Use of evidence based pharmacotherapy for cardiovascular disease in Scotland

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Author’s declaration

I declare that this thesis is my own work and has not been submitted for any other degree at the University of Glasgow or any other universities.

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Summary

Background

Cardiovascular disease (CVD) is one of the major causes of morbidity and mortality worldwide. Clinical guidelines, based on the results of randomised controlled trials, state that effective secondary prevention therapies should be prescribed following a diagnosis of particular CVD unless there are contraindications. Although evidence shows that use of evidence based pharmacotherapies after diagnosis of CVD reduces mortality and disease progression, many inequalities exist in prescribing practice. Many studies have documented that women and the elderly are less likely to receive evidence based therapies than men and the young, respectively. Greater socioeconomic deprivation has also been shown to be associated with lower rates of prescribing of therapies. However, prior studies have all focussed on one particular CVD or failed to adjust for confounders. Also, few studies have examined trends in the prescribing of evidence based pharmacotherapies over time and documented whether prescribing inequalities are static, narrowing or widening. This project aims to describe the pharmacotherapy received by patients with CVD in Scotland, and to describe the factors associated with prescribing of evidence based pharmacotherapy.

Methods

In this retrospective cohort study I examined a linked database of primary care records (Continuous Morbidity Records) and secondary care records (Scottish Morbidity Records) covering 238064 individuals in Scotland (approximately 6% of the total population) from 1997 to 2005. Patients with a first diagnosis (defined as a first hospitalisation or first recording of the diagnosis in primary or secondary care) of myocardial infarction (MI), angina, and peripheral arterial disease (PAD) were identified. Patients who died within the first 30 days of diagnosis/first hospitalisation were excluded from further analysis. Data on prescribing of evidence based therapies (angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARBs), β-blockers, statins and antiplatelet agents [aspirin or clopidogrel]) within 30 days of diagnosis was obtained from primary care database records. Multivariable logistic regression was conducted to examine the association between prescribing of evidence based pharmacotherapies and age, sex, socioeconomic status, comorbidities and year of diagnosis.

Results

Between 1997 and 2005, 4305 (83.4%) patients with a first diagnosis of MI, 7210 (98.6%) with angina, and 3385 (95.8%) with PAD had survived to 30 days after their first diagnosis.

Increasing age was associated with lower odds of being prescribed evidence based therapies. This association persisted after adjustment for sex, socioeconomic status, year of diagnosis, and comorbidities. In general, older patients ≥ 85 were significantly less commonly prescribed evidence based therapy (EBTs), however they were significantly prescribed nitrates (OR 1.29; 95% CI 1.05-1.59, P< 0.01) for angina.

Generally men were more likely to be prescribed evidence based therapies than women. After adjustment, prescribing of evidence based therapies was significantly higher in men with a MI for β-blockers (OR 1.18; 95% CI1.04-1.33, P< 0.01), ACEI/ARBs (OR1.26; 95% CI1.05-1.47, P< 0.01) in angina, and statins in men (OR 1.39; 95% CI1.01-1.93, P< 0.04) with PAD and coronary heart disease (CHD). In contrast, men diagnosed with isolated PAD were significantly less commonly prescribed statins than women (OR 0.73; 95% CI0.59-0.91, P< 0.004).

Prescribing of evidence based therapies varied negligibly between the most deprived and least deprived patients. These minor differences disappeared after adjustment except for β-blockers which were significantly less likely to be prescribed for patients who had been diagnosed with angina and were residing in quintile 9 compared to the least deprived area (OR 0.76, 95% CI 0.58-1.00, p= 0.05).

Prescribing of evidence based therapies increased between 1997 and 2005, particularly for ACEIs/ARBs, β-blockers, statins and antiplatelet agents.

Generally the presence of comorbidities was associated with lower odds of being prescribed evidence based therapies.

When comparing prescribing rates between the different diagnoses, patients with a first MI were more likely to be prescribed ACEI/ARBs, β-blockers, statins, aspirin and clopidogrel compared to angina. All evidence based therapies were less likely to be prescribed for those with PAD compared to patients with a MI or angina.

Conclusion

In conclusion, I have shown that prescribing of evidence based therapies has improved over time, though rates remain low. Prescribing evidence based therapies is inequitable, though not always significant, for age, sex, and socioeconomic status. Concomitant disease decreased the odds of being prescribed evidence based therapies. More studies are needed to identify the reasons for the prescribing inequalities and low rates observed. Further studies are needed to examine the existence of other inequalities in using evidence based therapies such as dosing and to find strategies to improve prescribing rates.

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Abbreviations

ACS	Acute coronary syndrome
ACEI	Angiotensin converting enzyme inhibitor
AF	Atrial fibrillation
AMI	Acute myocardial infarction
ARB	Angiotensin receptor blocker
ABI	Ankle-brachial index
ADR	Adverse drug reaction
β-blocker	Beta blockers
BMI	Body mass index
CCB	Calcium channel blockers
CHD	Coronary heart disease
CMR	Continuous Morbidity Recording
CT	Computed tomography
CABG	Coronary artery bypass graft
CRF	Chronic renal failure
COPD	Chronic obstructive pulmonary disease
CAD	Coronary artery disease
CKD	Chronic kidney disease
ECG	Electrocardiogram
ESRD	End stage renal disease
GORD	Gastro-oesophageal reflux disease
GP	General Practitioner
GPASS	General Practice Administration System for Scotland
GROS	General Register Office for Scotland records the causes of death
HF	Heart failure
HR	Hazard ratio

ICD	International Classification of Disease
ISD	Information and Statistics Division
LLD	Lipid lowering drug
LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic dysfunction
MI	Myocardial Infarction
OR	Odds ratio
PAD	Peripheral artery disease
PCI	Percutaneous coronary intervention
PTI	Practice Team Information
PVD	Peripheral vasodilator
PUD	Peptic ulcer disease
RF	Renal failure
RR	Relative risk
SIMD	Scottish Index of Multiple Deprivation
SMR	Scottish Morbidity Records
95% CI	95% confidence interval

List of peer-reviewed poster presentations at International meetings

Publication

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Abstract

SA Al-Suhaim, JJV McMurray, J Lewsey, PS Jhund. Lower prescribing rates of evidence based pharmacotherapy in patients with a first diagnosis of peripheral arterial disease compared with myocardial infarction. Poster presentation in the European Society of Cardiology (ESC). 3rd Sep. 2013.

1.0 Introduction

This thesis will examine the prescribing inequality of evidence-based therapy for cardiovascular disease, in particular myocardial infarction (MI), angina and peripheral arterial disease (PAD) using primary and secondary data sets in Scotland. For consistency I will refer to evidence-based therapy (EBT) in this thesis. Literature surrounding this topic will be reviewed to examine the relationship between age, sex, socio-economic, comorbidity and calendar year and prescribing EBT.

In chapter one, I will discuss different aspects related to this study including the pharmacological treatment for cardiovascular disease, patients' compliance and adherence to medications, socioeconomic measurement, and finally I will discuss the pharmacotherapy key trials for MI, angina and PAD. In chapter two, I will describe the literature examining the prescribing of EBT inequalities for age, sex, socioeconomic deprivation, comorbidities and the prescribing trend for MI, angina and PAD. In the next chapter I will state the aims and objectives of this thesis. In chapter four, I will describe the data sets resources (Continuous Morbidity records and Scottish Morbidity Records), the cohort studied in these analyses, and also the statistical methods used to analyse the data. In chapter five, I will present the results of the analyses performed which have examined the prescribing inequalities of EBTs for age, sex, socioeconomic deprivation, comorbidities and calendar year after first diagnosis of MI, angina, PAD and PAD/CHD, furthermore, I will discuss these results in subsequent sections under each disease. Chapter six is an overall discussion and summary of this thesis finding, then chapter 7 and 8 discuss the study's strength/ limitations and conclusion, respectively.

1.1 Background

CVD is one of the most common causes of death worldwide.[1,2] In the United Kingdom (UK) more than one in three deaths (35%) are due to CVD, and approximately 198000 deaths are attributable to CVD every year.[3]

Several risk factors can increase the likelihood of developing any CVD. These risk factors are either modifiable, for example hypertension or non-modifiable such as age. In addition, once a person develops CVD, modification of risk factors can reduce morbidity and mortality.[4]

A number of effective therapies exist that reduce the risk of morbidity and/or mortality in patients with CVD. These therapies are mainly, but are not limited to, pharmacotherapies. This thesis will examine a number of cardiovascular diseases, namely coronary heart disease (CHD) which includes (myocardial infarction (MI) and angina), and peripheral arterial disease (PAD) and examine the pharmacoepidemiology of evidence based drug therapies for each of these diseases.

1.1.1 Non-communicable disease

Non-communicable diseases (NCDs), also known as chronic disease, have been considered as a leading cause of death worldwide.[5,6] They account for 60% of all deaths and 44% of premature deaths.[7] These diseases are not transmissible disease and they form a group of diseases that are not mainly caused by infection such as HIV/AIDS.[5]

CVD such as stroke and MI, chronic respiratory disease such as asthma, cancer, and endocrine diseases such as diabetes are the main group of NCDs. It has been reported that more than 36 million die annually due to NCDs. These groups of diseases already disproportionately affect low and middle-income countries where nearly 80% of NCD deaths (29 million) are reported. With an expectation of Africa, NCDs have been considered the leading causes of death in all regions.[5,6] A large portion of countries healthcare budgets are already utilised by these diseases. For instance, World Economic Forum and Harvard University have reported that chronic diseases are currently costing 2% of the global gross domestic product (GDP), with a tendency to cost the global economy US$30 trillion over the next two decades.[5,7]

All age groups and all regions are affected by NCDs with a tendency to be more associated with older age groups. However, evidence shows that more than 9 million of all deaths attributed to NCDs occur before the age of 60, 90% of these "premature" deaths occurred

in low and middle income countries. Unhealthy diets, physical inactivity, exposure to tobacco smoke or the effects of the harmful use of alcohol have all been considered as the leading risk factors that contribute to NCDs .[5] Physical inactivity and smoking are the most common contributable risk factors.[7] In spite of the ability to modify and change these risk factors, they are still the main cause of NCDs and death. For example, tobacco is the main cause of six million deaths annually, physical inactivity accounts for 3.2 million deaths every year, and approximately 1.7 million deaths are due to low fruit and vegetable consumption.[5]

In May 2013, a set of measures to tackle the global NCDs challenge were adopted by the 66th World Health Assembly. They endorsed a new Global Action Plan on NCDs containing suggested actions for WHO, countries and international partners. These actions involved working to improve multi-stakeholder collaboration and adopting a global monitoring framework. Twenty-five indicators of progress and nine voluntary global targets have been laid out by the framework to:

- Reduce the percentage of avoidable, premature deaths from the leading NCDs by 25%
- Reduce the risk of NCDs by decreasing the previously mentioned leading behaviours such as tobacco use, harmful alcohol use, physical inactivity, and eating unhealthy diets including consuming excess salt/sodium
- Stop the increase in diabetes and obesity, and reduce population levels of high blood pressure
- Increase the ability of accessing essential medicines and technologies for NCDs as well as promoting suitable use of drug therapy to reduce the chances of heart attacks and strokes.

1.2 Pharmacological basis for medications used in the management of myocardial infarction, angina and peripheral arterial disease

1.2.1 Antiplatelet agents

Platelet aggregation and thrombosis play a central role in the development of a number of diseases caused by atherosclerosis. Ischaemic stroke, MI, angina and PAD are primarily caused by the occlusion of arteries by the formation of thrombus.[8] Antiplatelet agents are used to prevent and treat thrombosis related disease including MI, angina, PAD, stroke, and for secondary prevention in these disorders.[9] Antiplatelet agents inhibit platelet aggregation by different mechanisms of action. The antiplatelet agents currently available for clinical use are aspirin (a cyclo-oxygenase inhibitor), dipyridamole (phosphodiesterase inhibitor), thienopyridines derivatives (clopidogrel, ticlopidine, prasugrel), glycoprotein IIb/IIIa receptors antagonists (abciximab, tirofiban, eptifibatide), and nucleoside /nucleotide inhibitors (ticagrelor, cangrelor). Aspirin (acetylsalicylic acid) is the most widely used antiplatelet agent. It is the first line of treatment for patients with vascular disease unless contraindicated.[9-13] It works by inhibiting cyclooxygenase (COX)-1 which leads to platelet inhibition through inhibition of thromboxane A2.

There are several clinical indications for aspirin such as stable angina, unstable angina, the treatment of acute MI, post-MI, post coronary bypass surgery and after coronary angioplasty, PAD and stroke.[13] A number of clinical trials have demonstrated the beneficial effects of aspirin in CVD (I will discuss these in the next chapter). The most common side effects include dyspepsia, nausea, vomiting, gastrointestinal (GI) bleeding, increased bleeding time, and gastric irritation. The major contraindications are GI bleeding, history of GI bleeding and active peptic ulcers.[13] High doses of aspirin are associated with an increased risk of GI side effects though the risk is reduced by using lower daily doses (75-300mg daily). Despite this the population burden of bleeding on low dose aspirin used for the treatment of CVD is still high given the prevalence of the diseases for which it is indicated.[14,15] While aspirin does have serious side effects its efficacy and availability mean that it has a central role in the treatment of atherothrombotic disease.

Aspirin has been used for many years but more recently drugs that irreversibly inhibit the binding of adenosine diphosphate (ADP) to its receptor in the platelet surface ($P2Y_{12}$ receptor) thus inhibiting platelet aggregation have been developed. The thienopyridine

group of drugs including clopidogrel and ticlopidine were the first developed. They are also commonly used in patients at risk of atherothrombotic events. These drugs have been shown to reduce the risk of new or further thrombus formation.[9,10,16,17] Ticlopidine and clopidogrel can be used as an alternative when aspirin is contraindicated or the patient cannot tolerate the side effects of aspirin. The use of ticlopidine was limited because of its serious side effects of neutropenia and thrombotic thrombocytopenia.[13,18] Clopidogrel is more widely used as it does not have these side effects. It also has better GI tolerability than aspirin although the risk of bleeding is still present.[15] Prasugrel has been available more recently. It may be more efficacious than clopidogrel in the setting of acute MI, however this is at the expense of more bleeding.[19] Prasugrel only became available at the end of the period covered by the data and was not in use during the period of this study.

More recently the nucleoside /nucleotide inhibitors (ticagrelor, cangrelor) have been developed and tested. They again inhibit the $P2Y_{12}$ receptor to prevent platelet aggregation. They are more potent than clopidogrel and are associated with higher rates of bleeding. Their efficacy has only recently been demonstrated and they were not available for use during the period covered by the data in this thesis. Therefore they were not included in the analysis. The glycoprotein IIb/IIIa receptors antagonists (abciximab, tirofiban, eptifibatide) are only used in intravenous form in the setting of acute coronary syndromes (ACS) in hospital. They are indicated for use in unstable patients who are due to receive coronary angioplasty and during angioplasty for certain groups. They are therefore not included in the analysis of the data used in this thesis.

Of the antiplatelet drugs discussed above, only aspirin and clopidogrel are included in the analyses. The other drugs are only used in intravenous form in hospital or were developed and available for use after the period of this study. The evidence surrounding the use of aspirin and clopidogrel is discussed in the next chapter.

