cardiovascular death or hospital admission for worsening heart failure, n = 936	1.74 (1.53 to 1.98), <0.001	2.22 (1.95 to 2.53), <0.001	1.98 (1.72 to 2.28), <0.001	1.84 (1.59 to 2.15), <0.001
Mortality Endpoints				
All-cause mortality, n = 551	1.78 (1.50 to 2.11), <0.001	2.09 (1.76 to 2.48), <0.001	1.83 (1.53 to 2.20), <0.001	1.80 (1.48 to 2.18), <0.001
Cardiovascular mortality, n = 491	1.81 (1.50 to 2.17), <0.001	2.12 (1.78 to 2.55), <0.001	1.86 (1.53 to 2.26), <0.001	1.86 (1.51 to 2.28), <0.001
Death from heart failure, n = 151	2.12 (1.52 to 2.97), <0.001	2.32 (1.67 to 2.32), <0.001	1.92 (1.34 to 2.74), <0.001	1.87 (1.28 to 2.72), <0.001
Individual Hospital Admission Endpoints				
All-cause hospital admission, n = 1354	1.37 (1.23 to 1.53), <0.001	1.81 (1.62 to 2.02), <0.001	1.73 (1.54 to 1.95), <0.001	1.69 (1.49 to 1.92), <0.001
Hospital admission for worsening heart failure, n = 671	1.68 (1.44 to 1.96), <0.001	2.39 (2.05 to 2.79), <0.001	2.20 (1.86 to 2.61), <0.001	1.96 (1.64 to 2.34), <0.001
Any cardiovascular hospital admission, n = 1120	1.38 (1.23 to 1.56), <0.001	1.80 (1.60 to 2.03), <0.001	1.72 (1.51 to 1.96), <0.001	1.64 (1.43 to 1.89), <0.001
Hospital admission for non-fatal myocardial infarction, n = 86	0.93 (0.60 to 1.45), 0.750	1.18 (0.76 to 1.86), 0.459	1.25 (0.78 to 2.02), 0.354	1.27 (0.77 to 2.09), 0.359
Other Composite Endpoints				
Cardiovascular death or hospital admission for non-fatal myocardial infarction, n = 550	1.68 (1.41 to 1.99), <0.001	2.00 (1.69 to 2.37), <0.001	1.78 (1.48 to 2.15), <0.001	1.76 (1.45 to 2.14), <0.001
Cardiovascular death, or hospital admission for worsening heart failure, or hospital admission for non-fatal myocardial infarction, n = 977	1.71 (1.51 to 1.95), <0.001	2.18 (1.92 to 2.48), <0.001	1.95 (1.70 to 2.25), <0.001	1.83 (1.58 to 2.12), <0.001

Models were additionally adjusted for: beta-blocker intake; New York Heart Association (NYHA) class; left-ventricular ejection fraction (LVEF); whether the primary cause of heart failure (HF) was ischemic or not; age; systolic blood pressure (SBP); and estimated Glomerular Filtration Rate (eGFR).

Table A6-11: Results of fitting Cox proportional hazards models. Hazard ratios, 95% confidence intervals, and p-values for a 5bpm higher heart rate in the SHIFT placebo population.

	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Heart Rate Adjusted for Previous
	Hazard Ratio (95% Confidence Interval), p-value			
Primary Endpoint				
Cardiovascular death or hospital admission for worsening heart failure, n = 936	1.15 (1.12 to 1.18), <0.001	1.20 (1.17 to 1.23), <0.001	1.19 (1.16 to 1.22), <0.001	1.16 (1.13 to 1.20), <0.001
Mortality Endpoints				
All-cause mortality, n = 551	1.13 (1.09 to 1.18), <0.001	1.17 (1.14 to 1.21), <0.001	1.16 (1.13 to 1.20), <0.001	1.15 (1.11 to 1.19), <0.001
Cardiovascular mortality, n = 491	1.14 (1.09 to 1.18), <0.001	1.18 (1.14 to 1.21), <0.001	1.16 (1.13 to 1.20), <0.001	1.15 (1.11 to 1.20), <0.001
Death from heart failure, n = 151	1.18 (1.10 to 1.26), <0.001	1.24 (1.19 to 1.30), <0.001	1.24 (1.17 to 1.30), <0.001	1.22 (1.15 to 1.30), <0.001
Individual Hospital Admission Endpoints				
All-cause hospital admission, n = 1354	1.09 (1.07 to 1.12), <0.001	1.15 (1.13 to 1.17), <0.001	1.15 (1.12 to 1.18), <0.001	1.14 (1.11 to 1.17), <0.001
Hospital admission for worsening heart failure, n = 671	1.15 (1.11 to 1.19), <0.001	1.22 (1.19 to 1.25), <0.001	1.22 (1.17 to 1.26), <0.001	1.18 (1.14 to 1.22), <0.001
Any cardiovascular hospital admission, n = 1120	1.10 (1.07 to 1.13), <0.001	1.16 (1.14 to 1.19), <0.001	1.16 (1.14 to 1.19), <0.001	1.15 (1.12 to 1.18), <0.001
Hospital admission for non-fatal myocardial infarction, n = 86	0.99 (0.88 to 1.11), 0.829	1.09 (1.01 to 1.17), 0.030	1.12 (1.03 to 1.21), 0.010	1.12 (1.02 to 1.23), 0.016
Other Composite Endpoints				
Cardiovascular death or hospital admission for non-fatal myocardial infarction, n = 550	1.12 (1.08 to 1.16), <0.001	1.17 (1.13 to 1.20), <0.001	1.16 (1.12 to 1.19), <0.001	1.15 (1.11 to 1.19), <0.001
Cardiovascular death, or hospital admission for worsening heart failure, or hospital admission for non-fatal myocardial infarction, n = 977	1.14 (1.11 to 1.18), <0.001	1.20 (1.17 to 1.22), <0.001	1.19 (1.16 to 1.22), <0.001	1.16 (1.13 to 1.20), <0.001

Models were additionally adjusted for: beta-blocker intake; New York Heart Association (NYHA) class; left-ventricular ejection fraction (LVEF); whether the primary cause of heart failure (HF) was ischemic or not; age; systolic blood pressure (SBP); and estimated Glomerular Filtration Rate (eGFR).

Table A6-12: Results of fitting Cox proportional hazards models. Hazard ratios, 95% confidence intervals, and p-values for time-updated categorical heart rate patterns 'high-low', 'low-high' and 'high-high' relative to the category 'low-low' in the SHIFT placebo population.

	Heart Rate Category	Hazard Ratio (95% Confidence Interval), p-value
Primary Endpoint		
Cardiovascular death or hospital admission for worsening heart failure, n = 936	high-low	1.83 (1.49 to 2.26), <0.001
	low-high	2.25 (1.85 to 2.74), <0.001
	high-high	2.68 (2.29 to 3.13), <0.001
Mortality Endpoints		
All-cause mortality, n = 551	high-low	2.09 (1.60 to 2.71), <0.001
	low-high	2.55 (1.99 to 3.25), <0.001
	high-high	2.48 (2.01 to 3.05) <0.001
Cardiovascular mortality, n = 491	high-low	2.07 (1.56 to 2.74), <0.001
	low-high	2.65 (2.05 to 3.43), <0.001
	high-high	2.48 (1.98 to 3.09), <0.001
Death from heart failure, n = 151	high-low	2.45 (1.47 to 4.08), <0.001
	low-high	2.79 (1.71 to 4.55), <0.001
	high-high	3.05 (2.03 to 4.57), <0.001
Individual Hospital Admission Endpoints		
All-cause hospital admission, n = 1354	high-low	1.24 (1.03 to 1.49), 0.024
	low-high	1.80 (1.53 to 2.11), <0.001
	high-high	1.92 (1.69 to 2.19), <0.001
Hospital admission for worsening heart failure, n = 671	high-low	1.74 (1.35 to 2.25), <0.001
	low-high	2.21 (1.75 to 2.81), <0.001
	high-high	2.96 (2.46 to 3.55) <0.001
Any cardiovascular hospital admission, n = 1120	high-low	1.40 (1.15 to 1.70) <0.001
	low-high	1.86 (1.56 to 2.22) <0.001
	high-high	1.95 (1.69 to 2.25) <0.001
Hospital admission for non-fatal myocardial infarction, n = 86	high-low	1.39 (0.73 to 2.65) 0.314
	low-high	1.83 (1.02 to 3.25) 0.041
	high-high	0.95 (0.53 to 1.72) 0.871
Other Composite Endpoints		

Cardiovascular death or hospital admission for non-fatal myocardial infarction, n = 550	high-low	2.05 (1.57 to 2.66) <0.001
	low-high	2.55 (2.00 to 3.25) <0.001
	high-high	2.28 (1.84 to 2.81) <0.001
Cardiovascular death, or hospital admission for worsening heart failure, or hospital admission for non-fatal myocardial infarction, n = 977	high-low	1.84 (1.50 to 2.26) <0.001
	low-high	2.27 (1.88 to 2.75) <0.001
	high-high	2.60 (2.23 to 3.03) <0.001

Patients were classified as being in the low-low category if their heart rate measurement at both the current and previous visit was below 80bpm. Similarly, patients were classified as being in the high-high category if their heart rate measurement at both the current and previous visit was greater than or equal to 80bpm, and so on.

Models were additionally adjusted for: beta-blocker intake; New York Heart Association (NYHA) class; left-ventricular ejection fraction (LVEF); whether the primary cause of heart failure (HF) was ischemic or not; age; systolic blood pressure (SBP); and estimated Glomerular Filtration Rate (eGFR).

Table A6-13: C-statistics and likelihood ratio tests for the model excluding resting heart rate and the models including the heart rate variables that categorised subjects according to whether they had a heart rate less than, or greater than or equal to, 80bpm, which produced the results shown in Table A6-10 in the SHIFT placebo population.