1.2.2 Beta-blockers

Beta blockers (β-blockers) are indicated in the treatment of a number of CVDs including angina, MI and PAD.[20] β-blockers act by blocking the β-adrenoceptors found in the heart (β_1 receptor) and peripheral vascular and bronchial smooth muscle cells (β_2 receptor). Therefore the binding of epinephrine and norepinephrine to these receptors is blocked leading to inhibition of the effects of the sympathetic nervous system. [20-22] β-blockers reduce the work of the heart through negative chronotropic and inotropic effects (i.e. they

decrease heart rate and myocardial contractility) and therefore reduce myocardial oxygen demand. This reduction in myocardial oxygen demand improves the symptoms of angina. The increase in diastolic filling time due the negative inotropic effect of β-blockers prolongs myocardial perfusion through longer filling of the coronary arteries that occurs during diastole. Furthermore, β-blockers limit infarct size and improve survival in patients who have had a MI. [20,23]

The β-blockers can be broadly categorised according to their perceived cardioselectivity. The first generation β-blockers (e.g. propranolol, timolol) inhibit both β_1 and β_2 receptors and are therefore not cardioselective. They may lead to a greater risk of causing bronchospasm and vasoconstriction through smooth muscle contraction as a result of blocking β_2 receptors. The selective β-blockers (acebutolol, atenolol, betaxolol, bisoprolol, celiprolol and metoprolol) are potentially less likely to cause these side effects as they mainly act on the β_1 receptors. The cardioselectivity of these β-blockers falls as the dose increases. The non-selective but combined β-blockers (carvedilol, nadolol) have both β-blocker and other vasodilator effects. Nebivolol and carvedilol cause a direct vasodilation potentially via nitric oxide release, pindalol and acebutolol have an intrinsic sympathomimetic activity on β_2 receptors leading to smooth muscle relaxation and vasodilation and labetalol and carvedilol also have alpha blocking activity. A number of randomised clinical trials have demonstrated the efficacy of β-blockers leading to their central place in guidelines (these will be discussed in the next chapter). Although they are widely used and recommended this class of drugs have a number of side effects and contraindications. Their side effects arise from their mechanism of action. Smooth muscle effects cause bronchospasm and cold extremities and their negative chronotropic effect can cause excessive bradycardia.[22,24,25] In addition, the drugs can cause insomnia (which is thought to occur due to the drugs crossing the blood brain barrier).[22,26]

The use of β-blockers is recommended for the treatment and prevention of angina, MI and prevention of cardiovascular events in patients with PAD. In the current thesis all β-blockers were examined.

1.2.3 Angiotensin converting enzyme inhibitors/ angiotensin receptor blockers

Angiotensin converting enzyme inhibitors (ACEI) and angiotensin-II receptors blockers (ARB) both act on renin angiotensin system (RAS). ACEIs inhibit the conversion of angiotensin-I to angiotensin-II by angiotensin converting enzyme (which is found in the

pulmonary and renal endothelium) and ARBs block the angiotensin 1 and 2 receptors (AT1 and AT2) inhibiting the action of angiotensin II. Angiotensin II is a potent vasoconstrictor, it increases sympathetic activity, causes tubular sodium, chloride and water retention directly and through the formation of aldosterone by the adrenal cortex and via ADH secretion causes further water retention. All of these effects lead to an increase in blood pressure, afterload on the heart and coupled with its direct actions on the heart through inhibition of cardiac contractility, cell communication, and electrical impulse propagation and promotion of apoptosis (cell death) mean that angiotensin II is central to the development of CVD and the risk of death or other adverse outcomes in those with cardiovascular disease.[27-31]

The use of ACEI and ARBs has been shown to have many favourable effects in cardiovascular disease. They reduce blood pressure, reduce infarct size in MI and inhibit adverse remodelling preventing the onset of heart failure (HF). They also improve survival in those with cardiovascular or PAD (see next section). However, drugs inhibiting the RAS also have a number of side effects that can limit their use in practice. They promote the retention of potassium, as angiotensin II which they inhibit promotes the excretion of potassium. They also can cause worsening of renal failure and because of their effect on the RAS they are contraindicated in renal artery stenosis (as they cause a fall in renal perfusion pressure). All ACEIs can also cause angioedema through the inhibition of bradykinin breakdown which is also mediated by angiotensin converting enzyme.[30] This effect is also responsible for a dry cough which can occur with ACEIs. While these effects are particularly relevant for ACEIs a small subset who take an ARB can also develop angioedema.[32] In practice the commonest reason for this group of drugs not to be prescribed is impairment of renal function, hyperkalaemia and hypotension. [33] The final issue that has been discussed is whether ARBs are equivalent to ACEIs in their ability to prevent adverse outcomes. As noted above, their different mechanism of action may reduce the likelihood of certain side effects. Theoretically they were thought to be better at inhibiting the effects of angiotensin II as angiotensin II can still be produced through non-ACE dependant pathways even if an ACEI is used.[34] However, clinical outcome trials have established their equivalence and not superiority for a number of cardiovascular outcomes as will be discussed in the next section.

For this thesis I considered any ACEI or ARB as a potential drug. Given that ARBs can be used instead of ACEI for patients with side effects such as cough, they are combined into one group.

1.2.4 Calcium channel blockers

Calcium plays an important role in maintaining the tone of smooth muscle cells and in the contraction in the myocardium. Normally the concentration of calcium ions ($Ca2^{+}$) is higher outside cells than inside, and it influxes into vascular smooth muscle and myocardial cells through L-type calcium channels. This increase in intracellular $Ca2^{+}$ concentration stimulates smooth muscle and myocardial contraction. Calcium channel blockers (CCBs) antagonize this effect by blocking L-type calcium channels and preventing the influx of calcium ions into cells. This in turn leads to the drugs being negatively inotropic and causing peripheral vasodilation. This effect is common to both the non-dihydropyridene (non-DHP) subclass (which includes the drugs verapamil and diltiazem) and the dihydropyridenes (amlodipine, nifedipine, lecarnidipine, felodipine etc.). The DHP are more selective for the vascular smooth muscle and hence are less negatively inotropic than the non-DHP class of CCBs. The non-DHP drugs also inhibit the sino-atrial and atrioventricular node, reducing heart rate further, adding to their negative effect on cardiac output.[35-37]

The class of CCB used is therefore determined by comorbidities and interactions with other prescribed drugs. CCBs are useful for patients who have bronchospasm or airways disease who cannot tolerate β-blockers. The negatively inotropic effect of the non-DHP class means that they are contra-indicated in patients with HF and their rate-limiting effects means that they cannot be used with β-blockers or in those with existing atrioventricular disease (the DHP class can be used).[38,39] In general, CCBs are well tolerated but side effects occur from their vasodilation properties such as dizziness, hypotension, headache and flushing.[35,40,41] Constipation is a common side effect in the elderly with the non-DHP class. Some important drug interactions between the non-DHP and other drugs commonly prescribed in patients with CVD must be noted. In addition to lowering heart rate the non-DHP also inhibit the digoxin transporter increasing serum concentrations of digoxin, increasing the risk of digoxin toxicity and heart block. Verapamil is an inhibitor of the hepatic CYP3A enzyme involved in the breakdown of statins, theophylline (used in asthma, a common reason to use the non-DHP drugs over β-blockers) and cyclosporin.

Despite these issues the CCB drugs are used commonly as they improve angina, reduce blood pressure and in the case of the non-DHP verapamil may improve outcomes post-MI.[42] All CCBs were considered under one class for this thesis as there is not definitive evidence that one sub-class is preferable to another as will be discussed in the next chapter.

1.2.5 HMG-CoA reductase inhibitors

A number of drugs are available to reduce cholesterol. The fibrates (fenofibrate, gemfibrozil, benzofibrate, fenofibrate) reduce triglyceride levels. The nicotinic acid niacin is thought to act via inhibition of free fatty acid release from tissues therefore reducing the creation of cholesterols by the liver. The bile acid sequestrants (cholestyramine, colesevelam and colestipol bind to bile acids, which contain cholesterol, and promote their excretion in the gastrointestinal tract, reducing cholesterol levels. None of these drugs have convincingly shown reductions in mortality or morbidity in trial. The inhibitors of the liver enzyme responsible for forming cholesterol, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), have been shown to effectively lower lipid levels and reduce morbidity and mortality.[43-45] As such the statins (simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, lovastatin) are the drug of choice for reducing cholesterol and improving outcomes in patients with cardiovascular disease. Guidelines suggest commencing a statin therapy in patients established CHD with total cholesterol level >4.5 mmol/L, and LDL cholesterol >2.5 mmol/L.[44] In addition to lowering LDL cholesterol (associated with worse outcomes) they increase the levels of HDL cholesterol (with increased levels reducing the risk of cardiovascular events.[35,46] The statins may also have other so-called pleomorphic effects such as improving endothelial function, stabilising coronary plaques (the rupture of which are responsible for myocardial infarction) and inhibiting inflammatory response to atherosclerosis.[46,47] The statins are contraindicated in patients with liver impairment and they can cause an elevation in liver enzymes. The commonest side effect of the drugs is on the skeletal muscle and the drugs can cause muscle pain and more rarely rhabdomyolysis (disintegration or dissolution of muscle).[35] A number of clinical trials which will be discussed in the next chapter have demonstrated that statins reduce morbidity and mortality in primary and secondary prevention of CVD.[48] Therefore in this thesis I will examine statins as the evidence based therapy for the outcomes examined.

1.2.6 Nitrates

Nitrates are commonly used for the treatment of angina. Through a nitric oxide free radical the drugs induce vasodilation even when endogenous nitric oxide production is low or impaired. An unstable nitric oxide free radical is released from the nitrate molecule of the drugs. Prolonged administration of the drugs can lead to formation of a compound called peroxynitrate and this inhibits endothelial production of nitric oxide and may be one of the mechanisms behind the phenomenon of nitrate tolerance.[49,50] This occurs when the patients have been on nitrates without a break for a long time. To prevent this nitrates are administered with a nitrate free period usually overnight when the patient is less active. The nitrates preferentially dilate large coronary arteries and arterioles. As a result they lead to a reduction in afterload via arterial dilation, reduction in preload through venous dilatation and consequently reduced myocardial oxygen requirements. The nitrates are therefore used to relieve the symptom of angina. Short acting preparations (given sublingually to prevent metabolism in the liver) are effective at quickly relieving chest pain by their coronary vasodilation effects. The longer acting nitrate preparations (given in tablet form or as transdermal patches) are effective at improving symptoms and exercise tolerance in patients with angina.

As a result of their vasodilatory action the commonest side effect is headache, 30-60% of patients receiving nitrate therapy with long acting preparations will experience headache. Other side effects are postural hypotension, facial flushing and tachycardia, again all a consequence of their vasodilatory actions.[51-53] Nitrates have very few contraindications and may have to be used in caution with other vasodilating medications such as CCBs. The major interaction is between phosphodiesterase-5 inhibitors (e.g. sildenafil (Viagra)) where co-administration may lead to catastrophic vasodilation and circulatory collapse. Unlike many of the other drugs discussed the nitrates have not been shown to improve morbidity or mortality in patients with cardiovascular disease. The only exception is HF where the administration of isosorbide dinitrate may improve outcomes when administered with hydralazine (another vasodilator) in some patients. Nitrates are therefore used to treat symptoms and not improve outcomes.

1.2.7 Potassium channel opener "Nicorandil"

Nicorandil is relatively new class of anti-anginal medication. It is a potassium channel activator that is used in the management of stable angina. Nicorandil has a dual effect, a nitrate-like effect and activation of ATP sensitive potassium channels.[54] These actions

produce vasodilatation in systemic and coronary arteries. This mechanism leads to a reduction in both preload and afterload.[54,55] As with other vasodilators the drugs must be used with caution in those with low blood pressure or receiving other vasodilator medications. As with other vasodilators, the side effects reflect vasodilation and include headache, hypotension, dizziness, fatigue and flushing. A rare but more serious complication of gastrointestinal ulceration is recognised and resolves after stopping the drug.[54,56] There are studies of nicorandil that have demonstrated improvements in morbidity in patients with angina. Therefore nicorandil is considered a useful treatment for angina.

1.2.8 Ivabradine

Ivabradine is a new heart rate lowering drug which has selective and specific inhibitor effects on I_f channel in the sino-atrial node. This effect leads to a reduced heart rate at rest or during exercise. Therefore, ivabradine maintains myocardial contractility, atrioventricular conduction and ventricular repolarization and is thought to be purely a heart rate lowering drug. It therefore reduces the metabolic needs of the heart, improving angina symptoms. It is useful in patients who cannot tolerate or have a contraindication to β-blockers.[57,58] Ivabradine is contraindicated in patients with sino-atrial disease and should not be used with rate limiting CCBs (verapamil and diltiazem) as the risk of heart block and bradycardia is high.[59] Common side effects are bradycardia, first-degree heart block, headache, dizziness and blurred vision (as the I_f channel is also present in the retina). Less common side effects include: diarrhoea, nausea, constipation, palpitation, dyspnoea and muscle cramp. Ivabradine reduces angina and has been tested in angina and HF (see next section). As such is it considered a third or fourth line therapy in the treatment of angina.

1.2.9 Oral anticoagulants

Vitamin K plays an essential role in blood clotting. It is important in the formation and production of vitamin-K dependant clotting factors (VII, IX, X, and II). Warfarin inhibits the production of these clotting factors and is therefore an anticoagulant drug.[60] The drug must be monitored as it has unpredictable pharmacokinetics which alter between patients (due to genetic differences) and within patients (due to changes in catabolism, diet (see below) or concomitant drugs). It has a narrow therapeutic window where the benefits of its anticoagulant effects are observed. Over-anticoagulation increases the risk and rate of bleeding, most usually from the gastrointestinal tract or in the brain causing haemorrhagic

stroke. While the effects of over-anticoagulation can be reversed with vitamin K, administration of blood clotting factors may be needed in life threatening bleeding. Warfarin also interacts with a multitude of drugs and foods making it a difficult drug to safely administer. Coupled with the need for regular monitoring and dose adjustment it is a drug with low adherence rates. However, it is an effective anticoagulant and it is used for secondary prevention following MI where it may be used as an alternative for those intolerant of antiplatelet agents (mainly aspirin or clopidogrel). Also it is considered after MI in patients who are already taking warfarin for other comorbidities such as atrial fibrillation or deep-vein thrombosis (DVT).[61] Caution must be used when prescribing the drug in conjunction with aspirin as the risk of bleeding increases. Warfarin is contraindicated in haemorrhagic stroke, peptic ulcer disease, uncontrolled hypertension and clinically significant bleeding or bleeding disorders. More recently novel oral anticoagulants have been developed. These include direct factor Xa inhibitors (rivaroxaban, apixiban, edoxaban) and direct thrombin inhibitors (dabigatran). However, these were not available or indicated during the period of this study. At present they are not licenced for use in CHD or PAD. For this reason the anticoagulant examined is warfarin.

1.2.10 Cilostazol

Cilostazol is a 2-oxoquinolone derivative and selective inhibitor for the phosphodiesterase-3. It has antiplatelet aggregation, vasodilator and antithrombotic effects. It is used to improve blood flow in peripheral arteries and improves walking distance in those with PAD. It should be avoided in patients with a predisposition of bleeding, history of ventricular tachycardia, HF or severe renal impairment. The most common side effects that may appear when using cilostazol are tachycardia, palpitations, gastrointestinal disturbances, dizziness, headache and chest pain.[62,63]

1.2.11 Naftidrofuryl

Naftidrofuryl is a vasodilator drug use to improve walking distance in patients with intermittent claudication. It is a selective serotonin "5HT2" receptors antagonist in the smooth muscle cell which may lead to vasodilation in the peripheral circulation.[64,65] It is normally tolerated in the recommended dose, however few undesirable effects can be recognised such as nausea, diarrhoea, rashes, epigastric pain, headache, dizziness.[63]

1.2.12 Pentoxifilline (Oxpentifylline)

Pentoxifylline acts by lowering blood viscosity and increasing the flexibility of red blood cells both of which are thought to lead to improved blood flow in the peripheries. It may also decrease the risk of thrombus formation.[66] It is contraindicated in patients with cerebral haemorrhage, acute MI. Its side effects include nausea, vomiting, diarrhoea, dizziness, sleep disturbances, headache.[63] Its efficacy in reducing morbidity or mortality has not been proven but it may improve symptoms.

Summary

The drugs used to treat MI, angina and PAD overlap. As can be seen from the description of the pharmacological actions of the drugs above, the mechanisms of action of the drug mean that they are useful in each of these conditions. In the next chapter I will discuss the evidence base for the use of each of these drugs in MI, angina and PAD.

1.3 Coronary Heart Diseases

CHD occurs when atherosclerosis of the coronary arteries is present. An individual with CHD may have no symptoms, exertional chest pain (angina) or sudden occlusion of a coronary artery which leads to a MI. In the UK approximately 50% of CVD deaths are directly related to the CHD.[4] Annually around 8,000 people die in Scotland because of CHD [5] despite the observation that CHD mortality has declined in the last 10 years by 42%.[67,68] However, effective evidence based therapies, which reduce morbidity and mortality in those with CHD, i.e. for secondary prevention, are available and I will discuss these in relation to MI and angina.

1.3.1 Angina

1.3.1.1 Evidence based pharmacotherapy and secondary prevention in angina

A number of effective therapies for the treatment of angina exist. Drugs may be used to control symptoms and others to reduce mortality. The management of angina symptoms is usually initiated with one drug (mono therapy), however, if this is not sufficient to improve symptoms then combination therapy is required.[25,69]

Calcium channel blockers

CCBs are effective in the treatment of angina. The selection of a CCB is based on comorbidity and drug interactions. For example HF and bradycardia or AV block limit the choice to dihydropyridines (e.g. amlodipine or felodipine).[70] CCBs improve angina symptoms by coronary vasodilatation and reduction in myocardial oxygen demand.[41,71] Dizziness, hypotension, headache, palpitation, flushing, and nausea are commonly observed with dihydropyridines such as nifedipine, but less so with long acting diyhydropyridines such as amlodipine and non-dihydropyridines e.g. diltiazem or verapamil.[41] Rate limiting CCBs (diltiazem and verapamil) are contraindicated and should be avoided in patients with HF, and in patients with bradycardia or AV block.[39]

The extent of efficacy and tolerability of two different types of CCB has been assessed in a randomised double-blind study.[72] Amlodipine once daily and modified release diltiazem once daily were compared in one study. Patients were randomised to amlodipine (5mg/day) or diltiazem modified release (240mg/day) for two weeks, then the dose increased to (10mg/day) and (360mg/day), respectively. There was no significant difference between the two treatments. In comparison to the baseline, both treatments were significantly associated with increase in time to onset of angina (<0.001) for diltiazem and

(0.002) for amlodipine, time to maximal exercise (<0.001) for both treatments. In addition, both drugs were similarly effective in reducing the number of angina attacks and the frequency of use of glyceryl trinitrate. Amlodipine and diltiazem were associated with a low rate of side effects, and the most common reported side effects were oedema, headache and palpitations.[72]

A further study compared amlodipine (2.5-10 mg a day) with diltiazem (60-120 mg three times/ day).[73] Both drugs resulted in an improvement of time to onset of angina, time to maximal exercise, and time to 1 mm ST segment depression. They also reduced glyceryl trinitrate consumption (median decline in consumption for amlodipine was 0.75 tablet/week and 1 tablet/ week for diltiazem) and frequency of angina attacks (1.5 attacks/week for amlodipine and 3 attacks/ week for diltiazem).

Angina prognosis study in Stockholm (APSIS)[74] included 809 patients age under 70 years old with stable angina. Patients were blindly randomised to receive either verapamil (240mg/ twice a day) or metoprolol (200mg/ a day). After a median follow-up for 3.4 years, mortality was 6.2% in verapamil and 5.4% in metoprolol (p=0.63). At the end of the study 24.3% of verapamil treated and 26.1% of metoprolol treated patients had non-fatal cardiovascular events (MI, stroke, PAD and angina).

Nitrates

In the management of an acute angina attack the most effective drug is a nitrate taken either as a sublingual tablet or spray of glyceryl trinitrate.[25] Vascular smooth muscle dilatation is the principal effect of nitrates. This leads to reduced cardiac preload and afterload which results in decreasing myocardial oxygen requirement. A further effect is dilatation of the coronary arteries which increase the coronary artery blood flow and consequently increased oxygen supply.[51,53]

For the chronic treatment of angina in a double blind study, 97 elderly patients with stable angina were randomised for either to receive amlodipine (5-10 mg/day) or isosorbide mononitrate at dose (25-50 mg/day) for 28 weeks. At the end of this study amlodipine was significantly better than isosorbide mononitrate in improving the total exercise time p=0.016.[75]

Combination of isosorbide mononitrate with atenolol showed a preferable effect than nifedipine with atenolol or atenolol alone in a double blind study.[76] Eighteen patients (age rage 47-67 years) with angina were randomised to atenolol (100mg/day) and placebo,

atenolol (100mg/day) and nifedipine (40mg/day), atenolol (100mg/day) and isosorbide mononitrate (40mg/day), or triple therapy. After 4 weeks, there were no significant differences in all tested parameters including angina attack rates, glyceryl trinitrate consumption, exercise duration to onset of angina or 1mm ST depression or symptoms free. However, combination of atenolol/ isosorbide mononitrate was associated with longer exercise duration than atenolol alone (mean difference 46, 95% CI 18-88, p=0.005), atenolol with nifedipine (mean difference 36, 95% CI 2-71, p=0.04), triple therapy (mean difference 28, 95%CI 6-61, p=0.1).

Beta blocker

β-blockers are considered a first line therapy for the long term management of chronic angina. However, these should be avoided in patients with asthma, severe bradycardia, high degree atrioventricular block[77] and decompensated left ventricular failure.[25,78] β-blockers improve angina symptoms through reducing the heart rate and myocardial contractility which both lead to reduce myocardial oxygen demand.[79] Side effects include fatigue, lethargy, insomnia, nightmares, sexual dysfunction.[26]

The atenolol silent ischemic study (ASIST)[80] examined the effect of atenolol on daily ischaemia due to CHD in 306 outpatients. Patients were randomised to either placebo or atenolol (100mg/day). After four weeks of treatment, compared to placebo, atenolol reduced the frequency (mean ± SD, 3.6±4.2 vs. 1.7±4.6 episode, $p<0.001$) and average duration (30±3.3 vs. 16.4±6.7 minutes, $p<0.001$) of ischaemic episodes per 48 hours of ambulatory electrocardiography (ECG) monitoring. The average heart rate after four weeks for placebo was 74.9 beats/minutes vs. 63.2 beats/minutes (p=0.0001) for atenolol. Furthermore, atenolol improved event free survival (death, resuscitation of ventricular tachycardia/ fibrillation, myocardial infarction, hospitalisation for unstable angina, aggravation of angina or revascularisation, $p< 0.006$). However, there was no significant reduction in the endpoint of death or non-fatal MI among atenolol treated patients over placebo (relative risk [RR], 0.55; 95% confidence interval [CI], 0.22-1.33, p=0.175).[80]

Although the sample size in the ASIST study was small and the duration of follow-up was only one year, this study provided evidence of the beneficial effect of atenolol in the management of patients with silent ischaemia.[80]

Combination therapy of β-blocker and calcium channel blocker

The effect of combination treatment versus monotherapy of stable angina has been investigated in the International Multicentre Angina Exercise (IMAGE) study.[81,82] Patients who reported stable angina symptoms for ≥ 6 months and had a positive exercise tolerance test were enrolled in this study. This study took place over 10 weeks and was divided into two stages. Firstly patients had an exercise test at baseline and they were allocated to double-blind treatment for 6 weeks with either metoprolol (100mg/ day) or nifedipine (20mg twice/day). Then in the next four weeks patients treated with metoprolol were randomised additionally to either placebo or nifedipine and patients treated with nifedipine were also randomised to the addition of metoprolol or placebo. Exercise tolerance tests were repeated at week 6 and week 10. Both metoprolol and nifedipine were effective and mean exercise time increased in comparison to baseline ($p < 0.01$), metoprolol was significantly more effective than nifedipine ($p < 0.05$). Combination therapy led to a considerable increase in mean exercise tolerance ($p < 0.05$) compared to placebo.[81,82]

The total ischaemic burden European trial (TIBT)[83] included 608 patients aged between 40 and 79 years with stable angina. Patients were randomly selected to receive atenolol 50mg/ twice a day, nifedipine 20mg/twice a day, or combination therapy of atenolol/nifedipine. After 6 weeks follow-up atenolol and combination therapy were associated with significant ($p<0.01$) fall in heart rate, however, nifedipine was associated with slight increase in heart rate. Furthermore, after 6 weeks the total exercise time, time to 1 mm ST segment depression, and maximal ST segment depression, significantly improved in all treatment groups compared to the baseline.

A meta-analysis[84] of 22 randomised trials compared monotherapy with a β-blocker to combination of β-blocker and CCB, and 10 studies comparing monotherapy with a CCB to a combination of a CCB and a β-blocker. This meta-analysis demonstrated that combined therapies were significantly more effective than a β-blocker and increased the time to 1 mm ST segment depression by 8% ($p < 0.001$), increased total exercise duration by 5%, and increased the time to the onset of angina pain by 12% ($p < 0.001$). However, only the time to 1mm ST segment depression was significantly increased with the combined therapy compared to CCB alone by 9% ($p < 0.001$).[84]

“Potassium channel openers” nicorandil

Nicorandil is a potassium channel activator used in the management of stable angina. This drug is used in combination with other drugs in patients who have not achieved symptom control.[78] Nicorandil has a dual effect, a nitrate-like effect and activation of ATP sensitive potassium channels.[54] These actions produce vasodiltation in systemic and coronary arteries. This mechanism leads to a reduction in both preload and afterload.[55] The most common reported adverse effects of nicorandil are headache, hypotension, dizziness, fatigue, flushing, and, rarely, gastrointestinal ulceration such as small intestinal ulceration and anal ulceration. [56]

The efficacy of nicorandil in the management of patients with angina was investigated in the Impact of Nicorandil in Angina (IONA) study.[85,86] This was a randomised double-blind, placebo controlled trial. Over 5000 patients randomly assigned for either nicorandil (20 mg twice a day) or placebo. Patients were followed up for approximately 36 months in order to identify whether nicorandil could reduce the incidence of coronary events in patients with stable angina and additional risk factors. It was reported that nicorandil significantly reduced the primary end points (incidence of fatal CHD, non-fatal myocardial infarction or unplanned hospitalisation for cardiac chest pain) compared to placebo group from 15.5% to 13.1% (Hazard ratio [HR] 0.83; 95% CI 0.72–0.97; p=0.014).[87-89]

The efficacy of nicorandil in comparison to amlodipine in improving angina symptoms was examined in a double blind study (Study of Women's Health Across the Nation (SWAN) study).[90] Patients were randomised to receive either nicorandil (10mg/twice a day) or amlodipine (5mg/day) for 8 weeks, then after 2-4 weeks according to the patient’s clinical condition the doses were increased to 20 mg twice a day for nicorandil and 10 mg/ day for amlodipine, respectively. In both groups time to onset of ST segment depression was increased (from 4.7 to 5.1 for nicorandil, and from 5.1 to 5.7 for amlodipine), though it was not statistically significant in the nicorandil group. In addition, time to onset of angina was increased significantly (5.2 to 6.1 per minutes for nicorandil, and 5.6 to 7.0 per minutes for amlodipine).[90]

Other antianginal drugs

Ivabradine

Ivabradine is a new heart rate lowering drug which has selective and specific inhibitor effects on I_f channel in the sino-atrial node (SAN) pacemaker current. This effect leads to a reduced heart rate at rest or during exercise. Patients with stable angina who cannot tolerate β-blocker can alternatively use ivabradine.[57,58]

The safety and efficacy of ivabradine was demonstrated in a randomised double blind placebo controlled trial.[57,58,91] In this study 360 patients with stable angina were randomised to receive one of three doses of ivabradine (2.5, 5 or 10 mg twice a day) or a placebo. After two weeks of ivabradine use, there was a significant reduction in heart rate for all doses compared to the placebo ($p<0.05$). Furthermore, the time to 1 mm ST segment depression during exercise tolerance test (ETT) significantly increased in the ivabradine 5mg and 10mg doses compared to placebo. Ivabradine reduced the frequency of angina and the use of short acting nitrates.

A randomised double blind controlled trial,[92] including 939 patients with stable angina to compare ivabradine efficacy atenolol. Patients were randomised to receive one of the following regimens: ivabradine 5 mg twice daily for 4 weeks followed by ivabradine 7.5 mg twice daily for 12 weeks. Ivabradine 5 mg twice daily for 4 weeks followed by ivabradine 10 mg twice daily for 12 weeks, or atenolol 50 mg once daily for 4 weeks followed by atenolol 100 mg once daily for 12 weeks. At 16 weeks, patients who were assigned to receive ivabradine 7.5 mg twice daily and 10 mg twice daily had a mean increase of time to limiting angina of 91.8 +/- 131.1 s and 96.9 +/-121.1 s, respectively, at trough drug concentrations, versus 85.4 +/- 133.7 s for atenolol 100 mg once daily ($P<0.001$ for noninferiority of ivabradine). The efficacy of ivabradine relative to atenolol was also established for time to angina onset ($P<0.001$ for noninferiority).

A placebo-controlled randomised trial[93] assessed the frequency of angina attacks at the end of an open label phase. Hundred and sixty one patients with stable angina were assigned to ivabradine 10 mg twice daily for 3 months, then they were blindly randomised for two weeks to receive one of the following regimens: ivabradine 2.5 mg twice daily, ivabradine 5 mg twice daily, ivabradine 10 mg twice daily, or a placebo. At the end of this 3-month period, the number of angina attacks per week was significantly lower than at baseline, decreasing from 4.14 +/- 5.58 attacks per week to 0.95 +/- 2.24 attacks per week

(P<0.001). The consumption of short-acting nitrates decreased from 2.28 +/- 3.74 tablets/week to 0.50 +/- 1.14 tablet/week (P<0.001) during the same period. In a subsequent 1-week withdrawal period following the 3-month open-label phase, angina attack frequency increased by 0.74 +/- 1.95 attacks per week for patients assigned to the placebo (P=0.067).

Angiotensin converting enzyme inhibitor (ACEI)

The beneficial effect of ACEIs in patients with HF and MI has been proven in a number of trials, however, the benefits of ACEIs in patients with CHD is conflicting.[94] Six randomised controlled trials of patients with CHD and preserved left ventricular systolic function were combined in a meta-analysis. Approximately 33,500 patients with CHD were randomised to ACEI or placebo. Patients randomised to ACEI showed a decrease in cardiovascular mortality (RR 0.83; 95%CI 0.72-0.96, p=0.01), non-fatal MI (RR 0.84, 95% CI0.75-0.94, p=0.003).[94]

The heart outcomes prevention evaluation (HOPE) study randomised 9297 high risk patients who had evidence of vascular disease or diabetes with one other cardiovascular risk factor and without evidence of left ventricular dysfunction or HF, to ramipril 10mg/day or placebo. The ramipril group significantly reduced the risk of death, had MI or stroke compared to the placebo (RR 0.78; 95%CI 70-86, p<0.001).[95] In EUROPA,[96] there was a randomised control trial, in which patients with stable CHD were randomised to perindopril or placebo. Perindopril significantly reduced the composite outcome for cardiovascular mortality, non-fatal MI and resuscitated cardiac arrest (RR 0.80, 95% CI 9-29, p=0003).

In contrast, two studies showed no benefit of ACEI in patients with stable CHD. The quinapril ischaemic event (QUIET) and PEACE trials randomised patients with stable CHD to quinapril and trandolapril or placebo, respectively.[97,98] Compared to the placebo, these studies did not show significant difference in the rates of death due to cardiovascular causes, non-fatal MI, coronary revascularisation.

Lipid lowering drugs "statins"

Lipid lowering drugs reduce the risk of atherosclerosis.[43,99,100] The European guidelines suggest commencing a statin therapy in patients established CHD with total cholesterol level >4.5 mmol/L, and LDL cholesterol >2.5 mmol/L.[99] The Heart protection study (HPS),[101] randomised patients (with coronary disease, other occlusive arterial disease or

diabetes) to simvastatin 40mg/ day or a placebo. HPS demonstrated that simvastatin significantly reduced coronary mortality rate by 18% (5.7% vs. 6.9%, p<0.001), and also reduced the rate of a major coronary event including non-fatal MI and coronary death (RR 0.73; 95% CI 0.67-0.79, p<0.0001).

In a large meta-analysis of 14 randomised trials that included patients with stable angina,[102] there was a 19% reduction in coronary mortality (95% CI 0.76-0.85, p<0.0001), and reduction in MI or coronary mortality (RR 0.77; 95%CI 0.74-0.80, p<0.001) with statin therapy.

Antiplatelet therapy

In a large double blind trial, Swedish angina pectoris aspirin trial (SAPAT),[103] 2035 patients with stable angina were randomised to receive aspirin 75mg/ day or placebo. Patients were followed-up approximately for more than four years. Compared to the placebo group, aspirin reduced the composite outcome for cardiovascular event including MI and sudden death (RR 0.66; 95%CI 24-49, p=0.003).

A meta-analysis for randomised control trials,[104] included 135000 patients with CVD including angina. It involved 287 randomised trials and aspirin was the most studied antiplatelet therapy. The use of antiplatelet therapy reduced the serious vascular events include non-fatal MI, non-fatal stroke and vascular mortality. Other meta-analysis of six randomised trials for patients with stable CVD showed that aspirin reduced the risk of cardiovascular events including non-fatal MI, non-fatal stroke, and cardiovascular death (RR 0.79; 95% CI 0.76-0.98).