		C-statistic	Likelihood Ratio Test Statistic, p-value
Primary Endpoint			
Cardiovascular death or hospital admission for worsening heart failure, n = 936	Model	0.639	
	Model + Baseline	0.660	68.12, <0.001
	Model + Time-Updated	0.679	139.75, <0.001
	Model + Time-Updated + Baseline	0.683	155.96, <0.001
	Model + Time-Updated + Previous	0.687	163.24, <0.001
Mortality Endpoints			
All-cause mortality, n = 551	Model	0.651	
	Model + Baseline	0.672	43.20, <0.001
	Model + Time-Updated	0.682	71.17, <0.001
	Model + Time-Updated + Baseline	0.689	84.96, <0.001
	Model + Time-Updated + Previous	0.690	81.73, <0.001
Cardiovascular mortality, n = 491	Model	0.658	
	Model + Baseline	0.679	40.52, <0.001
	Model + Time-Updated	0.689	66.62, <0.001
	Model + Time-Updated + Baseline	0.695	79.43, <0.001
	Model + Time-Updated + Previous	0.695	74.13, <0.001
Death from heart failure, n = 151	Model	0.774	
	Model + Baseline	0.792	19.67, <0.001
	Model + Time-Updated	0.795	25.31, <0.001
	Model + Time-Updated + Baseline	0.802	32.59, <0.001
	Model + Time-Updated + Previous	0.804	30.96, <0.001
Individual Hospital Admission Endpoints			
All-cause hospital admission, n = 1354	Model	0.601	
	Model + Baseline	0.610	32.24, <0.001
	Model + Time-Updated	0.631	108.68, <0.001
	Model + Time-Updated + Baseline	0.632	112.02, <0.001
	Model + Time-Updated + Previous	0.632	112.84, <0.001
Hospital admission for worsening heart failure, n = 671	Model	0.646	
	Model + Baseline	0.665	42.58, <0.001
	Model + Time-Updated	0.691	120.73, <0.001
	Model + Time-Updated + Baseline	0.693	126.85, <0.001
	Model + Time-Updated + Previous	0.698	140.83, <0.001
Any cardiovascular hospital admission, n = 1120	Model	0.611	
	Model + Baseline	0.618	27.81, <0.001
	Model + Time-Updated	0.636	89.15, <0.001

	Model + Time-Updated + Baseline	0.636	92.33, <0.001
	Model + Time-Updated + Previous	0.639	95.74, <0.001
Hospital admission for non-fatal myocardial infarction, n = 86	Model	0.713	
	Model + Baseline	0.712	0.10, 0.75
	Model + Time-Updated	0.712	0.53, 0.46
	Model + Time-Updated + Baseline	0.712	0.95, 0.62
	Model + Time-Updated + Previous	0.713	0.85, 0.65
Other Composite Endpoints			
Cardiovascular death or hospital admission for non-fatal myocardial infarction, n = 550	Model	0.657	
	Model + Baseline	0.674	34.93, <0.001
	Model + Time-Updated	0.684	62.49, <0.001
	Model + Time-Updated + Baseline	0.689	72.64, <0.001
	Model + Time-Updated + Previous	0.689	69.68, <0.001
Cardiovascular death, or hospital admission for worsening heart failure, or hospital admission for non-fatal myocardial infarction, n = 977	Model	0.639	
	Model + Baseline	0.659	67.28, <0.001
	Model + Time-Updated	0.677	139.64, <0.001
	Model + Time-Updated + Baseline	0.681	155.40, <0.001
	Model + Time-Updated + Previous	0.684	161.71, <0.001

'Model' is the multivariate model excluding heart rate which included: beta-blocker intake; New York Heart Association (NYHA) class; left-ventricular ejection fraction (LVEF); whether the primary cause of heart failure (HF) was ischemic or not; age; systolic blood pressure (SBP); and estimated Glomerular Filtration Rate (eGFR).

'Model + Baseline' is the multivariate model described above including the baseline heart rate group variable.

'Model + Time-Updated' is the multivariate model described above including the time-updated heart rate group variable.

'Model + Time-Updated + Baseline' is the multivariable model described above including both the baseline and the time-updated heart rate group variables.

'Model + Time-Updated + Previous' is the multivariate model described above including both the time-updated heart rate group variable and the previous time-updated heart rate group variable.

The likelihood ratio test statistics and corresponding p-values were computed by comparing the multivariate models including the different heart rate variables to the multivariate model excluding resting heart rate.

Table A6-14: C-statistics and likelihood ratio tests for the model excluding resting heart rate and the models including the continuous heart rate variables, which produced the results shown in Table A6-11 in the SHIFT placebo population.

		C-statistic	Likelihood Ratio Test Statistic, p-value
Primary Endpoint			
Cardiovascular death or hospital admission for worsening heart failure, n = 936	Model	0.639	
	Model + Baseline	0.666	80.78, <0.001
	Model + Time-Updated	0.699	239.06, <0.001
	Model + Time-Updated + Baseline	0.700	241.20, <0.001
	Model + Time-Updated + Previous	0.703	250.80, <0.001
Mortality Endpoints			
All-cause mortality, n = 551	Model	0.651	
	Model + Baseline	0.674	39.43, <0.001
	Model + Time-Updated	0.696	119.86, <0.001
	Model + Time-Updated + Baseline	0.697	121.53, <0.001
	Model + Time-Updated + Previous	0.698	123.40, <0.001
Cardiovascular mortality, n = 491	Model	0.658	
	Model + Baseline	0.680	36.32, <0.001
	Model + Time-Updated	0.701	107.96, <0.001
	Model + Time-Updated + Baseline	0.702	109.60, <0.001
	Model + Time-Updated + Previous	0.703	111.24, <0.001
Death from heart failure, n = 151	Model	0.774	
	Model + Baseline	0.798	19.20, <0.001
	Model + Time-Updated	0.821	68.24, <0.001
	Model + Time-Updated + Baseline	0.822	68.60, <0.001
	Model + Time-Updated + Previous	0.824	69.19, <0.001
Individual Hospital Admission Endpoints			
All-cause hospital admission, n = 1354	Model	0.601	
	Model + Baseline	0.615	42.35, <0.001
	Model + Time-Updated	0.646	179.38, <0.001
	Model + Time-Updated + Baseline	0.646	179.42, <0.001
	Model + Time-Updated + Previous	0.646	180.45, <0.001
Hospital admission for worsening heart failure, n = 671	Model	0.646	
	Model + Baseline	0.673	57.83, <0.001
	Model + Time-Updated	0.715	212.57, <0.001
	Model + Time-Updated + Baseline	0.715	212.68, <0.001
	Model + Time-Updated + Previous	0.719	223.25, <0.001
Any cardiovascular hospital admission, n = 1120	Model	0.611	
	Model + Baseline	0.624	39.49, <0.001
	Model + Time-Updated	0.655	178.31, <0.001

	Model + Time-Updated + Baseline	0.655	178.52, <0.001
	Model + Time-Updated + Previous	0.656	179.40, <0.001
Hospital admission for non-fatal myocardial infarction, n = 86	Model	0.713	
	Model + Baseline	0.713	0.047, 0.83
	Model + Time-Updated	0.714	4.45, 0.035
	Model + Time-Updated + Baseline	0.716	6.20, 0.045
	Model + Time-Updated + Previous	0.715	5.50, 0.064
Other Composite Endpoints			
Cardiovascular death or hospital admission for non-fatal myocardial infarction, n = 550	Model	0.657	
	Model + Baseline	0.675	31.66, <0.001
	Model + Time-Updated	0.695	106.80, <0.001
	Model + Time-Updated + Baseline	0.696	107.53, <0.001
	Model + Time-Updated + Previous	0.696	108.87, <0.001
Cardiovascular death, or hospital admission for worsening heart failure, or hospital admission for non-fatal myocardial infarction, n = 977	Model	0.639	
	Model + Baseline	0.665	78.92, <0.001
	Model + Time-Updated	0.696	241.03, <0.001
	Model + Time-Updated + Baseline	0.697	242.76, <0.001
	Model + Time-Updated + Previous	0.700	249.81, <0.001

'Model' is the multivariate model excluding heart rate which included: beta-blocker intake; New York Heart Association (NYHA) class; left-ventricular ejection fraction (LVEF); whether the primary cause of heart failure (HF) was ischemic or not; age; systolic blood pressure (SBP); and estimated Glomerular Filtration Rate (eGFR).

'Model + Baseline' is the multivariate model described above including the continuous baseline heart rate variable.

'Model + Time-Updated' is the multivariate model described above including the continuous time-updated heart rate variable.

'Model + Time-Updated + Baseline' is the multivariable model described above including both the continuous baseline and time-updated heart rate variables.

'Model + Time-Updated + Previous' is the multivariate model described above including both the continuous time-updated heart rate variable and the previous time-updated heart rate variable.

The likelihood ratio test statistics and corresponding p-values were computed by comparing the multivariate models including the different heart rate variables to the multivariate model excluding resting heart rate.

Table A6-15: C-statistics and likelihood ratio tests for the model excluding resting heart rate and the models including the time-updated categorical heart rate patterns variable, which produced the results shown in Table A6-12 in the SHIFT placebo population.

		C-statistic	Likelihood Ratio Test Statistic, p-value
Primary Endpoint			
Cardiovascular death or hospital admission for worsening heart failure, n = 936	Model	0.639	
	Model + Pattern	0.687	171.56, <0.001
Mortality Endpoints			
All-cause mortality, n = 551	Model	0.651	
	Model + Pattern	0.693	98.22, <0.001
Cardiovascular mortality, n = 491	Model	0.658	
	Model + Pattern	0.699	90.06, <0.001
Death from heart failure, n = 151	Model	0.774	
	Model + Pattern	0.805	35.96, <0.001
Individual Hospital Admission Endpoints			
All-cause hospital admission, n = 1354	Model	0.601	
	Model + Pattern	0.632	141.11, <0.001
Hospital admission for worsening heart failure, n = 671	Model	0.646	
	Model + Pattern	0.698	143.05, <0.001
Any cardiovascular hospital admission, n = 1120	Model	0.611	
	Model + Pattern	0.638	99.92, <0.001
Hospital admission for non-fatal myocardial infarction, n = 86	Model	0.713	
	Model + Pattern	0.724	4.75, 0.19
Other Composite Endpoints			
Cardiovascular death or hospital admission for non-fatal myocardial infarction, n = 550	Model	0.657	
	Model + Pattern	0.694	89.12, <0.001
Cardiovascular death, or hospital admission for worsening heart failure, or hospital admission for non-fatal myocardial infarction, n = 977	Model	0.639	
	Model + Pattern	0.684	172.23, <0.001

'Model' is the multivariate model excluding heart rate which included: beta-blocker intake; New York Heart Association (NYHA) class; left-ventricular ejection fraction (LVEF); whether the primary cause of heart failure (HF) was ischemic or not; age; systolic blood pressure (SBP); and estimated Glomerular Filtration Rate (eGFR).