1.3.2 Myocardial Infarction (MI)

1.3.2.1 Evidence based pharmacotherapy in secondary prevention in MI

Patients with an acute MI are at high risk of recurrence or other cardiovascular events including cardiovascular death. Recurrence of MI within one year is between 8 and 10%.[3,4,67] Several groups of medications can be used to help prevent recurrence and death. These medications include antiplatelet agents (aspirin or clopidogrel), ACE inhibitors or ARBs, β-blockers and statins.[105-107] The effectiveness of these medications has been established in large randomised clinical trials.

Antiplatelet therapy

It is recommended that all patients post MI be prescribed an antiplatelet agent. A large meta-analysis of 25 trials demonstrated that antiplatelet agents reduced the risk of death and re-infarction by 25% post-MI.[105,108] At three years follow up, in the 1410 patients with MI included, aspirin reduced the incidence of new coronary events by 52%.[109]

In the Clopidogrel versus aspirin in patients at risk of ischaemic event (CAPRIE) trial[110,111] compared to aspirin, use of clopidogrel was associated with 8.7% relative risk reduction (95% CI 0.3–16.5 p=0.043) in ischaemic stroke, MI, or vascular death. Clopidogrel had a similar safety profile to aspirin, therefore, clopidogrel is considered as a suitable alternative for aspirin in patients who are intolerant of aspirin.

In the randomised control trial, Clopidogrel in Unstable angina to prevent Recurrent Event (CURE),[112] 12,562 patients with unstable angina or ST elevation MI to placebo or clopidogrel, in addition to different doses of aspirin. Patients were followed up from three months to a year. Compared to the placebo, the clopidogrel group had a significantly lower risk of cardiovascular death, MI or stroke (RR 0.8; 95% CI 0.72-0.9, p<0.001).

Beta blocker

The initiation of a β-blocker post-MI is strongly recommended on the basis of several pieces of evidence. Several trials and meta-analyses support the use of β-blockers due to their ability to reduce all-cause mortality, re-infarction and sudden cardiac death post MI.[113] Two trials were particularly instrumental in establishing the use of β-blockers. In the β-blocker heart attack trial (BHAT) patients were randomised to propranolol or placebo. Mortality was reduced by 26% in the propranolol group compared with placebo (p<0.05), and re-infarction by 23% within a 2 year follow up.[114,115] The Norwegian Multicentre

Study (NMS) showed that compared with placebo, timolol associated with a 31% reduction in mortality in patients <65 years and a 43% reduction in patients aged 65-74 years.[115-117] A meta-analysis of 31 trials found that initiation of β-blockers in patients post-MI reduced the odds of mortality by 23% in comparison to placebo.[118]

Angiotensin converting enzyme inhibitors (ACEI)

A number of trials have established strong evidence for adding an ACEI to the management of patients following a MI. These trials have shown that ACEIs reduce mortality post-MI, MI recurrence and the development of heart HF.[113,119]

In the Survival and Ventricular Enlargement (SAVE) trial,[120] patients with left ventricular ejection fraction (LVEF) $\leq$ 40% were randomised to receive captopril (50mg three times a day) or placebo. Captopril significantly reduced all-cause mortality by 19% (95% CI 3-32, p=0.019), cardiovascular mortality by 21% (95% CI 5-35, p=0.014), and reduced the risk of progression to severe HF by 36% (p<0.03).

In the Acute Infarction Ramipril Efficacy (AIRE),[121] patients with evidence of HF after MI were assigned to either ramipril (5mg twice a day) or placebo. Ramipril significantly reduced the risk of death (RR 0.73; 95% CI 11-40, p=0.002) and the risk of the composite endpoint of death, reinfarction, severe HF or stroke (RR 0.81; 95% CI 5-31, p=0.008).

The Trandolapril Cardiac Evaluation (TRACE) study,[122] randomised patients who had a MI with evidence of left ventricular systolic dysfunction (LVSD) to receive trandolapril (4mg/ day) or placebo. This study demonstrated that trandolapril reduced mortality by 22% (95% CI 0.67-0.91, p=0.001) and there was a 25% (95% CI 0.63-0.89, p=0.001) reduction in the risk of cardiovascular mortality. The relative risk reduction of recurrent MI was not significant (RR 0.86; 95% CI 0.66-1.13, p=0.29).

The effect of an ACEI post-MI in patient without HF or LVSD was assessed in the GISSI-3 trial.[123] In this trial approximately 20000 patients were assigned to receive lisinopril (10mg/day or open control for 6 weeks follow up). Lisinopril was associated with a significant reduction in overall mortality (OR 0.88; 95%CI 0.79-0.99).

In the ISSI-4 trial [124] patients were randomised to captopril at a target dose (50mg twice a day) or placebo. Treatment was initiated within the first 24 hours post MI. Captopril reduced mortality by 7% in the first five weeks.

In a randomised double blind trial,[125] patients who had experienced MI and complicated by HF or left ventricular dysfunction were randomised to receive valsartan (angiotensin receptor blocker "ARBs"), or captopril (ACEI), or both drugs. Patients were approximately followed up for 24 months. This study showed that valsartan is as effective as captopril in patients with high risk of cardiovascular events post MI. Compared to the captopril group, the hazard ratio [HR] for all causes of death in the valsartan group was 1.00 (97.5% CI 0.90-1.11; p=0.98). Furthermore, there was no difference in the mortality rate due to cardiovascular cause, reinfarction, or hospitalisation due to HF (p=0.2).

Lipid Lowering drugs – "Statins"

Dyslipidaemia is one of the major modifiable risk factors that increases the risk of CHD.[126] Improvement in CHD mortality and morbidity was demonstrated in several clinical trials.[119]

The Scandinavian Simvastatin survival study (4S) [127] included 4444 men and women with angina or acute MI who had elevated cholesterol concentrations (5.5-8.0 mmol/L). Patients were randomised to receive placebo or simvastatin (20mg/day). Simvastatin reduced all-cause mortality (HR 0.70; 95% CI 0.58-0.85, p=0.0003). Simvastatin also reduced the risk of major coronary events including coronary death, non-fatal MI, silent MI, or resuscitated cardiac arrest (HR 0.66; 95% CI0.59-0.75, p<0.0001).

The long-term intervention with pravastatin in ischemic disease (LIPID) study,[128] assessed the effect of pravastatin (40mg/ day) in reducing mortality in patients with CHD (acute MI or hospitalisation due to unstable angina). In a double-blind randomised design study, 9014 patients were followed up for six years. Patients' cholesterol levels ranged from 4-7 mmol/L and they all had a history of MI or hospitalisation for unstable angina. The primary end point was mortality from CHD. The relative risk reduction of death due to CHD with pravastatin was 24% (95% CI 12-35; p < 0.001), and for all-cause mortality was 22% (95% CI 13-31, p < 0.001).

The Cholesterol And Recurrent Events (CARE) [129] study recruited 4159 patients (3583 men and 576 women) post-MI who had a plasma total cholesterol level below 6.2 mmol/L and LDL levels of 3-4.5 mmol/L. Patients were randomised to pravastatin (40mg/ day) or placebo. The primary end point, which was a fatal coronary event or a nonfatal MI, occurred in 10.2% of the pravastatin group and in 13.2% of the placebo group, an absolute difference of 3% and a 24% relative reduction in risk (95% CI 9-36, P = 0.003).

Summary

CHD is a major public health problem and constitutes the majority of mortality due to cardiovascular diseases. A number of pharmacotherapies have been shown to reduce morbidity and/or mortality in patients and are therefore recommended in guidelines published by the major cardiovascular societies and guideline groups.[105,107,119,130]

1.3.3 Peripheral arterial disease (PAD)

1.3.3.1 Evidence based pharmacotherapy in secondary prevention in PAD

In the management of PAD the control of atherosclerotic risk factors is important to slow progression. As PAD is associated with further cardiovascular events such as MI and stroke the goal of pharmacological therapy in PAD is to reduce the risk of a further CVD event as well as reducing the risk of death.[131,132]

Pharmacological treatment of intermittent claudication

One of the aims of the treatment of PAD, particularly in those with intermittent claudication, is to improve a patient's quality of life. A number of drugs are said to improve symptoms and these include cilostazol, naftidrofuryl and pentoxifilline.

Cilostazol

Cilostazol is a 2-oxoquinolone derivative, selective inhibitors for the phosphodiesterase III with antiplatelet, vasodilator and antithrombotic effects. It is mainly used for PAD to improve walking distance. It is contraindicated in patients with HF, and can cause tachycardia and palpitations as side effect.[133]

Four randomised controlled trials have demonstrated that walking distance in patients with intermittent claudication improved when they were treated with cilostazol.[134-137] Walking distance improved with cilostazol from 40% to 60% compared with placebo after 12 to 24 weeks of treatment.[135,136] A meta-analysis of six trials which compared cilostazol to placebo showed that maximal treadmill walking distance improved significantly among cilostazol group ($p<0.0001$).[138] A meta-analysis of 8 randomised placebo control trials showed that cilostazol significantly ($p<0.05$) improved the maximal walk distance by 50% and pain-free by 67% compared to placebo.[139]

Naftidrofuryl

Naftidrofuryl is a vasodilator drug use to improve walking distance in patients with intermittent claudication. It is a selective serotonin "5HT2" receptors antagonist in the smooth muscle cell which may lead to vasodilation in the peripheral circulation.[140,141]

Naftidrofuryl has been shown to improve pain-free treadmill walking distance, however the maximum distance does not improve.[142-144] A meta-analysis of five studies with a total

of 888 patients showed that naftidrofuryl significantly ($p<0.002$) increased pain-free walking distance by 26% compared to the placebo.[145]

Pentoxifilline (Oxpentifylline)

Pentoxifylline acts through increasing red blood cell flexibility which may contribute to improving blood flow via blood vessels, also decreasing the potential of platelet and thrombus formation.[146]

In a meta-analysis pentoxifilline showed no significant effect compared to the placebo in increasing maximal treadmill walking distance. Therefore its clinical effectiveness in the management of intermittent claudication is considered marginal.[147,148]

Angiotensin converting enzyme inhibitors (ACEI)

ACEIs have been widely studied in CHD but they also reduce morbidity and mortality in patients with PAD. The Heart Outcomes Prevention Evaluation (HOPE) study[149] demonstrated that ramipril reduced the risk of MI, stroke or cardiovascular mortality in patients with symptomatic PAD by approximately 25%.[148,150] The double blind ongoing telmisartan alone and in combination with ramipril global endpoint trial (ONTARGET),[151] randomised patients who were at high risk of vascular events, including PAD, to telmisartan (ARBs), ramipril (ACEI) or both drugs. The difference between the two groups was not significant for the primary outcome including cardiovascular death, MI, stroke, or hospitalisation due to HF (RR 1.01; 95% CI 0.94-1.09, p=0.83).

Beta blocker

β-blockers have been shown in many randomised trials to reduce the risk of death due to CVD. However, it is considered to be controversial to prescribe a β-blocker for patients with PAD.[152,153] This issue arose after a number of case reports that use of β-blockers worsened claudication.[154] There is no evidence from randomised trials showing that β-blockers negatively affect walking distance in patients with PAD. In contrast, a few randomised trials were conducted and showed that β-blockers had no affect on walking distance.[153,155] Eleven randomised control trials were combined in a meta-analysis.[152] It demonstrated that β-blockers are not associated with worsening walking distance or symptoms of intermittent claudication in patients with mild to moderate PAD. A meta-analysis of 6 randomised control studies found that β-blockers (atenolol, propranolol, pindolol and metoprolol) did not adversely affect walking distance in patients with intermittent claudication.[156]

Lipid Lowering drugs – "Statins"

Lipid lowering therapy, mainly through statins, has been shown to reduce the onset of PAD and reduce vascular events in those with PAD. In the Scandinavian Simvastatin Survival Study (4S)[157] simvastatin reduced the frequency of new intermittent claudication in patients post-MI or with angina from 3.6% for placebo to 2.3% with simvastatin. [148,158] Furthermore, compared to patients who received a placebo, simvastatin was associated with lower relative risk of new or deteriorating intermittent claudication (RR 0.6; 95%CI 0.4-0.9).[147,159] The Heart Protection Study (HPS)[160] randomised a wide range of patients with CVD, including those with PAD, to either simvastatin or placebo. Simvastatin was associated with 22% relative risk reduction (95% CI 15-29, $p<0.0001$) in vascular events (non-fatal MI, coronary death, stroke, coronary and non-coronary revascularisation) in the subgroup of individuals with PAD.

Antiplatelet therapy

Antiplatelet therapy reduces the risk of thrombus formation which consequently reduces further vascular events including PAD. In large randomised controlled trial, aspirin alone or in combination with dipyridamole reduced progression of established PAD.[161] A systematic review of randomised controlled trials demonstrated the efficacy of antiplatelet drugs in high risk patients. Among patients with PAD, antiplatelet drugs reduced the risk of serious vascular events (non-fatal MI, non-fatal stroke, or vascular death) by 23% ($p=0.004$).[150,162] In the subgroup analysis of the CAPRIE trial,[110] clopidogrel was more effective than aspirin in reducing ischaemic events in patients with symptomatic PAD, a relative risk reduction of 23% (95% CI 8.9-36.2, $p=0.0028$).

Summary

In the secondary prevention of CVD in patients with PAD, ACEI/ARBs, β-Blockers, statins and antiplatelet agents are all recommended. Cilostazol and naftidrofuryl are recommended to reduce intermittent claudication symptoms in those with PAD.

Summary

A large number of clinical trials and meta-analyses have examined the use of a number of pharmacotherapies to reduce morbidity and/or mortality in patients with MI, angina and PAD. While each of these diseases occurs as a result of atherosclerosis of the arteries, not all drugs reduce morbidity and mortality in all groups. However, a consistent group of antiplatelet agents, β-blockers, ACEI/ARBs and statins emerges from the evidence. This combination of drugs is a core set of drugs that patients with angina, post-MI or with PAD should be taking. I will now go on to explore the pharmacoepidemiology of each of these drugs in patients with angina, post-MI or PAD.

1.4 Adherence and compliance

"Compliance" "adherence" and "concordance" are the three different terms used to describe the patient behaviours in using their medications after a diagnosis with a chronic disease such as MI. Following closely and correctly all the therapeutic indications prescribed by health care providers such as physicians is known as compliance which eventually means "the extent to which patients are obedient and follow the prescriber's recommendations".[163-165] To be defined as a "compliant patient", the patient has to accurately follow the directions for taking the medication and should adhere to any special instructions provided by the prescriber and/or pharmacist. The compliant patient takes medication at the appropriate strength, in the correct dosage form, at the requested time of day and night within the proper interval for the treatment period. Medication adherence, however, reflects an agreement between patient and prescriber (such as health care providers). This agreement mainly sets out the recommendations by the prescriber in terms of the extent to which patients take medications, the way that is agreed upon in the treatment plan.[165-167] As "compliance" suggests that the patient is passively following the prescriber's orders and that the treatment plan is not based on a therapeutic alliance or contract established between the patient and the physician, the word "adherence" is preferred by many health care providers.[165] The patient's agreement to the recommendations is an essential requirement in adherence which is not the case in compliance.[168] "Concordance", is a fairly recent term used in the UK and it is sometimes incorrectly used as a synonym for adherence. The definition of this term has changed over time from one which focused on the consultation process (where therapeutic decisions are agreed between a doctor and patient incorporating the latter's views) to a more detailed concept which includes patient support in medicine taking.[164]

A number of behavioural and system factors influence a patient's adherence to therapy. Living alone, low socioeconomic status, higher number of medications taken, higher medication costs, lack of prescription drug coverage by insurance plans in other health care systems, higher number of physicians caring for a patient, depression, cognitive impairment, treatment of asymptomatic disease, side effects of medications, complex treatment regimens, and financial issues have been considered as risk factors for poor adherence. Moreover, some other common modifiable predictors of poor adherence have been identified. These include treatment complexity, polypharmacy, cost and duration of medication regimen (for acute conditions).[165,169-172] These factors are all pertinent for

patients with CVD who are often elderly, with multiple comorbidities and are prescribed many medications for the rest of their life.

In developed countries, an average of 50% adherence to therapies has been described by extensive reviews of the literature.[168,173,174] Patients with CVD are commonly non-adherent to medications. In their study, Jackevicius *et al.*[175] found that approximately 24% of patients did not even fill their cardiac medications by day 7 of discharge following an acute MI. Furthermore, one study found that within one month around 34% of patients discharged after a MI had stopped at least one of their prescribed aspirin, statin or β-blocker and 12% had stopped all three medications.[175,176] These findings have been replicated by others, Newby *et al.*[177] reported that at 6-9 months after a diagnosis of CHD, only 71% continued to take aspirin, after a MI less than half of patients (46%) continued to take β-blockers, 44% lipid-lowering agents, and only 21% took all 3 medications. In another study, only 40% of patients have been shown to continue taking statins two years after a hospitalisation for acute coronary syndrome.[176,178]

Due to the serious consequences of poor adherence to long term therapies, it is an important issue in the management of chronic conditions. The consequences include worsening of the underlying disease, higher mortality, and greater health care costs.[165,167-169] Although many causes have been identified for non-adherence, they generally fall into two categories: intentional and unintentional. Unintentional non-adherence occurs when some barriers, that are beyond the patient's control, prevent patients from following the agreed treatment plan. Examples of these include instructions which are difficult to understand, poor recall of instructions or medication plan, problems with using the treatment such as physically administering the medication e.g. coordinating using a spray or inhaler, cost, or simply forgetting to take it. Intentional non-adherence, however, occurs when the patient deliberately decides not to follow the treatment recommendations.[166]

Medication adherence can be assessed by direct and indirect methods. In direct methods, patients can be observed in terms of taking medications, "direct observed therapy", and drug or metabolite concentrations and biological markers can be measured in the blood or urine. For some drugs, using the direct methods is a satisfactory and commonly used means of assessing adherence. For instance, the serum concentration of antiepileptic drugs such as phenytoin or valproic acid can be assessed using these methods as subtherapeutic

levels will probably reflect poor adherence or suboptimal dose strengths.[165] The drawbacks of direct methods include costs and susceptibility to distortion of samples by the patient.

In indirect methods, however, patients can be asked about the ease of taking their prescribed medications, or their diaries can be reviewed. In addition, the indirect methods can utilise prescription refill rates, pill counts, assessing clinical response, monitoring for clinical response, electronic monitoring devices, and collecting patient questionnaires, scales or surveys.[165,167] The most common method used to measure adherence is pill counts which involve counting the number of pills that remain in the patient's medication bottles or vials. This method is simple but it carries some drawbacks. For instance, medicines can be switched between bottles and pills can be discarded by patients before visits to demonstrate adherence to the treatment regimen. For these reasons, the reliability of this method is questionable and this technique should not be considered as a satisfactory tool for measuring adherence.[179-182]

In a health care system where there is no cost barrier to prescriptions (e.g. the NHS in Scotland or the Department of Veterans Affairs Health Care System in the USA, or other countries with universal drug coverage), rates of refilling of prescriptions has been considered as an accurate measure of overall adherence. Measuring the cashing of prescriptions at several points in time, however, is an essential factor for the reliability of this method.[183-185] Readily available objective information on rates of refilling prescriptions can be obtained by using a medical system that utilises electronic medical records. In addition, patient's responses to direct questions or on questionnaires can be corroborated using this method.

The time of opening bottles, dispensing drops (as in the case of glaucoma), or activating a canister (as in the case of asthma can be precisely recorded by electronic monitors. These expensive techniques have been used for approximately 30 years.[182,186-188] A precise and detailed insight into patients' behaviour in taking medication can be obtained by these indirect methods of measuring adherence. Although this approach provides the most accurate and valuable data on adherence in difficult clinical situations and in the setting of clinical trials and adherence research, it, however, does not document whether the patient actually ingested the correct drug or correct dose.[189,190] For instance, the data may be invalidated by opening a container and not taking the medication, taking the wrong amount

of medication, placing the medication into another container or taking multiple doses out of the container at the same time.

Adherence and compliance are therefore a major issue in CVD but difficult to accurately quantify in routine practice and therefore overcome. Using pill boxes and calendars are some of the more basic methods that have been used to improve adherence. Patient education and outreach are the most effective methods of improving adherence.[191,192] Giving free access to medications can help to a certain degree[193] but non-adherence is still common in those countries with little or no cost medication.[194] Therefore, non-adherence remains an issue that will require concerted efforts to overcome. It must be borne in mind as I discuss prescribing trends that most studies report prescribed therapies and on the basis of studies quoted above the proportion actually taking the drug on a regular and ongoing basis will be lower.

2.0 The Prescribing of Evidence Based Pharmacotherapy in CVD

2.1 The risk-treatment paradox

The treatment of chronic diseases such as CVD has been determined by the results of multiple randomised controlled clinical trials. This evidence is collected and assessed by professional groups such as the European Society of Cardiology, the American College of Cardiology and American Heart Association, and collated into guidelines that summarise the evidence into a form accessible to clinicians.[195] These guidelines make recommendations as to what medications should be prescribed in various conditions. Adherence to these guidelines is associated with better outcomes.[195] It has been demonstrated in numerous studies that the absolute benefits of evidence based therapies are highest in the patients at highest risk of morbidity and mortality. Patients may be at higher risk due to the presence of comorbidities, age and disease related factors e.g. size of a MI.[196] Therefore, more aggressive intervention may be needed in the highest-risk patients.[197] However, multiple studies have shown that these high-risk patients are less likely to receive appropriate medications and therapies to reduce risk and if they do receive them they may do so at a lower dose.[198-201] This phenomenon is referred to as the "risk-treatment paradox".

The risk-treatment paradox has been consistently described.[198,202,203] McAlister *et al.*[198] reviewed 3871 patients diagnosed with CHD by coronary angiography at three cardiac centres in Alberta between February 2004 and December 2005 and defined them as being at low, medium or high risk on the basis of coronary anatomy. They reported that high risk patients were less likely to be prescribed ACEI, 44.5% high risk vs. 55.6% low risk (OR 0.64; 95% CI, 0.51-0.81). Even after adjusting for sociodemographic factors the risk-treatment paradox was still evident (OR 0.66; 95% CI, 0.52-0.84).

Some factors such as older age, greater likelihood of comorbidities, and later presentation after symptom onset have contributed to this risk-treatment paradox in women.[202] However, as noted, even eligible patients are at risk of the risk-treatment paradox. In general, clinicians preferentially initiate treatment in low-risk individuals compared to higher risk patients. Clinicians tend to overestimate risks of preventative treatments and underestimate the benefits of preventative treatments.[204,205] This difference is thought to be partly responsible for the risk-treatment paradox.[198,200,206-210] Therefore creating and

adhering to guidelines may be one method by which to reduce this paradox and evidence suggests that involvement in guideline initiatives may reduce the paradox.[211]

The risk-paradox remains important for clinicians and patients but also for researchers. For clinicians and patients, avoiding the paradox is crucial as absolute benefits of therapy are greatest in those patients at the highest baseline risk. For researchers, drawing conclusions about treatment effects on the basis of associations between treatment and outcomes needs to be done with care in observational data as the risk-treatment paradox is an important confounder in these studies.[199]

2.2 Literature search

This literature review examines the pharmacoepidemiology of each of the therapies used in the prevention and treatment of MI, angina and PAD. I will focus on studies describing the prescribing inequalities of EBTs after MI, angina, PAD for sex, age, socioeconomic status and comorbidities. Furthermore, I searched for literature surrounding the trends in prescribing of EBTs. Search dates were not restricted to ensure that all articles describing trends over time were found.

The following databases were searched: Medline, EMBASE, Web of Knowledge and Google scholar (which searches conference proceedings). The search strategy was constructed using different key words including evidence based therapies, factors, prescribing, diseases and comorbidities, the full search strategy is given in Appendix 1. Appropriate synonyms were also used, for example gender, male, female, men and women were all used when searching for literature on sex differences. The grey literature was searched using the terms “prescribing inequalities”, or “prescribing trends” and MI, angina or PAD. Studies that examined invasive therapy such as percutaneous coronary intervention (PCI) and that did not include pharmacological therapy were excluded. A secondary search from the reference list of selected papers was reviewed and citation checks carried out to identify more related articles. Abstracts were excluded as a full assessment of the methods and potential biases of observational data is not possible for the limited information of an abstract. The literature search strategy was checked by the Medical, Veterinary and Life Science (MVLS) librarian. The number of studies that were identified and excluded at each stage of the review are presented in a flow diagram in Appendix 2. The reporting quality of observational studies was assessed using the Strengthening the Reporting of Observational studies in Epidemiology (STROBE). The

STROBE statement checklist consists of 22 items in a paper on epidemiological studies and defines appropriate reporting details. The statement covers reporting of results and also other aspects such as the title, abstract, introduction, methods and discussion. In this study the STROBE statement was used to assess each reviewed study and a score out of 22 was calculated for each study report. This score and assessment forms the basis for the discussion about the methods and results of the studies found in the literature review.

2.3 Evidence based therapies (EBTs)

Evidence based medicine has been defined as a conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.[212] Part of this decision making process is selecting appropriate pharmacotherapies that have been shown to improve outcomes in randomised clinical trials. While prescribing of evidence based therapies (EBTs) has improved over time, many studies suggest that there is suboptimal use of these medications among patients diagnosed with CHD and PAD. The prescribing of EBTs is influenced by many factors. A number of studies have demonstrated that inequalities in prescribing exist. I will discuss the literature examining differences in prescribing of EBTs for CHD, MI, angina and PAD by age, sex, socioeconomic status, calendar year and the presence of comorbidities.

2.4 Inequality in prescribing of EBTs for CHD

2.4.1 Inequalities by age in prescribing of EBTs for CHD

Unadjusted analyses

A number of studies demonstrated that older patients with CHD are less likely to receive EBTs for secondary prevention. This association has been reported in different studies from a number of countries (Table 1, unadjusted studies). The majority of unadjusted analysis studies reported that older people are less likely to be prescribed EBTs for secondary prevention. Three studies reported that aspirin was prescribed more frequently for younger patients.[213-215] However, one small study[214] reported that older women were more likely to be prescribed aspirin than younger women (66.7 vs. 51.9%), suggesting an interaction between age and sex. This interaction, however, was not confirmed, as no statistical analyses were carried out. The majority of unadjusted studies reported that older patients were more commonly prescribed ACEIs or ARBs than younger patients.[213-216] Prescription rates for β-blockers were generally higher among younger than older patients. However, one study[214] of 802 patients reported that older patients were prescribed β-

blockers more often than younger patients (80.4 vs. 79.8%, for men, 88.9 vs. 59.3%, for women), with this sex difference again suggesting an interaction. Statins were more often prescribed for younger than older patients.[214-218] Few studies examined age inequalities in prescribing of CCBs. Two unadjusted studies reported that CCBs were more commonly prescribed for older patients.[214,215] Two studies reported that older patients were more often prescribed nitrates than younger patients.[213,214]

Adjusted analyses

Age related prescribing inequalities were also demonstrated in a number of studies in adjusted analyses. Younger patients were more likely to be treated with aspirin than older patients.[219-221] Two studies, however, have reported that older age was associated with a higher odd of being prescribed an antiplatelet agent (aspirin or clopidogrel) and aspirin alone.[222,223] The study by Salomaa *et al.*[224] was the only study to show that the prescribing of ACEI was higher in older patients compared with younger (odds ratio (OR) 1.19; 95% confidence interval (CI) 1.15-1.24). All adjusted analyses reported that β-blockers were more frequently prescribed for younger as opposed to older patients.[220,222-226] Younger patients were also more likely to be prescribed a statin.[221,223,226-229] In the only adjusted study examining the association between age and the prescription of CCBs, the authors have adjusted for sex only and found that older patients were less likely to receive CCBs (OR 0.86; 95% CI 0.77-1.00).[226]

A number of studies examined the relationship between age and the prescribing of EBTs following a diagnosis of CHD. In different observational study designs, the majority of previous studies agreed that older age groups were less likely to have received EBTs compared to younger age groups (Table 1). These studies, however, were limited by a number of factors including study design, data collection methods, and/or statistical methods.

Limitations in the reporting of the literature

The STROBE scores for literature that described the association between age and prescribing of EBTs ranged from 45% to 73% (Table 1). While study design was mentioned in the majority of abstracts, this wasn't the case in a few studies, where no study design was evident in the title or abstract.[215,224,226,227,229] Moreover, a number of studies did not clearly define the background, objectives, study design, methods results and conclusions in the abstract.[224,226,227,229] Authors should state clear specific objectives to

clarify what is to be achieved by the study, the rationale of the study design and methods, statistical analysis and results. While most studies stated their objectives clearly, three studies did not.[214,216,224] One study did not describe the study design in the methods.[223] Furthermore, a few studies did not describe those who participated in their studies, or did not clearly define the variables used or the data sources utilised.[213,216,227-229]

Potential bias is one of the most important factors that may influence the results of an observational study. The STROBE guidelines state that biases should be identified and reported. I will discuss the biases below but only one study[222] discussed potential sources of bias. Although a number of studies were associated with potential biases, the authors, however, did not describe them either in the methods or limitations.[221,224] Two studies poorly described the methods that they used to examine age-related association in prescribing EBTs.[227,228] Reid *et al.*[228] did not explain how the data on EBTs prescriptions were obtained and what were the variables of interest. DeWilde *et al.*[227] did not describe the study design clearly, and were not clear on how they obtained EBT prescriptions for analysis. In addition, most studies did not describe any sensitivity analyses, subgroup analyses, or interactions.

Five studies did not report the final number of eligible patients that were included in theanalyses.[214,216,218,223,228] The characteristics of patients included were not described in four studies, making it hard to judge the generalisability of the results.[215,221,226,229] A clear and full presentation of outcomes including unadjusted results and results adjusted for potential confounders can significantly help the reader to compare and judge the magnitude and direction of the influence of the confounders. In seven studies, this was not performed and no confounders were included.[213,216,222,223,225,226,228] Finally, a number of studies failed to recognise and discuss their limitations.[214-216,221,223,225]

Limitations in the design and analysis of studies included in the literature review

Observational studies are associated with a number of potential sources of bias. Bias in observational research is a systematic deviation or error that can influence the validity of the results.[230,231] It can occur at any stage of the research including study design, data collection, patient recruitment and data analysis. Different types of biases are often found in observational studies including selection bias, observer or measurement bias, recall bias, and for systematic reviews and meta-analyses, publication bias.[232,233] Three studies were limited by recall bias as prescribing of EBTs was obtained from patient self-

reporting.[214,219,228] Furthermore, patient's self-reporting of a diagnosis of CHD occurred in two studies.[219,228] Self-reporting is less accurate than electronic records as it depends on a patient's memory to recall information and it is therefore potentially biased, as under-reporting may occur.[232,233] Thus, data obtained from electronic records or case notes should be more accurate than self-reported data. Four studies were limited by selection bias.[221,222,224,225,227] Selection bias occurs if there is a systematic difference between the subjects enrolled in a study and those who were not.[233] The sample is therefore unrepresentative of the patient population in general. For instance, Salomaa *et al.*[224] excluded patients who died within 180 days, which could lead to a survivor bias and selection of healthier individuals, on average, compared to the entire cohort who may have been more likely to be prescribed EBTs. Similarly, Mathour *et al.*[222] excluded patients who did not tolerate drugs, therefore potentially excluding sicker patients. DeWilde *et al.*[227] selected 142 out of 300 primary care practices that participated in a specific reporting programme, with a potential overestimation in prescribing as patients were already in self-selected practices that were more likely to have higher prescribing standards.

All previous studies were conducted using primary care data sets, secondary care data sets, or single hospital study. Stable angina is commonly diagnosed in a primary care setting based on patients' presentation. This therefore might lead to the fact that diagnosing angina in primary care is less valid when compared to diagnosing this medical condition in a hospital setting. PAD is often diagnosed in primary care whereas MI is rarely first diagnosed in primary care and most often presents to secondary care as an emergency (excluding those who die suddenly). Therefore using primary care records to identify those with MI may lead to under ascertainment bias.[224,227]

A number of studies were limited by the validity of the diagnoses of CHD. A number of studies identified patients diagnosed with angina based on whether the patient was receiving a prescription for nitrates and aspirin prescriptions.[215,226,229] Although these drugs are commonly used for CHD, they also can be prescribed for other conditions where the EBTs examined may not be indicated, thus potentially underestimating the prescribing rates of EBTs.