'Model + Pattern' is the multivariate model described above including the time-updated categorical heart rate patterns variable.

The likelihood ratio test statistic and corresponding p-value were computed by comparing the multivariate model including the time-updated categorical heart rate patterns variable to the multivariate model excluding resting heart rate.

Table A6-16: P-values for the Grambsch and Therneau 1994 test for non-proportionality of hazards for a heart rate ≥80bpm compared to a heart rate <80bpm in the SHIFT placebo population.

	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Heart Rate Adjusted for Previous
	P-value			
Primary Endpoint				
Cardiovascular death or hospital admission for worsening heart failure, n = 936	0.019	0.21	0.72	0.50
Mortality Endpoints				
All-cause mortality, n = 551	0.28	0.64	0.98	0.67
Cardiovascular mortality, n = 491	0.34	0.36	0.61	0.41
Death from heart failure, n = 151	0.77	0.42	0.28	0.38
Individual Hospital Admission Endpoints				
All-cause hospital admission, n = 1354	0.0086	0.29	0.85	0.46
Hospital admission for worsening heart failure, n = 671	0.022	0.83	0.27	0.52
Any cardiovascular hospital admission, n = 1120	0.030	0.89	0.50	0.82
Hospital admission for non-fatal myocardial infarction, n = 86	0.48	0.045	0.067	0.26
Other Composite Endpoints				
Cardiovascular death or hospital admission for non-fatal myocardial infarction, n = 550	0.54	0.71	0.93	0.58
Cardiovascular death, or hospital admission for worsening heart failure, or hospital admission for non-fatal myocardial infarction, n = 977	0.020	0.30	0.90	0.51

Table A6-17: P-values for the Grambsch and Therneau 1994 test for non-proportionality of hazards for a 5bpm higher heart rate in the SHIFT placebo population.

	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Heart Rate Adjusted for Previous
	P-value			
Primary Endpoint				
Cardiovascular death or hospital admission for worsening heart failure, n = 936	0.042	0.11	0.38	0.37
Mortality Endpoints				
All-cause mortality, n = 551	0.11	0.16	0.41	0.40
Cardiovascular mortality, n = 491	0.061	0.065	0.25	0.16
Death from heart failure, n = 151	0.46	0.33	0.39	0.75
Individual Hospital Admission Endpoints				
All-cause hospital admission, n = 1354	0.028	0.15	0.39	0.48
Hospital admission for worsening heart failure, n = 671	0.34	0.99	0.91	0.77
Any cardiovascular hospital admission, n = 1120	0.047	0.62	0.90	0.84
Hospital admission for non-fatal myocardial infarction, n = 86	0.15	0.12	0.069	0.066
Other Composite Endpoints				
Cardiovascular death or hospital admission for non-fatal myocardial infarction, n = 550	0.11	0.22	0.49	0.31
Cardiovascular death, or hospital admission for worsening heart failure, or hospital admission for non-fatal myocardial infarction, n = 977	0.046	0.20	0.56	0.56

Table A6-18: P-values for the Grambsch and Therneau 1994 test for non-proportionality of hazards for time-updated categorical heart rate patterns 'high-low', 'low-high' and 'high-high' relative to the category 'low-low' in the SHIFT placebo population.

	Heart Rate Category	P-value
Primary Endpoint		
Cardiovascular death or hospital admission for worsening heart failure, n = 936	high-low	0.81
	low-high	0.997
	high-high	0.17
Mortality Endpoints		
All-cause mortality, n = 551	high-low	0.92
	low-high	0.56
	high-high	0.77
Cardiovascular mortality, n = 491	high-low	0.94
	low-high	0.42
	high-high	0.48
Death from heart failure, n = 151	high-low	0.67
	low-high	0.87
	high-high	0.60
Individual Hospital Admission Endpoints		
All-cause hospital admission, n = 1354	high-low	0.22
	low-high	0.55
	high-high	0.22
Hospital admission for worsening heart failure, n = 671	high-low	0.43
	low-high	0.13
	high-high	0.95
Any cardiovascular hospital admission, n = 1120	high-low	0.30
	low-high	0.18
	high-high	0.55
Hospital admission for non-fatal myocardial infarction, n = 86	high-low	0.55
	low-high	0.60
	high-high	0.0047
Other Composite Endpoints		
Cardiovascular death or hospital admission for non-fatal myocardial infarction, n = 550	high-low	0.76
	low-high	0.61
	high-high	0.99
Cardiovascular death, or hospital admission for worsening heart failure, or hospital admission for non-fatal myocardial infarction, n = 977	high-low	0.66
	low-high	0.99
	high-high	0.29

Patients were classified as being in the low-low category if their heart rate measurement at both the current and previous visit was below 80bpm. Similarly, patients were classified as being in the high-high category if their heart rate measurement at both the current and previous visit was greater than or equal to 80bpm, and so on.

Table A6-19: Results of fitting Cox proportional hazards models. Hazard ratios, 95% confidence intervals, and p-values for each of the five or six heart rate groups greater than or equal to 65bpm, or 60bpm, relative to a heart rate <65bpm, or <60bpm, for the baseline and time-updated models, respectively, in the pooled left-ventricular dysfunction placebo population.

	Heart Rate Group	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate adjusted for Baseline	Time-Updated Heart Rate adjusted for Previous
		Hazard Ratio (95% Confidence Interval), p-value			
Individual Endpoints					
All-cause death, n = 1098	60-64bpm	-	1.14 (0.85 to 1.53), 0.38	1.15 (0.85 to 1.54), 0.36	1.15 (0.85 to 1.55), 0.38
	65-69bpm	1.00 (0.77 to 1.30), 0.98	1.27 (0.96 to 1.69), 0.094	1.29 (0.97 to 1.72), 0.082	1.29 (0.95 to 1.74), 0.097
	70-74bpm	1.06 (0.84 to 1.35), 0.61	1.66 (1.26 to 2.19), <0.001	1.67 (1.26 to 2.22), <0.001	1.64 (1.21 to 2.21), 0.0013
	75-79bpm	1.18 (0.92 to 1.51), 0.20	1.81 (1.36 to 2.39), <0.001	1.79 (1.34 to 2.38), <0.001	1.74 (1.28 to 2.36), <0.001
	80-84bpm	1.55 (1.20 to 2.00), <0.001	2.08 (1.56 to 2.78), <0.001	2.01 (1.49 to 2.70), <0.001	1.91 (1.39 to 2.64), <0.001
	≥85bpm	1.89 (1.49 to 2.39), <0.001	3.14 (2.43 to 4.06), <0.001	2.91 (2.21 to 3.84), <0.001	2.66 (1.97 to 3.61), <0.001
Cardiovascular mortality, n = 926	60-64bpm	-	1.20 (0.86 to 1.67), 0.28	1.19 (0.86 to 1.66), 0.30	1.20 (0.86 to 1.68), 0.29
	65-69bpm	1.19 (0.88 to 1.60), 0.26	1.33 (0.97 to 1.82), 0.081	1.31 (0.95 to 1.80), 0.099	1.34 (0.96 to 1.87), 0.090
	70-74bpm	1.21 (0.92 to 1.59), 0.17	1.71 (1.26 to 2.33), <0.001	1.67 (1.22 to 2.29), 0.0013	1.67 (1.19 to 2.34), 0.0027
	75-79bpm	1.30 (0.97 to 1.72), 0.077	1.90 (1.39 to 2.60), <0.001	1.83 (1.33 to 2.51), <0.001	1.81 (1.29 to 2.55), <0.001
	80-84bpm	1.77 (1.32 to 2.36), <0.001	2.11 (1.53 to 2.91), <0.001	1.96 (1.41 to 2.74), <0.001	1.92 (1.34 to 2.74), <0.001
	≥85bpm	2.16 (1.64 to 2.83), <0.001	3.33 (2.50 to 4.44), <0.001	2.99 (2.20 to 4.06), <0.001	2.80 (2.00 to 3.92), <0.001
Hospital admission for heart failure, n = 1098	60-64bpm	-	1.45 (1.01 to 2.08), 0.043	1.45 (1.01 to 2.08), 0.045	1.28 (0.88 to 1.85), 0.19
	65-69bpm	1.21 (0.88 to 1.65), 0.25	1.72 (1.22 to 2.43), 0.0020	1.70 (1.20 to 2.41), 0.0026	1.43 (0.99 to 2.05), 0.054
	70-74bpm	1.24 (0.94 to 1.64), 0.13	2.13 (1.52 to 2.99), <0.001	2.11 (1.50 to 2.97), <0.001	1.67 (1.16 to 2.39), 0.0054
	75-79bpm	1.62 (1.23 to 2.15), <0.001	3.12 (2.25 to 4.34), <0.001	3.04 (2.17 to 4.25), <0.001	2.30 (1.61 to 3.29), <0.001
	80-84bpm	1.76 (1.31 to 2.35), <0.001	2.98 (2.11 to 4.20), <0.001	2.86 (2.01 to 4.07), <0.001	2.09 (1.43 to 3.04), <0.001
	≥85bpm	2.59 (1.97 to 3.40), <0.001	5.65 (4.13 to 7.73), <0.001	5.23 (3.76 to 7.27), <0.001	3.74 (2.62 to 5.34), <0.001
Hospital admission for non-fatal myocardial infarction, n = 312	60-64bpm	-	1.24 (0.78 to 1.99), 0.36	1.24 (0.77 to 1.98), 0.37	1.22 (0.75 to 1.98), 0.42
	65-69bpm	0.85 (0.56 to 1.28), 0.44	1.21 (0.76 to 1.92), 0.43	1.19 (0.74 to 1.91), 0.47	1.17 (0.71 to 1.91), 0.54
	70-74bpm	1.28 (0.88 to 1.84), 0.19	1.54 (0.97 to 2.45), 0.066	1.49 (0.93 to 2.40), 0.097	1.48 (0.90 to 2.44), 0.13
	75-79bpm	1.48 (1.01 to 2.19), 0.047	1.72 (1.07 to 2.75), 0.025	1.64 (1.00 to 2.68), 0.048	1.64 (0.97 to 2.75), 0.063
	80-84bpm	1.41 (0.91 to 2.18), 0.12	1.73 (1.04 to 2.88), 0.035	1.68 (0.99 to 2.86), 0.055	1.66 (0.94 to 2.91), 0.080
	≥85bpm	1.34 (0.88 to 2.04), 0.17	2.36 (1.50 to 3.71), <0.001	2.40 (1.47 to 3.92), <0.001	2.36 (1.39 to 4.01), 0.016