Potential confounders including socioeconomic status, comorbidities, age and sex can influence the prescribing of EBTs. They could influence the association between the exposure and the outcome. This, therefore, will result in unadjusted results being less

reliable compared to adjusted results. Although it is well known that socioeconomic status is associated with poorer health outcomes and prescribing of EBTs, only three studies, however, adjusted their analyses for socioeconomic status.[219,222,223]

A number of other limitations were also identified in the literature. For example studies were limited to examining one or two EBTs only.[219,227] Although this may not affect a study's quality, examining prescribing for more EBTs provides a more complete overview of how drugs are prescribed after a particular diagnoses. Using a general drug class such as "lipid lowering drugs" may lead to overestimation of prescribing for recommended secondary prevention drugs such as statins by including drugs that are not indicated or less recommended such as fibrates. Three studies grouped "lipid lowering" drugs including statins to examine in the association between age and prescribing of EBTs.[213,222,224] Finally, a number of studies limited their analyses to specific age categories such as those over 64 years or those less than 75 years of age, limiting the generalisability of the results.[215,221,225,226,229]

In summary, there were a number of limitations in the literature surrounding the association between age and the prescribing of EBTs in CHD. There was also a wide range in the quality of reporting of studies as assessed by the STROBE guidelines. A few studies achieved a quality score of over 70%. These studies, however, were associated with a number of limitations that have already been discussed above such as selection bias and small sample size. Although the studies by Salomaa *et al.*[224] and Simpson *et al.*[223] were not the best reported studies, they did have a number of strengths over other studies such as adequate sample size, a long period of study, wide range of medications and analyses adjusted for different confounders. Despite the limitations of the literature, these studies demonstrated that older patients are generally less commonly prescribed most EBTs than younger patients.

Table 1 Inequalities by age in prescribing of EBTs for CHD

Study	Design /year	Age range/subject	Prescribing	Medications	Prescribing percentage Eldest vs. youngest age group	OR, 95% CI Old vs. young	Adjustment	P values / statistical significance	STROBE Score (%)
Williams et al[215]	Cross-sectional	>65 vs. ≤ 65	From national primary care prescribing data (GMS	ACEI Aspirin β-blockers Statins CCB	Not reported	1.51 (1.41-1.63) 0.92 (0.85-0.99) 0.66 (0.62-0.71) 0.50 (0.46-0.53) 1.14 (1.10-1.20)	Unadjusted	Not reported <0.001 <0.001 <0.001 Not reported	12/22
Ireland	1999-2000	N=15590							(54%)
Maggioni et al[218]	Longitudinal cohort	<50 50-59 60-69 70-79 ≥ 80	Discharge records (administrative data sets)	Statins	Not reported	1.00 1.38 (0.78-2.46) 1.21 (0.72-2.04) 0.82 (0.50-1.36) 0.28 (0.17-0.47)	Unadjusted	Not reported	14/22 (64%)
Italy	Jan-June 2007	N= 3078							
Lee H Y et al[217]	Longitudinal cohort	<40, 45-64, ¶ 65-79, ≥ 80	Following patients prescription for 3 months	ACEI/ARBs β-blockers Statins	Not reported	0.47 (0.28-0.78) 0.25 (0.15-0.42) 0.27 (0.17-0.45)	Unadjusted	0.003 P<0.001 P<0.001	14.5/22
USA	2003-05	N=1135							(68%)
Bischoff et al[216]	Cross-sectional survey	18-34,35-44,45-54 ¶,55-64,65-74, ≥ 75	Primary care datasets	ACEI‡ ARBs β-blocker statins	54 vs. 52 20 vs. 18 50 vs. 68 38 vs. 54	Not reported	Unadjusted	Not reported	10/22 (45%)
		N=6969	men						
			Women	ACEI‡ ARBs β-blocker statins	48 vs. 42 17 vs. 15 45 vs. 55 34 vs. 39				
Germany	NA								
Michou et al[214]	Longitudinal cohort	<30, 30-64 ¶, 65-74 & ≥ 75	Patient reported	ACEI ARBs Aspirin β-blockers CCB Clopidogrel Nitrates Statins Warfarin	29.4 vs. 32.1 8.80 vs. 5.4 68.6 vs.70.0 80.4 vs. 79.8 15.7 vs. 14.3 3.90 vs. 14.9 60.8 vs. 26.2 68.6 vs. 73.8 29.4 vs. 13.1	Not reported	Unadjusted	Not reported	13/22 (59%)
		Men=581							
Finland	2001-04	Women=221		ACEI	18.5 vs. 22.2				

				ARBs Aspirin β-blockers CCB Clopidogrel Nitrates Statins Warfarin	17.6 vs. 13.3 66.7 vs. 51.9 88.9 vs. 59.3 29.6 vs. 13.9 7.40 vs. 8.30 70.4 vs. 18.5 55.6 vs. 85.2 7.40 vs. 10.2				
Ferrari et al[213] **Multi-national**	Prospective Longitudinal cohort Nov 2009-July 10	<65, 65-74, ≥ 75 Men N=33280 Women	Confirmed by physician (outpatients clinic)	ACEI ARBs Aspirin β-blockers LLD Long nitrate ACEI ARBs Aspirin β-blockers LLD Long nitrate	47.0 vs. 55.5 29.0 vs. 22.1 79.2 vs. 91.5 68.4 vs. 78.4 90.2 vs. 94.2 26.8 vs. 19.1 39.6 vs. 49.7 38.5 vs. 27.3 82.8 vs. 89.1 69.1 vs. 77.9 88.5 vs. 90.9 30.1 vs.23.5	Not reported	Unadjusted	Not reported	14/22 (64%)
Salomaa et al[224] **Finland**	Longitudinal cohort 1995-2003	35-64 65-74 N=53353	Within 3 months post discharge, 1st CHD	ACEI β-blocker LLD	Not reported	1.19 (1.15-1.24) 0.77 (0.74-0.81) 0.55 (0.53-0.58)	Sex, study year, diabetes status and university hospital district	Not reported	13.5/22 (61%)
Reid et al[228] **UK**	Cross-sectional 1998	<65 , 65-74 ≥ 75 N=760	Confirmed by patients	Statins	Not reported	0.75 (0.38-0.85) 0.11 (0.06-0.21)	Sex	Not reported	11/22 (50%)
Simpson et al[223] **Scotland**	Cross-sectional 1997-2002	<55, 55-64 65-74, ≥ 75* N=14453	Data obtained from GP records CMR	ACEI Antiplatelet β-blocker Statins	Not reported	0.8 (0.7-0.9) 1.8 (1.6-2.0) 0.5 (0.4-0.6) 0.3 (0.3-0.4)	Sex, deprivation, diabetes, hypertension, heart failure, and practice differences	Not reported	13/22 (59%)
Schoenenberger et al[220] **Switzerland**	Prospective Longitudinal cohort 2001-2006	<55, 51-60, 61-70, 71-80 & ≥ 81 N=11930	At hospital	Aspirin β-blocker Clopidogrel	87.2 vs. 96.7 60.0 vs. 78.5	0.97 (0.96-0.98) 0.98 (0.98-0.99)	Sex, comorbidities, and Killip class	p<0.001 p<0.001	
Teeling et al[229] **Ireland**	Cross-sectional Jan1998-Dec 2002	< 65 vs. ≥ 65¶ N=344000	Post discharge	Statins	Not reported	2.16 (2.07-2.25)	Sex	Not reported	10/22 (45.5%)

Mathur et al[222] **UK**	Cross-sectional 2009-10	35-44, 45-54, ¶ 55-64, 56-74, 75-84, ≥ 85 N=10933	Collect the last drug record in the GP	ACEI/ARBs Aspirin β-blockers LLD	68.2 vs. 75.4 86.7 vs. 87.3 66.7 vs. 80.0 84.3 vs. 92.8	0.75 (0.63-0.90) 1.20 (0.91-1.59) 0.60 (0.48-0.74) 0.45 (0.34-0.60)	Sex, ethnicity, deprivation, comorbidity, drug exclusion	Not reported	15.7/22 (73%)
DeWilde et al[227] **England & Wales**	Not clear 1998	35-44, 45-54, 55-64 ¶, 56-74, 75-84 N=30448	Prescribing data from GP	Statins	10.4 vs. 43.8	0.16 (0.15-0.18)[+]	Sex, regional health authority, time since diagnosis, smoking status	Not reported	11.5/22 (53%)
Kassab et al[225] **Malaysia**	Cross-sectional 2009-10	≥ 65 vs. <65 N=380	Clinical records for discharge medications 1st CHD	β-blockers	Not reported	0.39 (0.17-0.88)	Sex, CHD subtype, diabetes, hypertension, hyperlipidaemia, current smoking, previous MI, CABG, PCI	0.02	13.5/22 (60%)
Vermeer et al[221] **Australia**	Cross-sectional 4 months Jan-April 2007	>65 vs. ≤ 65 N=169	At discharge from medical records database 1st CHD	ACEI/ARBs Aspirin/clopidogrel β-blockers	Not reported	0.28 (0.11-0.70) 0.19 (0.07-0.54) 0.35 (0.14-0.89)	Sex, CHD type, diabetes, hypertension, current smoking, MI, CABG, PCI	0.007 0.028 0.002	16/22 (72%)
Opotowsky et al[219] **USA**	Cross-sectional 2000-02	<65, 65-74¶ >75 N=1869	Confirmed by patients	Aspirin	Not reported	0.74 (0.54-1.01)[§]	Sex, insurance status, education level, ethnicity, demographic, diabetes, MI, asthma, hypertension	Not available	17/22 (77.7%)
Usher et al[226] **Ireland**	Cross-sectional January-December 2001	65-69, 70-74 ≥ 75 N=9124	From national primary care prescribing data (GMS)	ACEI ARBs β-blocker CCB Statins	Not reported	0.99 (0.89-1.12) 0.83 (0.64-1.07) 0.57 (0.51-0.64) 0.86 (0.77-1.00) 0.34 (0.31-0.39)	Sex	Not significant Not significant <0.0001 Not significant <0.0001	11/22 (50%)

* presented OR is only for patients over 75 for year 2002, ¶= reference, + Unadjusted OR 0.15 (0.14-0.16), §=after excluding patients with contraindication 0.58 (0.38-0.88), ‡ All results were approximated from the figure and first raw for men and the follow raw for women, ‖ patients with contraindication for each drug were excluded from the analysis. GMS=General Medical Services scheme, LLD=Lipid lowering drugs, CABG=Coronary artery bypass graft, PCI=Percutaneous coronary intervention, AF=Arterial fibrillation, PAD= peripheral arterial disease, DM=diabetes mellitus, CKD=chronic kidney disease, COPD= chronic obstructive pulmonary disease, PUD=peptic ulcer disease, GERD= gastro-esophageal reflux disease, ADR=adverse dug reaction, LVEF= Left ventricular ejection fraction, PTCA= Percutanous transluminal coronary angioplasty

2.4.2 Inequalities by sex in prescribing of EBTs for CHD

Unadjusted analyses

Sex inequalities in prescribing of EBTs have been reported in several studies (Table 2, unadjusted studies). It has been reported that men are more likely to receive a range of EBTs than women.[234-237] In unadjusted studies the prescription of EBTs including aspirin, ACEI/ARBs, β-blockers, statins, clopidogrel, and warfarin was more frequent in men.[217,218,238-241] Only one cohort study of patients with a history of CHD reported an opposite trend though it was not statistically significant.[214]

Adjusted analyses

In multivariable adjusted analyses, five studies reported that women were less likely to be prescribed aspirin than men.[215,219,222,242,243] After excluding patients with a contraindication for aspirin, the difference was attenuated though women remained significantly less likely to receive aspirin (OR 0.68; CI 95% 0.48-0.97, p=0.002).[219] Use of ACEI or ARBs was higher among men compared to women in most studies.[215,222,223,226] However, three studies found no statistically significant difference in prescribing of ACEI by sex. Three of these studies, however, were limited by a small sample size.[243-245] In an age-adjusted analysis, women were significantly more likely to receive ARBs (OR 1.56; 95% CI 1.28-1.88, p<0.0001).[226] β-blockers were more likely to be prescribed for men than women.[215,222-224,226,243-245] Similarly, studies reported that men were more likely than women to be receiving a statin.[215,221,223,226-229,242-244,246,247] Two studies reported that women were more likely to receive statins, though one was not significant and the other was only adjusted for age.[226,244] Prescribing of CCBs was higher among women in one study (p=0.16).[245]

Although a number of studies examined differences in EBT use between men and women after a diagnosis of CHD, and reported that men are more likely to receive EBTs than women, particularly β-blockers and statins, there was wide variation in reporting. Due to the variation of the quality of the reporting in the studies the literature was also assessed using STROBE checklist.

Limitations in the reporting of the literature

A number of studies that reported sex inequalities have also been discussed in section 2.4.1 where they were discussed in relation to prescribing inequalities by age.[214,219,221-224,226-229] Therefore the limitations in reporting of the literature will only be discussed in relation to literature that was not discussed in section 2.4.1. The score for the literature that described

the association between sex and prescribing of EBTs after CHD ranged from 50% to the highest score 72% (Table 2).

One study did not report the study design either in the title or abstract,[243] although all other studies did. The abstract included and described the background, objectives, methods, finding and conclusion in all of the studies. All studies described a clear scientific introduction and specific objectives, with the exception of one study.[246] Different items should be included in the methods section including the study design. All studies reported their study design except the study by Doyle *et al.*[246] Eligibility criteria determine which patients are included in the analyses and these were not described in one study.[241] Studies' variables including exposure, outcome, predictors and potential confounders were not documented in two studies, making interpretation of the results difficult.[245,246] Doyle *et al.*[246] did not describe the medications and the diagnoses clearly, i.e. it is not clear whether the diagnosis was a new case or prevalent case, definite or suspected.

Observational studies can be subject to different potential sources of biases. To minimize this, the researcher, ideally, should explain for readers what measures have been taken. Different types of bias were identified in three of the previous studies[241,246,247], however, only one study explained and discussed those biases.[242] All studies described the sample size and subject recruitment. Studies reported the analysis methods and the type of tests that were used including adjustment for possible confounders, however, one study did not.[243]

The number of eligible patients included in the analyses was not mentioned in three studies.[238,241,243] Patient characteristics were not reported in two studies.[238,241] Moreover, three studies neither explained clearly their study outcomes nor did they report the number of outcomes.[238,242,246] The main finding is usually summarized briefly in the discussion section. All except one study discussed the main outcome measure in the discussion.[238] Although it is essential to report study limitations to identify any source of potential bias and confounding that could have affected results, four studies failed to discuss their limitations.[238,241,245,246] Two studies were limited by selection bias,[242,247] and one by recall bias.[241] Lack of interpretation and explanation of association between sex inequalities and prescribing of EBTs were identified in five studies.[240,241,242,245,247] Three studies acknowledged the financial support for their studies to allow for assessment of potential conflicts of interest.[241, 243, 244]

Limitations in the design and analysis of studies included in the literature review

A number of gaps were also identified in the previous literature. Since the prescribing of EBTs is the main focus of these studies, many of the previous studies were limited to one or two drugs.[219,221,227,228,229,240,242,246,247] One study included a wide range of EBTs to identify prescribing inequalities by sex. This study, however, was unadjusted and had a small sample size. Furthermore, this study obtained data about prescribing of EBTs from patient recall leading to "recall bias".[214] This bias was also identified in the study by Nilsson *et al.*[241] Two studies identified patients with CHD using nitrates and aspirin which may be insensitive.[215,226] Furthermore, these studies were only adjusted for age. Enriquez *et al.*[243] adjusted their results for various confounders and EBTs but this study examined prescribing in small sample sizes and did not report how prescriptions of EBTs were obtained. Also, the same study examined prescribing of EBTs based on a single hospital database.

In summary, there were a number of limitations in the literature surrounding the association between sex and prescribing of EBTs in CHD. There was also a wide range in the quality of reporting of studies as assessed by the STROBE guidelines. Although some studies were well reported, they were, however, associated with some limitations. Hippisley-Cox *et al.*[240] for instance, limited their analyses to unadjusted analyses, and used non-specific drug therapy. Ye Xin *et al.*[247] had a large sample size in their study and results were adjusted for potential confounders, but not deprivation and their study was limited to statins. Two studies were reported to a high standard and had a number of strengths over other studies.[223,244] These studies were adjusted for a wide range of confounders, included essential EBTs, and used a medical records database to obtain diagnoses and medications. The consistent message from these studies was that women are less commonly prescribed β-blockers. There were some conflicting results for other EBTs but in general women were less likely to receive EBTs than men.

Table 2 Inequalities by sex in prescribing of EBTs for CHD

Study	Design/year	subject	Prescribing	Medications	Prescribing percentage Women vs. men	OR, 95% CI Women vs. men	Adjustment	P values / statistical significance	STROBE Score (%)
Hippisley-Cox et al[240]	Cross-sectional	Women=2783	From GP records	Aspirin β-blockers	71 vs. 76 49 vs. 51	Not reported	Unadjusted	p<0.0001 0.14	15.5/22
England	Not reported	Men=3108		LLD	31 vs. 21				(70%)
Michou et al[214]	Retrospective cohort	Women=221	Obtained from patients	ACEI ARBs	20.4 vs. 32.9 12.4 vs. 6.90	Not reported	Unadjusted	p<0.001 Not significant	13/22
Finland	2001-04	Men=581		β-blockers CCB Nitrates Statins Aspirin Warfarin Clopidogrel	68.3 vs. 80.8 22.2 vs. 17.4 36.7 vs. 36.5 75.6 vs. 69.9 58.8 vs. 69.7 10.0 vs. 16.9 6.80 vs. 11.9			p<0.001 Not significant Not significant Not significant p<0.01 p<0.05 p<0.05	(59%)
Maggioni et al[218]	Cross-sectional	N=3078	Discharge records	Statins	Not reported	0.71 (0.58-0.88)	Unadjusted	Not reported	14/22
Italy	Jan-June 2007								(64%)
Lee H Y et al[217]	Cohort	N=1135	Following patients prescription for 3 months	ACEI/ARBs β-blockers Statins	Not reported	0.80 (0.59-1.08) 0.97 (0.72-1.31) 0.65 (0.48-0.87)	Unadjusted	0.15 0.83 0.01	14.5/22
USA	2003-05								(68%)
Brady et al[239]	Cross-sectional	Women=9898	Practice records	Aspirin β-blockers	46 vs. 53 19 vs. 23	Not reported	Unadjusted	Not reported	12/22
UK	4 weeks in Mrch1997, and in August 1998	Men=14533		statins	13 vs. 18				(54%)
Nilsson et al[241]	Longitudinal cohort	N=9135	At discharge patients self-reported	ACEI/ARBs β-blockers	38.2 vs. 40.6 86.2 vs. 86.6	Not reported	Unadjusted	0.05 0.56	11.5/22
Sweden	1998, for 3 years Follow up			LLD	84.6 vs. 82.7			0.03	(52%)
Bennett et al[238]	Cross-sectional	Women=22524	Post discharge	ACEI Aspirin	37.4 vs. 41.3 67.7 vs. 74.7	Not reported	Unadjusted	Not reported	13/22
Ireland	1999-2000	Men=24751		β-blockers Statins	37.0 vs. 43.0 28.0 vs. 32.0				(59%)
Williams et al[215]	Cross-sectional	Women=7839	From national primary care prescribing data (GMS)	ACEI Aspirin	Not reported	0.83 (0.78-0.89) 0.72 (0.67-0.78)	Age	P<0.01 P<0.01	12/22
Ireland		Men=7751		CCB β-blockers		0.89 (0.79-0.89) 0.84 (0.79-0.89)		P<0.01 P<0.01	(54%)

	1999-2000			Statins		0.97 (0.91-1.05)		Not significant	
Simpson et al[223] **Scotland**	Cross-sectional 1997-2002	N=14435	Data obtained from GP records	ACEI Antiplatelet β-blocker Statins	28.1 vs. 36.2 70.2 vs. 72.3 44.1 vs. 50.7 45.0 vs. 54.6	0.6 (0.5-0.6) 0.8 (0.8-0.9) 0.8 (0.8-0.9) 0.8 (0.7-0.8)	Age, deprivation comorbidities, and practice differences	Not reported	13/22 (59%)
Kattainen et al[245] **Finland**	cross-sectional 2000-2001	Women=300 Men=300	Confirmed by patients during the interview	ACEI/ARBs CCB β-blocker LLD	23.0 vs. 23.4 22.1 vs. 17.7 65.6 vs. 69.9 31.0 vs. 36.8	Not reported	Age	p=0.90 p=0.16 p=0.29 p=0.18	13/22 (59%)
Opotwasky et al[219] **USA**	Cross-sectional 2000-02	Women=771 Men= 1098	Confirmed by patients	Aspirin	62.4 vs. 75.6	0.62 (0.48-0.79)	Age, socioeconomic, demographic, diabetes, MI, asthma, hypertension	<0.01	17/22 (77.7%)
Usher et al[226] **Ireland**	Cohort 2001	Women=4663 Men=4461	From national primary care prescribing data (GMS	ACEI ARBs β-blocker CCB Statins	Not reported	0.83 (0.76-0.91) 1.56 (1.28-1.88) 0.97 (0.89-1.05) 0.97 (0.89-1.05) 1.15 (1.03-1.23)	Age	P<0.0001 P<0.0001 Not significant Not significant p<0.05	11/22 (50%)
DeWilde et al[227] **England & Wales**	Cross-sectional 1998	N=30448	Prescribing data from GP after discharge	Statins	23.5 vs. 33.2	0.94 (0.88-1.00)*	Age, regional health authority, time since diagnosis, smoking status	Not reported	11.5/22 (53%)
Mathur et al[222] **UK**	Cross-sectional‡ 2009-10	N=10933	Collect the last drug record in the GP	ACEI/ARBs Aspirin β-blockers LLD	71.2 vs. 79.1 85.9 vs. 88.9 70.7 vs. 79.1 91.6 vs. 93.7	0.66 (0.60-0.73) 0.74 (0.66-0.83) 0.64 (0.57-0.72) 0.77 (0.66-0.90)	Age, ethnicity, deprivation, comorbidity, drug exclusion	Not reported	15.7/22 (73%)
Reid F D A[228] **UK**	1998 Cross-sectional	N=760	Confirmed by patients	Statins	Not reported	0.92 (0.63-1.35)	Age	0.68	11/22 (50%)
Vermeer et al[221] **Australia**	Cross-sectional 4 months Jan-April 2007	N=169	At discharge from medical records database	statins	Not reported	0.30 (0.10-0.9)	Age group, CHD type, diabetes, hypertension, current smoking, MI, CABG, PCI	Not reported	16/22 (72%)
Salomaa et al[224] **Fenland**	Retrospective cohort 1995-2003	Women=16764 Men= 36589	Post discharge within 3 months, 1st CHD	ACEI β-blocker LLD	Not reported	0.94 (0.90-0.98) 0.96 (0.91-1.00) 1.02 (0.98-1.06)	Age, study year, diabetes status and university hospital district	Not reported	13.5/22 (61%)

Ye Xin et al[247]	Retrospective cohort study	Women=6486 Men=11145	Post discharge within 6 months, 1st CHD	Statins	Not reported	0.85 (0.79-0.9)	Age, dyslipidaemia, hypertension, diabetes, psychosis, comorbidity index, count of medication , non-statins LLD, CHD type, enrol type, plan type, co-payment, cardiologist visit and year of CHD hospitalisation	Not reported	15.5 (70.5%)
USA	2000-03								
Enriquez et al[243]	Cross-sectional	Women=151 Men=153	Not reported	ACEI Aspirin β-blockers statins	55.0 vs. 60.1 85.4 vs. 91.5 80.8 vs. 77.8 78.1 vs. 90.8	1.00 (0.43-1.57) 0.16 (0.08-0.32) 0.18 (0.09-0.35) 0.30 (0.17-0.52)	Age, HF, MI, PCI, CABG, cerebrovascular disease, hypertension, AF, PAD, angina, DM CKD, COPD, PUD, GERD, drugs and their ADR	Not significant 0.001 0.001 0.001	12/22 (55%)
USA	January-march 2005								
Bongard et al[244]	Cross-sectional	Women=705 Men=1921	Medical records	ACEI Antiplatelet β-blockers statins	44.3 vs. 39.9 91.5 vs. 93.4 63.7 vs. 73.4 40.7 vs. 47.0	1.06 (0.87-1.29) 1.01 (0.72-1.41) 0.82 (0.67-1.01) 1.15 (0.94-1.42)	Age, year, hospital, diagnosis, history of CHD factors, LVEF after acute coronary event, PTCA and CABG during hospitalisation	0.58 0.96 0.06 0.17	15.25 (69.3%)
France	1998-99								
Doyle et al[246]	Prospective Cross-sectional	Women=386 Men=979	On time to treatment	Statins±	Not reported	0.51 (0.27-0.98) 0.74 (0.99-0.55)	Age (65 years) and total cholesterol level	0.045 0.043	11/22 (50%)
Ireland	2003								
Teeling et al[229]	Cross-sectional	N=2399	Post discharge	Statins	Not reported	0.96 (0.92-1.01)	Age	Not significant	10/22 (45.5%)
Ireland	Jan1998-Dec2002								
Carroll et al[242]	Cross-sectional	Women=2787 Men= 3991	Primary care	Aspirin Statin	58.5 vs. 64.8 38.2 vs. 49.3	0.92 (0.97-0.78) 0.94 (0.89-1.00)	Age	Not reported	16/22 (72%)
England	Sep 2000-May 01								

* Unadjusted OR 0.61 (0.58-0.64), ‡ patients with contraindication for each drug were excluded from the analysis, ± First OR for patients with history of ACS/revascularization (39% of sample size) and second without (61%) of sample size, ǁ= men vs. women OR 1.42 (95% CI 1.22-1.65; P< 0.0001), General Medical Services scheme , LLD=Lipid lowering drugs , CABG=Coronary artery bypass graft, PCI=Percutaneous coronary intervention, AF=arterial fibrillation, PAD= peripheral arterial disease, DM=diabetes mellitus, CKD=chronic kidney disease, COPD= chronic obstructive pulmonary disease, PUD=peptic ulcer disease, GERD= gastro-esophageal reflux disease, GMS=General Medical Services scheme , ADR=adverse dug reaction , LVEF= Left ventricular ejection fraction, PTCA= Percutanous transluminal coronary angioplasty .

2.4.3 Inequalities by socioeconomic status in prescribing of EBTs for CHD

Unadjusted analyses

Many studies have shown that the prevalence,[217] incidence,[248] mortality and morbidity[249,250] of CHD are commonly associated with low socioeconomic status.[251] little is known however, about the possible socioeconomic inequalities in prescribing EBTs in patients with CHD (Table 3). Three studies reported in unadjusted analyses that those living in the most deprived areas were less likely to be treated with any EBTs including aspirin, ACEI/ARBs, β-blocker, statins, CCB and clopidogrel.[252-254] However, the most deprived patients were demonstrated to be more likely to be prescribed a nitrate (48.3 vs. 52.6%).[254]

One multi-national study examined differences in prescribing by socioeconomic status.[252] It included 153,996 individuals (age from 35-75 years) from 17 countries. From 2005 to 2009, 5650 patients had been diagnosed of CHD. According to the World Bank classification, the PURE study classified countries into four categories: low-income countries, upper middle-income countries, lower middle-income countries and high-income countries. Overall, living in the low-income countries was associated with the lowest rate of drug use. The rate of EBTs' prescription declined with a country's economic wealth. For example, the rate of β-blockers' prescription in high-income countries was 64.1%, upper middle-income countries 27.1%, lower middle-income countries 20.1%, and 11.0% ($p < 0.0001$) in the lower-income countries. Correspondingly, the use of statins was 70.9%, 21.1%, 4.9% and 4.5% ($p < 0.0001$).[252] However, the use of country level data means that this study was limited by the ecological fallacy. The ecological fallacy arises from the incorrect assumption that associations at a population level are also true at an individual level which may not be the case. Therefore we cannot draw any assumption about the relationship between socioeconomic status and the relationship with prescribing of EBTs from this study at an individual level.

Adjusted analyses

Adjusted analyses did not report such consistent findings. The most deprived patients were more likely to receive aspirin or an antiplatelet agent (aspirin or clopidogrel).[222,223] ACEI or ARBs were more often prescribed to the most rather than least deprived patients, though the difference was not significant.[222,223] Simpson *et al.*[223] reported that the most deprived patients were more likely to be prescribed a β-blocker than the least deprived. In another

study, after age and sex adjustment, the most deprived were significantly less likely to receive β-blockers.[255] In a further study, the socioeconomic differences narrowed after adjusting for more covariates.[222] Lower socioeconomic status was associated with lower rates of prescribing of statins.[222,223,255] However, only one study which was adjusted for sex and age reported that those who live in the most deprived areas are significantly less commonly prescribed statins than whose live in the least deprived areas.[255]

Few studies examined the relationship between socioeconomic status and the prescribing of EBTs following a diagnosis of CHD. Different health systems associated with different strategies in providing health care, particularly prescribing medications after a diagnosis of a chronic disease such as CHD. In Scotland, medications are provided freely for such patients but in some other countries different strategies of payment methods such as co-payment strategy have been adopted (Table 3).

Limitations in the reporting of the literature

The quality of the reporting of studies describing the association between socioeconomic status and prescribing of EBTs was assessed using STROBE checklist, and ranged from 50% to 75%. Only one study did not mention the study design in the title or abstract.[255] All studies described a scientific background and the rationale for the study to be conducted. Specific objectives were mentioned in all studies. However, this was not described clearly in one study.[254] Exposures and outcome variables including confounders were not described clearly in two studies, [228,255] but other studies described these variables in the methods. None of the previous studies explained or described the sources of potential bias in the methods. Two studies were identified by the authors as suffering from potential selection bias[252] and recall bias.[253] One study did not describe how they performed the statistical analysis of their data.[228] Further analyses including subgroup analyses, interaction or sensitivity analyses were only described in two studies.[222,252] All studies reported the number of eligible individuals included in the analyses. The demographic or clinical characteristics were not described in one study.[255] All previous studies presented their results in the format of proportions or odds ratios and none of them conducted unadjusted analyses. Moreover, two studies did not describe the limitations of their study. [223,254]

Limitations in the design and analysis of studies included in the literature review

Although a few studies were identified as examining the association between prescribing EBTs and socioeconomic status, a number of limitations were noted. Adjustments for

confounders were not comparable as these studies were unadjusted and only reported the proportional differences in prescribing EBTs between the social classes.[252,253,254] Two studies that examined prescribing inequalities used patient self-report databases which may lack accuracy and have recall bias. In addition, most studies examined prescribing inequalities based on one measurement of deprivation, e.g. income.[252,253,254,255,228] Two studies[222,223] avoided these limitations by adjusting their results for multiple confounders and examining socioeconomic status using deprivation measurements based on different domains such as income and education. One of these two studies,[222] however, was limited by selection bias as they excluded patients who were unable to tolerate the medication's side effects.

In summary, there were a number of limitations in the literature surrounding the association between socioeconomic status and the prescribing of EBTs in CHD. There was also a wide range in the quality of reporting of studies as assessed by the STROBE guidelines. Although studies by Mathour *et al.*[222] and Simpson *et al.*[223] were associated with limitations, these well reported and designed studies were adjusted for different confounders and used a domain measurement instead of a single measurement. These studies generally reported that the most deprived patients were less likely to be prescribed EBTs.