Combined Endpoints					
Cardiovascular mortality or hospital admission for heart failure, n = 1659	60-64bpm	-	1.18 (0.91 to 1.53), 0.20	1.18 (0.91 to 1.52), 0.22	1.07 (0.82 to 1.40), 0.61
	65-69bpm	1.24 (0.98 to 1.57), 0.070	1.35 (1.06 to 1.73), 0.017	1.33 (1.04 to 1.71), 0.024	1.18 (0.91 to 1.53), 0.22
	70-74bpm	1.24 (1.01 to 1.54), 0.044	1.77 (1.40 to 2.25), <0.001	1.74 (1.36 to 2.24), <0.001	1.46 (1.13 to 1.90), 0.0039
	75-79bpm	1.42 (1.14 to 1.77), 0.0017	2.25 (1.78 to 2.85), <0.001	2.17 (1.70 to 2.77), <0.001	1.78 (1.37 to 2.30), <0.001
	80-84bpm	1.75 (1.40 to 2.19), <0.001	2.24 (1.75 to 2.87), <0.001	2.10 (1.62 to 2.71), <0.001	1.67 (1.27 to 2.20), <0.001
	≥85bpm	2.39 (1.94 to 2.95), <0.001	3.80 (3.04 to 4.75), <0.001	3.40 (2.68 to 4.31), <0.001	2.64 (2.03 to 3.42), <0.001
Cardiovascular mortality or hospital admission for non-fatal myocardial infarction, n = 1143	60-64bpm	-	1.24 (0.93 to 1.64), 0.14	1.24 (0.93 to 1.64), 0.14	1.23 (0.92 to 1.65), 0.16
	65-69bpm	1.03 (0.80 to 1.33), 0.81	1.28 (0.97 to 1.68), 0.079	1.28 (0.97 to 1.69), 0.081	1.27 (0.95 to 1.70), 0.10
	70-74bpm	1.14 (0.91 to 1.43), 0.26	1.69 (1.30 to 2.21), <0.001	1.68 (1.28 to 2.20), <0.001	1.64 (1.23 to 2.20), <0.001
	75-79bpm	1.23 (0.97 to 1.57), 0.090	1.83 (1.40 to 2.40), <0.001	1.79 (1.35 to 2.36), <0.001	1.74 (1.29 to 2.35), <0.001
	80-84bpm	1.59 (1.24 to 2.03), <0.001	1.98 (1.50 to 2.63), <0.001	1.89 (1.41 to 2.53), <0.001	1.81 (1.32 to 2.48), <0.001
	≥85bpm	1.88 (1.49 to 2.37), <0.001	3.03 (2.36 to 3.89), <0.001	2.79 (2.13 to 3.66), <0.001	2.60 (1.94 to 3.50), <0.001
Cardiovascular mortality or hospital admission for heart failure or non-fatal myocardial infarction, n = 1809	60-64bpm	-	1.18 (0.93 to 1.49), 0.18	1.17 (0.93 to 1.49), 0.19	1.08 (0.85 to 1.38), 0.53
	65-69bpm	1.15 (0.93 to 1.43), 0.19	1.26 (1.00 to 1.58), 0.047	1.25 (0.99 to 1.58), 0.056	1.12 (0.88 to 1.43), 0.35
	70-74bpm	1.17 (0.96 to 1.42), 0.12	1.68 (1.35 to 2.10), <0.001	1.67 (1.33 to 2.09), <0.001	1.42 (1.12 to 1.81), 0.0039
	75-79bpm	1.37 (1.12 to 1.67), 0.0025	2.10 (1.69 to 2.62), <0.001	2.04 (1.63 to 2.56), <0.001	1.70 (1.34 to 2.17), <0.001
	80-84bpm	1.65 (1.34 to 2.04), <0.001	2.11 (1.67 to 2.66), <0.001	2.00 (1.57 to 2.55), <0.001	1.63 (1.26 to 2.11), <0.001
	≥85bpm	2.18 (1.80 to 2.65), <0.001	3.54 (2.88 to 4.36), <0.001	3.24 (2.59 to 4.04), <0.001	2.57 (2.01 to 3.28), <0.001

Models were additionally adjusted for: age; sex; smoking; body mass index (BMI); systolic blood pressure (SBP); diastolic blood pressure (DBP); left-ventricular ejection fraction (LVEF); New York Heart Association (NYHA) class; previous myocardial infarction (MI); diabetes; previous stroke; and intake of beta-blockers; angiotensin-converting enzyme (ACE) inhibitors; diuretics; and anti-aldosterone agents at randomisation; and study.

Table A6-20: Results of fitting Cox proportional hazards models. Hazard ratios, 95% confidence intervals, and p-values for a 5bpm higher heart rate in the pooled left-ventricular dysfunction placebo population.

	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Heart Rate Adjusted for Previous
	Hazard Ratio (95% Confidence Interval), p-value			
Individual Endpoints				
All-cause death, n = 1098	1.10 (1.08 to 1.13), <0.001	1.16 (1.14 to 1.19), <0.001	1.16 (1.13 to 1.19), <0.001	1.14 (1.11 to 1.17), <0.001
Cardiovascular death, n = 926	1.11 (1.08 to 1.14), <0.001	1.17 (1.14 to 1.19), <0.001	1.16 (1.13 to 1.19), <0.001	1.14 (1.11 to 1.18), <0.001
Hospital admission for heart failure, n = 1098	1.15 (1.12 to 1.18), <0.001	1.22 (1.20 to 1.25), <0.001	1.21 (1.18 to 1.24), <0.001	1.18 (1.15 to 1.21), <0.001
Hospital admission for non-fatal myocardial infarction, n = 321	1.05 (0.99 to 1.11), 0.085	1.12 (1.08 to 1.17), <0.001	1.14 (1.08 to 1.19), <0.001	1.14 (1.09 to 1.20), <0.001
Combined Endpoints				
Cardiovascular death or hospital admission for heart failure, n = 1659	1.13 (1.11 to 1.16), <0.001	1.19 (1.17 to 1.21), <0.001	1.17 (1.15 to 1.20), <0.001	1.15 (1.12 to 1.18), <0.001
Cardiovascular death or hospital admission for non-fatal myocardial infarction, n = 1143	1.10 (1.07 to 1.13), <0.001	1.15 (1.13 to 1.18), <0.001	1.15 (1.12 to 1.18), <0.001	1.14 (1.11 to 1.17), <0.001
Cardiovascular death or hospital admission for heart failure or non-fatal myocardial infarction, n = 1809	1.13 (1.10 to 1.15), <0.001	1.18 (1.16 to 1.20), <0.001	1.17 (1.15 to 1.19), <0.001	1.15 (1.13 to 1.18), <0.001

Models were additionally adjusted for: age; sex; smoking; body mass index (BMI); systolic blood pressure (SBP); diastolic blood pressure (DBP); left-ventricular ejection fraction (LVEF); New York Heart Association (NYHA) class; previous myocardial infarction (MI); diabetes; previous stroke; and intake of beta-blockers; angiotensin-converting enzyme (ACE) inhibitors; diuretics; and anti-aldosterone agents at randomisation; and study.

Table A6-21: C-statistics and likelihood ratio tests for the model excluding resting heart rate and the model including the heart rate groups variable, which produced the results shown in Table A6-19 in the pooled left-ventricular dysfunction placebo population.

		C-statistic	Likelihood Ratio Test Statistic, p-value
Individual Endpoints			
All-cause death, n = 1098	Model	0.681	
	Model + Baseline	0.692	59.25, <0.001
	Model + Time-Updated	0.706	148.68, <0.001
	Model + Time-Updated + Baseline	0.707	156.41, <0.001
	Model + Time-Updated + Previous	0.711	168.68, <0.001
Cardiovascular death, n = 926	Model	0.692	
	Model + Baseline	0.704	56.84, <0.001
	Model + Time-Updated	0.715	132.61, <0.001
	Model + Time-Updated + Baseline	0.717	140.12, <0.001
	Model + Time-Updated + Previous	0.720	149.25, <0.001
Hospital admission for heart failure, n = 1098	Model	0.739	
	Model + Baseline	0.751	95.29, <0.001
	Model + Time-Updated	0.772	289.16, <0.001
	Model + Time-Updated + Baseline	0.773	294.29, <0.001
	Model + Time-Updated + Previous	0.777	319.00, <0.001
Hospital admission for non-fatal myocardial infarction, n = 321	Model	0.661	
	Model + Baseline	0.666	9.15, 0.10
	Model + Time-Updated	0.673	20.30, 0.0024
	Model + Time-Updated + Baseline	0.675	25.60, 0.0074
	Model + Time-Updated + Previous	0.675	22.71, 0.030
Combined Endpoints			
Cardiovascular death or hospital admission for heart failure, n = 1659	Model	0.708	
	Model + Baseline	0.719	120.23, <0.001
	Model + Time-Updated	0.735	297.63, <0.001
	Model + Time-Updated + Baseline	0.736	309.17, <0.001
	Model + Time-Updated + Previous	0.740	339.52, <0.001
Cardiovascular death or hospital admission for non-fatal myocardial infarction, n = 1143	Model	0.663	
	Model + Baseline	0.674	52.06, <0.001
	Model + Time-Updated	0.687	132.93, <0.001
	Model + Time-Updated + Baseline	0.688	138.54, <0.001
	Model + Time-Updated + Previous	0.690	144.05, <0.001
Cardiovascular death or hospital admission for heart failure or non-fatal myocardial infarction, n = 1809	Model	0.690	
	Model + Baseline	0.702	113.53, <0.001
	Model + Time-Updated	0.719	300.01, <0.001

	Model + Time-Updated + Baseline	0.719	309.07, <0.001
	Model + Time-Updated + Previous	0.723	334.66, <0.001

'Model' is the multivariate model excluding heart rate which included: age; sex; smoking; body mass index (BMI); systolic blood pressure (SBP); diastolic blood pressure (DBP); left-ventricular ejection fraction (LVEF); New York Heart Association (NYHA) class; previous myocardial infarction (MI); diabetes; previous stroke; and intake of beta-blockers; angiotensin-converting enzyme (ACE) inhibitors; diuretics; and anti-aldosterone agents at randomisation; and study.

'Model + Baseline' is the multivariate model described above including the baseline heart rate groups variable.

'Model + Time-Updated' is the multivariate model described above including the time-updated heart rate groups variable.

'Model + Time-Updated + Baseline' is the multivariable model described above including both the baseline and the time-updated heart rate groups variables.

'Model + Time-Updated + Previous' is the multivariate model described above including both the time-updated heart rate groups variable and the previous time-updated heart rate groups variable.

The likelihood ratio test statistics and corresponding p-values were computed by comparing the multivariate models including the different heart rate variables to the multivariate model excluding resting heart rate.

Table A6-22: C-statistics and likelihood ratio tests for the model excluding resting heart rate and the models including the continuous heart rate variables, which produced the results shown in Table A6-20 in the pooled left-ventricular dysfunction placebo population.

		C-statistic	Likelihood Ratio Test Statistic, p-value
Individual Endpoints			
All-cause death, n = 1098	Model	0.681	
	Model + Baseline	0.691	48.11, <0.001
	Model + Time-Updated	0.708	181.90, <0.001
	Model + Time-Updated + Baseline	0.709	182.20, <0.001
	Model + Time-Updated + Previous	0.710	186.65, <0.001
Cardiovascular death, n = 926	Model	0.692	
	Model + Baseline	0.703	46.28, <0.001
	Model + Time-Updated	0.718	159.12, <0.001
	Model + Time-Updated + Baseline	0.718	159.77, <0.001
	Model + Time-Updated + Previous	0.719	163.65, <0.001
Hospital admission for heart failure, n = 1098	Model	0.739	
	Model + Baseline	0.752	97.25, <0.001
	Model + Time-Updated	0.776	319.19, <0.001
	Model + Time-Updated + Baseline	0.776	320.07, <0.001
	Model + Time-Updated + Previous	0.778	335.38, <0.001
Hospital admission for non-fatal myocardial infarction, n = 321	Model	0.661	
	Model + Baseline	0.664	2.86, 0.091
	Model + Time-Updated	0.674	26.62, <0.001
	Model + Time-Updated + Baseline	0.673	27.39, <0.001
	Model + Time-Updated + Previous	0.674	27.91, <0.001
Combined Endpoints			
Cardiovascular death or hospital admission for heart failure, n = 1659	Model	0.708	
	Model + Baseline	0.720	118.40, <0.001
	Model + Time-Updated	0.739	337.77, <0.001
	Model + Time-Updated + Baseline	0.739	341.41, <0.001
	Model + Time-Updated + Previous	0.741	357.48, <0.001
Cardiovascular death or hospital admission for non-fatal myocardial infarction, n = 1143	Model	0.663	
	Model + Baseline	0.674	44.34, <0.001
	Model + Time-Updated	0.689	161.28, <0.001
	Model + Time-Updated + Baseline	0.689	161.65, <0.001
	Model + Time-Updated + Previous	0.690	163.66, <0.001
Cardiovascular death or hospital admission for heart failure or non-fatal myocardial infarction, n = 1809	Model	0.690	
	Model + Baseline	0.703	113.55, <0.001
	Model + Time-Updated	0.722	345.80, <0.001

	Model + Time-Updated + Baseline	0.722	348.28, <0.001
	Model + Time-Updated + Previous	0.724	360.11, <0.001

'Model' is the multivariate model excluding heart rate which included: age; sex; smoking; body mass index (BMI); systolic blood pressure (SBP); diastolic blood pressure (DBP); left-ventricular ejection fraction (LVEF); New York Heart Association (NYHA) class; previous myocardial infarction (MI); diabetes; previous stroke; and intake of beta-blockers; angiotensin-converting enzyme (ACE) inhibitors; diuretics; and anti-aldosterone agents at randomisation; and study.

'Model + Baseline' is the multivariate model described above including the continuous baseline heart rate variable.

'Model + Time-Updated' is the multivariate model described above including the continuous time-updated heart rate variable.

'Model + Time-Updated + Baseline' is the multivariable model described above including both the continuous baseline and time-updated heart rate variables.

'Model + Time-Updated + Previous' is the multivariate model described above including both the continuous time-updated heart rate variable and the previous time-updated heart rate variable.

The likelihood ratio test statistics and corresponding p-values were computed by comparing the multivariate models including the different heart rate variables to the multivariate model excluding resting heart rate.

Table A6-23: P-values for the Grambsch and Therneau 1994 test for non-proportionality of hazards for each of the five or six heart rate groups greater than or equal to 65bpm, or 60bpm, relative to a heart rate <65bpm, or <60bpm, for the baseline and time-updated models, respectively, in the pooled left-ventricular dysfunction placebo population.

	Heart Rate Group	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate adjusted for Baseline	Time-Updated Heart Rate adjusted for Previous
		P-value			
Individual Endpoints					
All-cause death, n = 1098	60-64bpm	-	0.99	0.96	0.95
	65-69bpm	0.29	0.32	0.30	0.34
	70-74bpm	0.94	0.80	0.77	0.69
	75-79bpm	0.60	0.62	0.70	0.81
	80-84bpm	0.24	0.87	0.99	0.92
	≥85bpm	0.52	0.71	0.61	0.44
Cardiovascular mortality, n = 926	60-64bpm	-	0.55	0.54	0.51
	65-69bpm	0.72	0.29	0.27	0.31
	70-74bpm	0.81	0.66	0.63	0.56
	75-79bpm	0.48	0.83	0.94	0.995
	80-84bpm	0.39	0.96	0.86	0.86
	≥85bpm	0.44	0.79	0.59	0.55
Hospital admission for heart failure, n = 1098	60-64bpm	-	0.71	0.64	0.60
	65-69bpm	0.24	0.46	0.63	0.67
	70-74bpm	0.076	0.79	0.93	0.86
	75-79bpm	0.030	0.98	0.58	0.57
	80-84bpm	0.0077	0.70	0.82	0.85
	≥85bpm	<0.001	0.29	0.85	0.82
Hospital admission for non-fatal myocardial infarction, n = 312	60-64bpm	-	0.95	1.00	0.97
	65-69bpm	0.89	0.90	0.80	0.74
	70-74bpm	0.75	0.89	0.71	0.57
	75-79bpm	0.35	0.79	0.53	0.47
	80-84bpm	0.26	0.85	0.57	0.53
	≥85bpm	0.97	0.45	0.28	0.35
Combined Endpoints					
Cardiovascular mortality or hospital admission for heart failure, n = 1659	60-64bpm	-	0.86	0.80	0.78

	65-69bpm	0.29	0.70	0.88	0.84
	70-74bpm	0.29	0.69	0.93	0.995
	75-79bpm	0.046	0.73	0.89	0.87
	80-84bpm	0.031	0.33	0.76	0.71
	≥85bpm	<0.001	0.11	0.61	0.51
Cardiovascular mortality or hospital admission for non-fatal myocardial infarction, n = 1143	60-64bpm	-	0.50	0.50	0.47
	65-69bpm	0.77	0.20	0.20	0.19
	70-74bpm	0.71	0.46	0.43	0.31
	75-79bpm	0.56	0.78	0.64	0.54
	80-84bpm	0.44	0.66	0.47	0.42
	≥85bpm	0.53	0.44	0.26	0.23
Cardiovascular mortality or hospital admission for heart failure or non-fatal myocardial infarction, n = 1809	60-64bpm	-	0.93	0.89	0.89
	65-69bpm	0.079	0.80	0.93	0.93
	70-74bpm	0.053	0.99	0.79	0.68
	75-79bpm	0.012	0.88	0.88	0.73
	80-84bpm	0.0056	0.38	0.91	0.77
	≥85bpm	<0.001	0.19	0.52	0.68

Table A6-24: P-values for the Grambsch and Therneau 1994 test for non-proportionality of hazards for a 5bpm higher heart rate in the pooled left-ventricular dysfunction placebo population.

	Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Heart Rate Adjusted for Previous
	P-value			
Individual Endpoints				
All-cause death, n = 1098	0.32	0.58	0.65	0.85
Cardiovascular death, n = 926	0.089	0.20	0.41	0.32
Hospital admission for heart failure, n = 1098	<0.001	0.025	0.21	0.32
Hospital admission for non-fatal myocardial infarction, n = 321	0.85	0.27	0.31	0.28
Combined Endpoints				
Cardiovascular death or hospital admission for heart failure, n = 1659	<0.001	0.0012	0.067	0.075
Cardiovascular death or hospital admission for non-fatal myocardial infarction, n = 1143	0.13	0.67	0.96	0.97
Cardiovascular death or hospital admission for heart failure or non-fatal myocardial infarction, n = 1809	<0.001	0.0068	0.23	0.25

Table A6-25: Likelihood ratio test results comparing the models containing the interaction, heart rate group x study, and the models containing only heart rate and study additively in the pooled left-ventricular dysfunction placebo population.

		Baseline Heart Rate	Time-Updated Heart Rate	Time-Updated Heart Rate Adjusted for Baseline	Time-Updated Heart Rate Adjusted for Previous
	Model	**P-values for Interaction**			
Individual Endpoints					
All-cause death, n = 1098	Categorical Heart Rate Groups	0.27	0.092	0.10	0.094
	Continuous Heart Rate	0.11	0.26	0.25	0.26
Cardiovascular death, n = 926	Categorical Heart Rate Groups	0.36	0.20	0.21	0.20
	Continuous Heart Rate	0.24	0.35	0.32	0.35
Hospital admission for heart failure, n = 1098	Categorical Heart Rate Groups	0.60	0.89	0.88	0.90
	Continuous Heart Rate	0.39	0.70	0.73	0.60
Hospital admission for non-fatal myocardial infarction, n = 321	Categorical Heart Rate Groups	0.99	0.11	0.13	0.12
	Continuous Heart Rate	0.49	0.58	0.56	0.60
Combined Endpoints					
Cardiovascular death or hospital admission for heart failure, n = 1659	Categorical Heart Rate Groups	0.48	0.61	0.65	0.56
	Continuous Heart Rate	0.63	0.29	0.26	0.35
Cardiovascular death or hospital admission for non-fatal myocardial infarction, n = 1143	Categorical Heart Rate Groups	0.21	0.12	0.11	0.12
	Continuous Heart Rate	0.12	0.10	0.094	0.10
Cardiovascular death or hospital admission for heart failure or non-fatal myocardial infarction, n = 1,809	Categorical Heart Rate Groups	0.38	0.38	0.42	0.35
	Continuous Heart Rate	0.29	0.14	0.12	0.17

Models were additionally adjusted for: age; sex; smoking; body mass index (BMI); systolic blood pressure (SBP); diastolic blood pressure (DBP); left-ventricular ejection fraction (LVEF); New York Heart Association (NYHA) class; previous myocardial infarction (MI); diabetes; previous stroke; and intake of beta-blockers; angiotensin-converting enzyme (ACE) inhibitors; diuretics; and anti-aldosterone agents at randomisation; and study.

Appendix 7

Supplementary Tables for Chapter 9

Table A7-1: PRISMA 2009 checklist[94] for the meta-analyses of the predictive value of resting heart rate measured at a single point in time, and time-updated resting heart rate measurements, for all-cause and cardiovascular mortality.

Section/Topic	Item No.	Checklist Item	Reported On Page No.
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	228
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	N/A as thesis chapter as opposed to journal article
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	228
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes and study design (PICOS).	228
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as Web address), and, if available, provide registration information including registration number.	No review protocol, noted as limitation in discussion
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria of eligibility, giving rationale.	229 and 240
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	229 and 240 See 22-3 for details of the initial search
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	N/A See 22-3 and Table A1-2 provided in Appendix 1 for details of the initial electronic search strategy
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	229 and 240

Data collection process	10	Describe the method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	229 and 240-1
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made.	229 and 240-1
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at study or outcome level), and how this information is to be used in any data synthesis	85
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	229 and 240
Synthesis of results	14	Describe the method of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistics) for each meta-analysis.	85-7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selecting reporting within studies).	87
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	232-3
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	229-231 and 241-2, Figure 9-1 and Figure 9-7
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations.	Tables A7-2 to A7-5
Risk of bias within studies	19	Present data on risk bias of each study and, if available, any outcome-level assessment (see item 12).	230 and 241, Tables A7-2 and A7-4
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables A7-2 to A7-5, Figures 9-2, 9-4, 9-8 and 9-9
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of inconsistency.	231-3, 242 and 244, Figures 9-2, 9-4, 9-8 and 9-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	238-240 and 244
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16).	232-3, Figures 9-3 and 9-5
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, uses, and policy makers).	246-250
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias).	250-1
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	251
Funding			

Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	PhD funded by Servier; meta-analyses not specifically funded

Table A7-2: An overview of studies which investigated baseline heart rate as a risk marker and satisfied the inclusion criteria to be included in the meta-analysis, along with the hazard ratios and 95% confidence intervals for a 5bpm higher baseline heart rate for all-cause and/or cardiovascular death.

Study	Population	Number of Subjects included in Study	Follow-Up	Study Quality Based on the Newcastle-Ottawa Scale[96]	Type of Heart Rate	Model and Associated Adjusters	Hazard Ratio (95% Confidence Interval), and the Corresponding Number of First Events that Occurred	
							All-Cause Death	CV Death
Legeai et al. 2011[206]	General	7147	6 years	7	Baseline resting heart rate measured using a validated digital electronic tensiometer	Model 2: age; sex; study centre; SBP; smoking status; wine consumption; regular fish consumption; BMI; total and HDL cholesterol; diabetes status; previous CV disease; living alone; disability status; and beta-blocker and calcium antagonist use	1.10 (1.05 to 1.14) n = 615	1.09 (1.00 to 1.20) n = 110
Jensen et al. 2012[128]	General	6518	14 years	8	Baseline resting heart rate measured by ECG	Model adjusting for conventional CV risk factors, figrinogen and high-sensitive C-reactive protein: blood pressure; BMI; smoking; drinking habits; log(FEV_1), log(triglycerides); physical activity; log(high-senstivie C-reactive protein); and fibrinogen	1.04 (1.02 to 1.07) n = 1923	1.07 (1.03 to 1.10) n = 634
Johansen et al. 2013[132]	General	653	6.3 years	7	Baseline resting heart rate	Model 5: SBP; age; sex; smoking; diabetes; total cholesterol; high-sensitive C-reactive protein; NT-proBNP; use of beta-blockers; ACE-inhibitors/ARBs; diuretics; and calcium channel blockers	1.11 (1.01 to 1.22) n = 80	-
Wang et al. 2014[134]	General	92562	4 years	7	Baseline resting heart rate measured by ECG	Model 3: age; sex; average monthly income of each family member; education level; marital status; BMI; waist circumference; smoking status; drinking status; physical activity; high-sensitive C-reactive protein; hypertension; diabetes; and dyslipidaemia	1.09 (1.06 to 1.11) n = 1589	-
Ho et al. 2014[204]	General	4058	19 years	8	Baseline resting heart rate measured by ECG	Multivariable model: age; sex; SBP; use of antihypertensive treatment; BMI; diabetes; smoking status; physical activity index; valvular heart disease; ECG LV hypertrophy; total/HDL cholesterol ratio; minor CV disease; and PR and QRS duration	1.07 (1.05 to 1.10) n = 1186	1.08 (1.02 to 1.14) n = 252

Hillis et al. 2012[141]	Type 2 Diabetes	11138	4.4 years	7	Baseline resting heart rate measured using a digital monitor	Multiple covariate adjusted model: age; sex; ADVANCE Study BP treatment arm; ADVANCE Study glycaemic control arm; BMI; duration of diabetes; HbA_{1c}; urinary albumin/creatinine ratio; eGFR; SBP; DBP; history of hospitalisation for HF; participation in moderate and/or vigorous exercise for >15 min at least once weekly; total cholesterol; triacylglycerol level; AF; treatment with calcium channel blockers and treatment with beta-blockers	1.07 (1.04 to 1.10) n = 879	1.08 (1.03 to 1.12) n = 468
Palatini et al. 2002[147]	Hypertensive	4682	2 years	7	Baseline resting heart rate, referred to as clinical heart rate in the paper	Sex; age; CV complications at entry; diabetes at entry; smoking and drinking habits; SBP; and haemoglobin levels	1.18 (1.08 to 1.30) n = 145	1.11 (0.97 to 1.26) n = 80
Julius et al. 2012[212]	Hypertensive	15193	5 years	7	Baseline resting heart rate measured by ECG	Model 3: SBP; age; gender; race; BMI; total cholesterol; smoking; diabetes mellitus; history of CHD; history of cerebrovascular disease; history of PAD; LV hypertrophy; use of beta-blockers, calcium antagonists or other antihypertensive drugs	1.09 (1.07 to 1.11) n = 1612	-
Ortiz et al. 2010[151]	CHD	1264	2.1 years	8	Baseline resting heart rate measured by ECG	Final multivariable model also adjusted for LVEF: age; DBP; AF; treatment with beta-blockers, diuretics or digoxin; LVEF	1.05 (0.86 to 1.22) n = 33	-
Parodi et al. 2010[159]	Post-MI/ACS	2477	0.5 years	7	Presenting/baseline heart rate assessed by a calliper in the patient diagnostic ECG	Age; peak creatinine-kinase value; cardiogenic shock; suboptimal PCI result; previous infarction	1.32 (1.23 to 1.42) n = 174	-
Timoteo et al. 2011[161]	Post-MI/ACS	1126	1 year	7	Admission heart rate	Age; previous PCI; smoking; diabetes; SBP; ACE inhibitors; beta-blocker; statins; LVEF <35%; STEMI; PCI; and natural log(CK)	1.05 (1.02 to 1.12) n = 120	-
Antoni et al. 2012[169]	Post-MI/ACS	1429	1 year and 4 years	8	Discharge heart rate measured by ECG	Age; Killip class ≥2; the left anterior descending coronary artery as culprit vessel; and LVEF	1-Year 1.35 (1.22 to 1.50) n = 44 4- Years 1.26 (1.16 to 1.36) n = 83	1-Year 1.29 (1.13 to 1.46) n = 32 4-Years 1.24 (1.12 to 1.37) n = 52
Noman et al. 2013[164]	Post-MI/ACS	2310	1.6 years	8	Admission heart rate measured by ECG	Age; sex; haemoglobin; creatinine; diabetes; previous MI; anterior MI; SBP; multivessel disease; onset to balloon; TIMI 3-flow post-primary PCI	1.08 (1.04 to 1.12) n = 236	-

Jensen et al. 2013[170]	Post-MI/ACS	2029	2 years	7	Discharge heart rate measured by ECG	Age; sex; HF at admission; indication for PCI; and use of ACE-inhibitors/ARBs at discharge	1.22 (1.10-1.36) n missing	-
Seronde et al. 2013[171]	Post-MI/ACS	3079	1 year and 5 years	8	Discharge heart rate	Type of infarction (STEMI or NSTEMI); age; sex; previous infarction; previous stroke; previous HF; history of cancer or chronic pulmonary disease; eGFR; SBP; Killip Class; haemoglobin level; LV dysfunction; treatments; use of coronary angiography; revascularisation; and the TIMI risk score	1-Year 1.06 (1.01 to 1.11) n = 242	-
							5-Years 1.04 (1.01 to 1.08) n = 643	-
Vazir et al. 2014[215]	HF	7599	3.17 years	7	Baseline resting heart rate recorded by palpation, or from auscultation of the heart, or from ECG	Age; sex; randomisation to candesartan; ejection fraction; previous hospitalisation for HF; history of diabetes; BMI; DBP; NYHA class; beta-blocker dose and digoxin use; cardiomegaly on chest X-ray; AF	1.03 (1.01 to 1.05) n = 1831	1.03 (1.01 to 1.05) n = 1460
Fox et al. 2008[184] (equivalent to BEAUTIFUL in Table A7-2)	LV Dysfunction and CHD	5438	1.58 years	7	Baseline resting heart rate measured by ECG	Age, smoking, body mass index, history of diabetes, previous MI, previous PCI or CABG, PAD, SBP, DBP, LVEF, NYHA class, and treatment with aspirin, beta-blocker, statin, diuretics (excluding anti-aldosterone), organic nitrates, and anti-aldosterone agents at randomisation	-	1.08 (1.03 to 1.12) n = 435
Fosbol et al. 2010[183] (DIAMOND-HF)	LV Dysfunction and HF	1518	10 years	7	Baseline resting heart rate measured by ECG	Age; sex; history of CHD; smoke status; QRS duration; PR-interval; history of diabetes; renal function (creatinine clearance); AF; Wall Motion Index; NYHA class; haemoglobin levels; and presence of clinical HF	1.04 (1.02 to 1.07) n = 1336	-
Fosbol et al. 2010[183] (DIAMOND-MI)	LV Dysfunction and Post-MI/ACS	1510	10 years	7	Baseline resting heart rate	Age; sex; history of CHD; smoke status; QRS duration; PR-interval; history of diabetes; renal function (creatinine clearance); AF; Wall Motion Index; NYHA class; haemoglobin levels; and presence of clinical HF	1.08 (1.05 to 1.11) n = 2412	-
Bemelmans et al. 2013[188]	Vascular Disease	4272	4.4 years	8	Baseline resting heart rate measured by ECG	Age; gender; beta-blockers; calcium channel blockers; alpha-blockers; diuretics; current smoking; inclusion diagnosis (CHD, AAA, PAD or CV disease); BMI; eGFR; type 2 diabetes; SBP	1.07 (1.04 to 1.10) n = 513	-
Nanchen et al. 2013[138] (equivalent to PROSPER in Table A7-2)	Vascular Disease	4084	3.2 years	7	Baseline resting heart rate measured by ECG	Multivariate basic model: age; smoking status; baseline diabetes; history of vascular disease; history of angina; hypertension; BMI; HDL-cholesterol; TSH; and eGFR	-	1.11 (1.05 to 1.16) n = 200

Lonn et al. 2014[216]	Vascular Disease	31531	4.7 years	7	Baseline resting heart rate measured using an automated validated device	Model 3: age; sex; diabetes; hypertension; dyslipidaemia; current smoking; creatinine; use of beta-blocker; use of diltiazem/verapamil; and stratified by treatment allocation in the trial	1.07 (1.05 to 1.08) n = 3779	1.08 (1.06 to 1.09) n = 2269
Fox et al. 2013[191] (equivalent to PERFORM in Table A7-2)	Post-Stroke	18980	2.4 years	7	Baseline resting heart rate measured by palpitation, auscultation, or 12-lead ECG	Country; age; gender; smoking; BMI; previous ischemic stroke; previous MI; previous TIA; hypertension; diabetes; and beta-blockers; statins; and antiplatelet agents after qualifying event	1.08 (1.05 to 1.11) n = 1174	1.11 (1.07 to 1.15) n = 683

Note that the result for: Noman et al. 2013[164] is the long-term result, not the in-hospital result; Seronde et al. 2013[171] does not include the result that excluded patients who had died in the first year of follow-up; Bemelmans et al. 2013[188] is the result for all of the patients. Follow-up duration for each study is median or mean follow-up depending on what was stated in the publication; if follow-up was given in months or days it was converted to the approximate time in years.

AAA = Abdominal Aortic Aneurysm; ACE = Angiotensin-Converting Enzyme; ACS = Acute Coronary Syndrome; AF = Atrial Fibrillation; ARB = Angiotensin II Receptor Blocker; BMI = Body Mass Index; CABG = Coronary Artery Bypass Graft; CHD = Coronary Heart Disease; CK = Creatin Kinase; CV = Cardiovascular; DBP = Diastolic Blood Pressure; ECG = Electrocardiography; eGFR = estimated Glomerular Filtration Rate; FEV = Forced Expiratory Volume; HDL = High-Density Lipoprotein; HF = Heart Failure; HbA = Glycated Haemoglobin; LV = Left-Ventricular; LVEF= Left-Ventricular Ejection Fraction; MI = Myocardial Infarction; NSTEM = Non-ST-Segment Elevation MI; NYHA = New York Heart Association; PAD = Peripheral Artery Disease; PCI = Percutaneous Coronary Intervention; SBP = Systolic Blood Pressure; STEMI = ST-Segment Elevation MI; TIA = Transient Ischemic Attack; TIMI = Thrombolysis in Myocardial Infarction; TSH = Thyroid-Stimulating Hormone.

Table A7-3: An overview of studies conducted in this thesis which investigated baseline heart rate as a risk marker and satisfied the inclusion criteria to be included in the meta-analysis, along with the hazard ratios and 95% confidence intervals for a 5bpm higher baseline heart rate for all-cause and/or cardiovascular death.

Study	Population	Number of Subjects included in Study	Follow-Up	Type of Heart Rate	Adjusters	Hazard Ratio (95% Confidence Interval), and the Corresponding Number of First Events that Occurred	
						All-Cause Death	CV Death
EUROPA	CHD	12208	4.2 years	Baseline resting heart rate (measured at Study Visit 3)	Age; sex; history of PCI; history of CABG; peripheral vascular disease; diabetes mellitus; hypercholesterolemia; treatment with platelet inhibitors; lipid-lowering therapies; beta-blockers; calcium channel blockers; and diuretics (potassium-sparing and other); and SBP and DBP	1.09 (1.05 to 1.13) n = 795	1.06 (1.02 to 1.11) n = 464
CAPRICORN	Post-MI with LVSD	981 (Placebo Population Only)	1.3 years	Baseline resting heart rate	Sex, previous diabetes, LVEF, site of MI, and treatment for MI with intravenous diuretics	1.05 (0.98 to 1.12) n = 150	1.05 (0.98 to 1.12) n = 138
EPHESUS	Post-MI with HF or LVSD	6606	1.33 years	Baseline resting heart rate	Age; sex; race; BMI; smoking history; diabetes; hypertension; angina; prior MI; AF; dyslipidaemia; HF; COPD; DBP; Killip class; and intake of certain drugs at randomisation which were aspirin, statins, vitamin K antagonists, diuretics and digitalis cardiac glycosides	1.08 (1.05 to 1.11) n = 1028	1.08 (1.05 to 1.11) n = 887
OPTIMAAL	Post-MI with HF or LVSD	5461	2.7 years	Baseline resting heart rate	Age; sex; race; BMI; smoking history; diabetes; hypertension; angina; prior MI; AF; dyslipidaemia; HF; COPD; DBP; Killip class; and intake of certain drugs at randomisation which were aspirin, statins, vitamin K antagonists, diuretics and digitalis cardiac glycosides	1.09 (1.07 to 1.11) n = 944	1.10 (1.07 to 1.12) n = 781
VALIANT	Post-MI with HF or LVSD	14669	2.06 years	Baseline resting heart rate	Age; sex; race; BMI; smoking history; diabetes; hypertension; angina; prior MI; AF; dyslipidaemia; HF; COPD; DBP; Killip class; and intake of certain drugs at randomisation which were aspirin, statins, vitamin K antagonists, diuretics and digitalis cardiac glycosides	1.07 (1.05 to 1.08) n = 2870	1.07 (1.06 to 1.09) n = 2477
BEAUTIFUL (equivalent to Fox et al. 2008[184] in Table A7-1)	LV Dysfunction and CHD	5438	1.58 years	Baseline resting heart rate measured by ECG	Age, smoking, BMI, history of diabetes, previous MI, previous PCI or CABG, PAD, SBP, DBP, LVEF, NYHA class, and treatment with aspirin (not including other antithrombotic agents as it was not available in the dataset used for the current analysis), beta-blocker, statin, diuretics (excluding anti-aldosterone), organic nitrates, and anti-aldosterone agents at randomisation	1.07 (1.03 to 1.11) n = 547	1.08 (1.03 to 1.13) n = 435
SHIFT	LV Dysfunction and HF	3261	1.91 years	Baseline resting heart rate measured by ECG	Beta-blocker intake; NYHA class; LVEF; whether the primary cause of HF was ischemic or not; age; SBP; and estimated glomerular filtration rate	1.13 (1.09 to 1.18) n = 551	1.14 (1.09 to 1.18) n = 491

PROSPER (equivalent to Nanchen et al. 2013[138] in Table A7-1)	Vascular Disease	5680	3.2 years	Baseline resting heart rate measured by ECG	Age; smoking status; diabetes; history of vascular disease; hypertension; BMI; HDL-cholesterol; thyroid stimulating hormones; estimated glomerular filtration rate eGFR; treatment group (pravastatin or placebo); and intake of aspirin, nitrates, diuretics, ACE inhibitors and ARBs	1.08 (1.05 to 1.12) n = 590	1.07 (1.02 to 1.13) n = 287
PERFORM (equivalent to Fox et al. 2013[191] in Table A7-1)	Post-Stroke	18993	2.4 years	Baseline resting heart rate measured by palpitation, auscultation, or 12-lead ECG, according to the investigator's decision	Age, gender, smoking, BMI, prior ischemic stroke, prior MI, prior TIA, hypertension, diabetes and the intake of beta-blockers, statins, and antiplatelet agents after the qualifying event	1.08 (1.05 to 1.11) n = 1174	1.12 (1.08 to 1.17) n = 436

Note that the CAPRICORN results are taken from the time-updated CAPRICORN analysis (Chapter 4 Section 4.2) that included only the placebo patients.

ACE = Angiotensin-Converting Enzyme; ARB = Angiotensin II Receptor Blocker; BMI = Body Mass Index; CABG = Coronary Artery Bypass Graft; CHD = Coronary Heart Disease; COPD = Chronic Obstructive Pulmonary Disease; DBP = Diastolic Blood Pressure; HF = Heart Failure; LV = Left-Ventricular; LVEF = Left-Ventricular Ejection Fraction; MI = Myocardial Infarction; NYHA = New York Heart Association; PCI = Percutaneous Coronary Intervention; TIA = Transient Ischemic Attack.

Table A7-4: An overview of studies which investigated time-updated heart rate as a risk marker and satisfied the inclusion criteria to be included in the meta-analysis, along with the hazard ratios and 95% confidence intervals for a 5bpm higher time-updated heart rate for all-cause and/or cardiovascular death.

Study	Population	Number of Subjects included in Study	Follow-Up	Study Quality Based on the Newcastle-Ottawa Scale[96]	Type of Heart Rate	Model and Associated Adjusters	Hazard Ratio (95% Confidence Interval), and the Corresponding Number of First Events that Occurred	
							All-Cause Death	CV Death
Ho et al. 2014[204]	General	4058	19 years	8	Time-updated resting heart rate measured at baseline and updated over 8 years post-baseline, measured using an ECG	Multivariable-adjusted model for heart rate as a time-dependent variable: age; sex; SBP; use of antihypertensive treatment; BMI; diabetes; smoking status; physical activity index; valvular heart disease; ECG LV hypertrophy; total/HDL cholesterol ratio; minor CV disease; and PR and QRS duration	1.08 (1.05 to 1.11) n = 1186	1.08 (1.02 to 1.13) n = 252
O'Hartaigh et al. 2015[207]	General	5691	7.9 years	8	Time-updated resting heart rate measured at baseline and at 6 annual assessments post-baseline	Multivariable model: age; sex; smoke; exercise intensity; education level; BMI; type 2 diabetes mellitus; C-reactive protein; interleukin-6; CHD; congestive HF; race; hypertension; HDL and LDL cholesterol; AF; ACE-inhibitors; aspirin; beta-blocker; and calcium channel blocker therapy	1.15 (1.12 to 1.18) n = 974	-
Okin et al. 2010[210]	Hypertensive	9190	4.8 years	7	Time-updated heart rate measured at baseline and throughout follow-up, using an ECG	Multivariable model: baseline heart rate; treatment with losartan vs. atenolol; age; gender; race; prevalent diabetes; history of CHD; AF; congestive HF; stroke; peripheral vascular disease; smoking; albumin/creatinine ratio; total and HDL cholesterol; serum creatinine; BMI; incident MI; baseline and time-updated systolic and diastolic blood pressure; QRS duration; Sokolow-Lyon voltage; and Cornell voltage-duration product	1.12 (1.08 to 1.15) n = 814	1.08 (1.03 to 1.13) n = 438
Vazir et al. 2014[215]	HF	7599	3.17 years	7	Time-updated heart rate measured at baseline and throughout follow-up, recorded by palpation, or from auscultation of the heart, or from ECG	Age; sex; randomisation to candesartan; ejection fraction; previous hospitalisation for HF; history of diabetes at baseline; BMI; DBP; NYHA functional class; beta-blocker dose; and digoxin use at any time during the study; cardiomegaly on chest X-ray; AF at baseline; and baseline heart rate	1.09 (1.07 to 1.11) n = 1831	1.08 (1.06 to 1.10) n = 1460

ACE = Angiotensin Converting Enzyme; AF = Atrial Fibrillation; BMI = Body Mass Index; CHD = Coronary Heart Disease; CV = Cardiovascular; DBP = Diastolic Blood Pressure; ECG = Electrocardiographic/Electrocardiography; HDL = High Density Lipoprotein; HF = Heart Failure; LDL = Low Density Lipoprotein; LV = Left-Ventricular; MI = Myocardial Infarction; NYHA = New York Heart Association.

Table A7-5: An overview of studies conducted in this thesis which investigated time-updated heart rate as a risk marker and satisfied the inclusion criteria to be included in the meta-analysis, along with the hazard ratios and 95% confidence intervals for a 5bpm higher time-updated heart rate for all-cause and/or cardiovascular death.

Study	Population	Number of Subjects included in the Study	Follow-Up	Type of Heart Rate	Adjusters	Hazard Ratio (95% Confidence Interval), and the Corresponding Number of First Events that Occurred	
						All-Cause Death	CV Death
EUROPA	Stable CHD	12208	4.2 years	Baseline (measured at Study Visit 3) and time-updated resting heart rate measured at 3, 6 and 12 months after randomisation, and at 6-montly intervals thereafter	Age; sex; history of PCI; history of CABG; peripheral vascular disease; diabetes mellitus; hypercholesterolemia; treatment with platelet inhibitors; lipid-lowering therapies; beta-blockers; calcium channel blockers; and diuretics (potassium-sparing and other); and SBP and DBP	1.17 (1.13 to 1.20) n = 795	1.11 (1.07 to 1.16) n = 464
					Additionally adjusted for baseline heart rate	1.16 (1.13 to 1.20) n = 795	1.10 (1.06 to 1.15) n = 464
BEAUTIFUL	CHD with LV Dysfunction	5438	1.58 years	Baseline and time-updated resting heart rate measured at 2 weeks, 1, 3 and 6 months after randomisation, and every 6 months thereafter	Age, smoking, BMI, history of diabetes, previous MI, previous PCI or CABG, PAD, SBP, DBP, LVEF, NYHA class, and treatment with aspirin (not including other antithrombotic agents as it was not available in the dataset used for the current analysis), beta-blocker, statin, diuretics (excluding anti-aldosterone), organic nitrates, and anti-aldosterone agents at randomisation	1.14 (1.10 to 1.17) n = 547	1.14 (1.10 to 1.18) n = 435
					Additionally adjusted for baseline heart rate	1.14 (1.10 to 1.19) n = 547	1.14 (1.09 to 1.19) n = 435
CAPRICORN	Post-Acute MI with LV Dysfunction	981	1.3 yeras	Baseline and time-updated resting heart rate measured at 3-month intervals during the first year of follow-up, and at 4-month intervals thereafter	Sex, previous diabetes, LVEF, site of MI, and treatment for MI with intravenous diuretics	1.12 (1.06 to 1.18) n = 150	1.10 (1.04 to 1.07) n = 138
					Additionally adjusted for baseline heart rate	1.12 (1.06 to 1.18) n = 150	1.10 (1.03 to 1.17) n = 138
SHIFT	HF with LV Dysfunction	3261	1.91 years	Baseline and time-updated resting heart rate measured at 28 days post-baseline, and every four months thereafter	Beta-blocker intake; NYHA class; LVEF; whether the primary cause of heart failure was ischemic or not; age; SBP; and estimated glomerular filtration rate	1.17 (1.14 to 1.21) n = 551	1.18 (1.14 to 1.21) n = 491

					Additionally adjusted for baseline heart rate	1.16 (1.13 to 1.20) n = 551	1.16 (1.13 to 1.20) n = 491
PROSPER	Vascular Disease	5680	3.2 years	Baseline and time-updated resting heart rate measured annually	Age; smoking status; diabetes; history of vascular disease; hypertension; BMI; HDL-cholesterol; thyroid stimulating hormones; estimated glomerular filtration rate; treatment group (pravastatin or placebo); and intake of aspirin, nitrates, diuretics, ACE inhibitors and ARBs	1.12 (1.09 to 1.15) n = 590	1.11 (1.06 to 1.16) n = 287
					Additionally adjusted for baseline heart rate	1.12 (1.08 to 1.17) n = 590	1.11 (1.05 to 1.18) n = 287
PERFORM	Post-Stroke	18993	2.4 years	Baseline and time-updated resting heart rate measured at 1, 3 and 6 months after randomisation, and at 6-monthly intervals thereafter	Age, gender, smoking, BMI, prior ischemic stroke, prior MI, prior TIA, hypertension, diabetes and the intake of beta-blockers, statins, and antiplatelet agents after the qualifying event	1.16 (1.13 to 1.19) n = 1174	1.16 (1.11 to 1.21) n = 436
					Additionally adjusted for baseline heart rate	1.15 (1.11 to 1.18) n = 1174	1.13 (1.08 to 1.16) n = 436

ACE = Angiotensin Converting Enzyme; ARB = Angiotensin II Receptor Blocker; BMI = Body Mass Index; CABG = Coronary Artery Bypass Graft; CHD = Coronary Heart Disease; DBP = Diastolic Blood Pressure; HDL = High Density Lipoprotein; HF = Heart Failure; LV = Left-Ventricular; MI = Myocardial Infarction; NYHA = New York Heart Association; PAD = Peripheral Artery Disease; PCI = Percutaneous Coronary Intervention; SBP = Systolic Blodd Pressure; TIA = Transient Ischemic Attack.

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