Table 3 Inequalities by socioeconomic status in prescribing in EBTs for CHD

Study	Design /year/ subject	Reference	Prescribing/ Deprivation measure	Medications	Prescribing percentage Affluent vs. deprived	OR, 95% CI Affluent vs. deprived	Adjustment	P values / statistical significance	STROBE Score (%)
Yusuf et al[252]	Longitudinal cohort study	High-income countries vs. Low-income countries	Patients self-reported	ACEI/ARBs Antiplatelet CCB β-blocker	51.7 vs. 6.50 64.1 vs. 11.0 22.4 vs. 7.30 46.5 vs. 11.1	Not reported	Unadjusted	<0.0001 <0.0001 <0.0001 <0.0001	16.5/22 (75%)
17 countries	2005-2009	N=5650 with CHD	*World bank classification*	Statins	70.9 vs. 4.50			<0.0001	
Niu et al[253]	Cross-sectional	High-income vs. Low-income	Confirmed by patients	ACEI/ARBs Aspirin Clopidogrel	63.8 vs. 53.6 87.8 vs. 80.2 33.3 vs. 13.4	Not reported	Unadjusted	<0.05 <0.05 <0.05	14.0/22 (63%)
China	March-June 2006	N=2278	*Income*	β-blockers Statins	67.8 vs. 56.2 68.6 vs. 44.3			<0.05 <0.05	
Munoz et al[254]	Cross-sectional	Social class I&II+ Vs. Social class IV-V	From medical records	ACEI Antiplatelet CCB	35.0 vs. 28.2 80.0 vs. 79.6 35.0 vs. 42.8	Not reported	Unadjusted	0.39 0.87 0.45	16.5/22 (75%)
Spain	1999-2000 Within 6 years prior to study conducted	N=878	*Occupational measure*	β-blockers LLD Nitrates	50.0 vs. 36.4 35.0 vs. 42.8 48.3 vs. 52.6			0.12 0.27 0.81	
Reid F D A et al[228]	Cross-sectional 1998	Non-manual vs. manual	Confirmed by patients	Statins	Not reported	1.24 (0.85-1.82)	Sex and age	Not reported	11/22 (50%)
UK		N=760	*Occupation*						
Odubanjo et al[255]	Cross-sectional	Relatively affluent vs. Relatively deprived	From national primary care prescribing data (GMS)	β-blockers statins	54.0 vs. 49.0 48.0 vs. 43.0	1.17 (1.07-1.29) 1.22 (1.11-1.35)	Age and sex	<0.001 <0.001	12/22 (54.5%)
Ireland	July 2001-december 2002	Deprived=66521 Affluent=28534	*Income*						
Simpson et al[223]	Cross-sectional	Least deprived vs. Most deprived	Data obtained from GP records	ACEI* Antiplatelet* β-blocker* Statins*	Not reported	0.9 (0.71-1.25) 0.9 (0.71-1.25) 0.9 (0.71-1.25) 1.11 (0.9-1.40)	Sex, age, comorbidities, and practice differences	Not reported	13/22 (59%)
Scotland	1997-2002	N=14435	*SIMD*						

Mathur et al[222]	Cross-sectional¶	least deprived vs. Most deprived	Collect the last drug record in the GP	ACEI/ARBs Aspirin β-blockers	74.5 vs. 77.0 87.6 vs. 89.7 77.2 vs. 76.2	0.90 (0.75-1.09) 0.83 (0.66-1.04) 1.11 (0.91-1.33)	Sex, age, ethnicity, comorbidity, drug exclusion	Not reported	15.7/22 (73%)
	2009-10	N=10933		LLD	93.0 vs. 93.0	0.97 (0.73-1.28)			
UK			*Townsend score*						

***** OR is only for patients over 75 for year 2002. Result for year 2002. ¶ Patients with contraindication or not tolerated the drug were excluded from the analysis, + Social class I&II= professional and intermediate occupations, social class IV-V= unskilled and manual occupation, SIMD= Scottish Index of Multiple deprivation, LLD=Lipid lowering drug

2.4.4 Trends in prescribing of EBTs for CHD

Since 1990 the rate of prescribing EBTs has generally improved but the improvement has not been the same for all drugs and for some drugs prescription rates have fallen (Table 4). The few studies that examined trends in prescribing EBTs all reported that the prescribing of aspirin, ACEI, ARBs and β-blockers increased moderately across the study years.[256-259] The majority of previous studies demonstrated the proportion of patients prescribed EBTs but only two studies used multivariable models to test the trends in prescribing.

Bennett *et al.*[256] examined the trends in prescribing for patients diagnosed with CHD from 1990 to 2002 using the general medical services prescription database. In this study, patients with CHD were identified based on nitrate and aspirin prescription. This study showed that prescribing of statins was very low during the early 1990s, which was supported by two other studies[257,258] that used prescribing data between 1994 and 2002. Since 1994 the prescribing of statins has increased dramatically. In a multinational European study (EUROASPIRE I & II), two cohorts of patients (between 1995 and 1996, and 1999 and 2000) diagnosed with CHD were compared with respect to prescribing of EBTs after a diagnosis of CHD. Prescriptions after diagnosis were obtained either from medical records or patients' self-reporting. In this study, the prescribing of EBTs increased over the time particularly for statins which increased approximately by 40% between 1995 and 2000.[259] While statins were the drugs most commonly examined, all drugs classes demonstrated a rise in prescribing rates over time with the exception of one study that reported a falling rate of prescribing for CCBs. [256]

In studies that were adjusted for other confounders, this rising rate of statin prescribing was still evident.[229,247] In an age-adjusted study,[229] it was shown that the prescribing of statins significantly increased over the time between 1998 and 2002. Ye Xin *et al.*[247] followed statin prescriptions for six months after first diagnosis and showed that those more recently diagnosed with CHD were more likely to be prescribed statins.[247]

Limitations in the reporting of the literature

A small number of studies were identified that examined the prescribing trend after diagnosis with CHD. The quality of the reporting of studies describing the prescribing trends over the time was also assessed by using STROBE checklist and ranged from 50% and 75%. All studies provided a clear summary in the abstract including background,

methods, results and conclusion. One study indicated the study design in the abstract.[247] Rayn *et al.*[258] did not state a specific objective for their study. The method section in a scientific paper should provide a clear description of how the study has been conducted including the study design e.g. cross-sectional, prospective or retrospective longitudinal cohort study. However only three studies described that in their methods.[247,256,260] All previous studies described the setting and the date of their study. Eligibility criteria of patients' recruitment was not described in one study.[260] Birkhead *et al*.[260] did not describe the variables that were included in the analyses clearly. However, this is the only study that addressed the potential source of bias in their methods. Two studies did not state how the sample size approached the final number that was included in the analyses.[256, 258]

Statistical methods were described in all studies but Rayn *et al.*[258] did not describe how the analyses were carried out. Furthermore, none of the previous studies described further analyses or explained how missing data were addressed. Four studies did not report the number of eligible patients included in the study nor the reasons for those who were excluded from the analyses.[229,257,256, 258] Teeling *et al.*[229] did not confirm the number of patients prescribed statins. The author, however, just described the trends ratio. All previous studies summarised their study key results in the discussion, however, one study did not do that.[256] Although it is important to discuss the study limitations including the source of potential bias and confounding that could have affected results, three studies failed to discuss their limitations.[256,259,260] Two studies explained and interpreted the outcome and described the reasons for trend improvement.[259,260] None of the previous studies discussed the possibility of their outcome generalisability. Three studies acknowledged the financial support for their studies. [229,257,258]

Limitations in the design and analysis of studies included in the literature review

A number of gaps and limitations were also identified in the previous literature. Two studies did not use updated data which did not represent the current clinical prescribing of EBTs. Only two studies described the association between the prescribing of EBTs with year using adjusted analyses. One of these adjusted analyses was only adjusted for age. Two studies were limited by the validity of the diagnosis of CHD using prescription of nitrates or aspirin as a proxy for a diagnosis of CHD.[229,256] Selection bias was identified in one study, excluded patients who died during the study.[258] One study was limited by recall bias as noted before in the study by Bennett *et al.*[256] No studies reported adjusted rates of prescribing of drugs other than statins.

In summary, a number of limitations were identified in the previous studies surrounding the association between trend and prescribing EBTs after CHD. Also, there was a variation in the quality of reporting of studies as assessed using STROBE guidelines. Although the study by Birkhead *et al.*[260] was not very well reported, this study included a wide specific range of EBTs, used electronic data sets collected between 2000 and 2003, and had a large sample size. This study demonstrated that the prescribing of EBTs has improved over time.

Table 4 Trends in prescribing of EBTs for CHD

Study	Design/year	Reference	Prescribing	Medications	Prescribing percentage	OR, 95% CI	Adjustment	P values / statistical significance	STROBE Score (%)
DeWilde et al[257] **UK**	Cross-sectional 1994-2005	1994 vs. 2005 Men=30000	UK primary care database	ACEI Antiplatelet β-blockers Statins	13.5 vs. 57.0 31.0 vs. 75.0 29.0 vs.55.0 4.00 vs. 80.0	Not reported	Unadjusted	Not reported	11.5/22 (53%)
		Women= 21000		ACEI Antiplatelet β-blockers Statins	12.0 vs. 51.0 37.0 vs. 74.0 25.0 vs. 48.0 3.00 vs. 70.0				
Bennett et al[256] **Ireland**	Cross-sectional Not report subject 1990-2002	1990 vs. 2002	From national primary care prescribing data (GMS)	ACEI β-blockers CCB Statins*	8.00 vs. 35.0 37.0 vs. 55.0 55.0 vs. 35.0 6.00 vs. 55.0	Not reported	Unadjusted	Not reported	11/22 (50%)
Ryan et al[258] **England & Wales**	Cross-sectional 1994-1998	1994 vs.1998 Men= 18485	Obtained from GP database General practice research database (GPRD)	Aspirin Statins	46.3 vs. 61.5 4.2 vs. 29.0	Not reported	Unadjusted	Not reported	10/22 (45%)
		Women= 15407		Aspirin Statins	36.0 vs. 53.4 3.00 vs. 18.9				
EUROASPIRE I & II[259] **9 countries**	Retrospective/prospective patients interview 1995-1996 1999-2000	EUROASPIRE I Vs. II N=3569 N=3379	Medical records and patients	ACEI Antiplatelet β-blockers statins	29.5 vs. 42.7 81.2 vs. 83.9 53.7 vs. 66.4 18.5 vs. 57.7	Not reported	Unadjusted	Not reported	14.2/22 (65%)
Birkhead et al [260] **England & Wales**	Observational Study 2000-2003	2000 vs. 2003 N=156902	At discharge, MINAP dataset	ACEI Antiplatelet β-blockers Statins	62.4 vs. 72.4 89.3 vs. 90.2 76.3 vs. 82.6 69.6 vs. 83.8	Not reported	Unadjusted	Not reported	12.5/22 (54.5%)
Ye Xin et al[247]	Retrospective cohort study	2001 vs. 2000 2002 vs. 2000 2003 vs. 2000	Post discharge within 6 months, 1st CHD	Statins	Not reported	1.28 (1.17-1.40) 1.47 (1.34-1.60) 1.77(1.61-1.94)	Age, sex, dyslipidaemia, hypertension, diabetes, psychosis, comorbidity index,	<0.001	15.5/22 (70.5%)

USA	2000-03						count of medication , non-statins LLD, CHD type, enrol type, plan type, copayment, cardiologist visit and year of CHD hospitalisation		
Teeling et al[229]	Cross-sectional	1999 vs. 1998 2000 vs. 1998 2001 vs. 1998 2002 vs. 1998	From national primary care prescribing data (GMS)	Statins	Not reported	1.47 (1.36-1.58) 1.95 (1.82-2.08) 2.63 (2.46-2.80) 3.76 (3.52-4.00)	Age	<0.0001	10/22 (45.5%)
Ireland	Jan1998-Dec2002	N=344000							

LLD=Lipid lowering drugs, GMS=General Medical Services prescription database, * The trend starts from 1994, at the time of date study 1990 prescribing of statins was 0.00.

2.4.5 Inequalities in prescribing of EBTs for CHD by comorbidities

The presence of other comorbidities disease in patients with CHD may influence prescribing rates of EBTs. A number of studies examined the prescribing of EBTs in patients with CHD according to the presence of comorbidities (Table 5).

Unadjusted analyses

In unadjusted analyses prescribing rates of aspirin were lower in patients with renal failure (RF).[261] Two studies reported small differences in aspirin (or any antiplatelet agent) prescription rates between diabetic and non-diabetic patients.[262-264] Contrary to this, in one study, patients identified as having CHD based on nitrate prescriptions, patients with diabetes were significantly more likely to receive aspirin compared to non-diabetics (OR 1.23; 95% CI 1.09-1.38, p<0.001).[265] ACEI or ARBs were more frequently prescribed for patients with RF or diabetes.[261-265] The prescriptions of β-blockers were less common among patients with diabetes or RF,[261-265] however, one study reported that patients with diabetes were as likely to be prescribed a β-blocker compared to those without.[263] In an unadjusted study, patients with hypertension (HTN) were more likely to be prescribed a statin but no differences were seen in those with diabetes or PAD.[218] Other studies have reported that patients with diabetes are more likely to be prescribed a statin.[262,266] In contrast, prescribing of statins was lower in patients with RF (77.2 vs. 80.6%).[261] The proportion of patients prescribed a CCB was higher for patients with diabetes (40.1 vs. 35.5%) and RF (29.3 vs. 23.2%).[261,262] Patients with RF were more likely to be prescribed nitrates (53.5 vs. 50.6%), though patients with diabetes were less likely to be prescribed nitrates (38.8 vs. 41.5%).[261,264]

Adjusted analyses

In adjusted analyses patients with the comorbidities of diabetes or HTN were more likely to be prescribed aspirin compared with patients without these comorbidities.[219,222] However, patients with RF or asthma were less likely to receive aspirin.[219,267] Similar to unadjusted studies, patients with diabetes were more commonly prescribed ACEI/ARBs,[224,266,268,269] but patients with RF were less likely to be prescribed ACEI/ARBs.[225,267] Vehoke *et al.*[269] and Mathur *et al.*[222] reported that β-blockers were more commonly prescribed for patients with diabetes, though not all studies reported this finding.[224] As expected, β-blockers were less commonly prescribed for patients with asthma or chronic obstructive pulmonary disease (COPD).[225] In conflicting studies statins were shown to be less often prescribed for patients with diabetes, RF and HTN,[247]

however, in another study statins were prescribed more frequently in those with diabetes and hypertension.[228]

A number of studies examined the relationship between comorbidities and the prescribing of EBTs in those with a diagnosis of CHD. In different observational study designs, the majority of previous studies examined the association between diabetes and prescribing EBTs in those with a diagnosis of CHD. This may be because it is known that diabetes is a strong predictor for poor outcome in CHD. However, there are many other comorbidities that may lead to a contraindication in prescribing of cardiovascular secondary prevention protective therapy or reduce the likelihood of the medication being prescribed, such as asthma or renal failure. Few studies examined comorbidities other than diabetes.

Limitations in the reporting of the literature

The quality of the reporting for most of the studies in Table 5 has been discussed previously with regard to age, sex and socioeconomic status, therefore I will focus on studies that have not been discussed yet.[261,263,265,267,269] The STROBE scores for literature that described the association between comorbidities[267] and the prescribing of EBTs ranged from 54% to 66% (Table 5). The abstracts provided a clear summary of what had been done including the study design, however, three studies did not use common terms to indicate their study design.[261,267,269] A scientific background was detailed, providing information about what had been done previously in all studies except in the reports from Lahoz *et al.*[261] Pyorala *et al.*[266] All previous studies described the study setting, the date of recruiting the sample, and the eligibility criteria of patients included in the analyses. However, two studies did not describe the variables included in the analyses clearly, including the outcomes, exposures and potential confounders.[266,267] Potential sources of bias were not addressed in any of the studies. All studies described their statistical methods, but none of them described any further analyses such as examining subgroups and interaction, sensitivity analysis or how missing data were addressed. The number of patients who were potentially eligible for analysis was not reported in two studies.[265,269] Two studies discussed the reasons for excluding patients from their analyses.[263, 267] Han *et al.*[267] is the only the study that used a flow diagram to describe eligible patients included in the study, and reasons for excluding patients. The number of patients with comorbidities who were prescribed any EBTs was not reported in two studies,[261,267] and unadjusted analyses were only reported in one study. [267] Three studies failed to discuss their study's limitation and the potential source of bias.[261,263,265] However, two studies were identified with selection bias.[263, 267] Only one study discussed the generalisability of the study result.

Limitations in the design and analysis of studies included in the literature review

A number of other limitations were identified in the literature. The main issue was that studies were limited to examining the association between prescribing of EBTs and only one comorbidity such as renal failure or diabetes.[222,224,265,269,270] The lack of range of comorbidities makes assessment of the relative prescribing patterns difficult. Different studies with their different eligibility criteria, adjustment for other factors and other biases make it hard to compare studies. Studies were limited to examining one or two EBTs only and did not examine the range of EBTs indicated for CHD.[218,219,228,247] The validity of the diagnosis of CHD was also poor in some studies that relied on the proxy measure of a prescription of nitrates. One study used a prescription of insulin to define the comorbidity of diabetes. [265] While this may be acceptable for type 1 diabetes where all patients require insulin it is not sensitive for type 2 diabetes. This is important as the most common form of diabetes in the population with CHD is type 2 diabetes. Furthermore, two studies did not describe how the diagnosis of a comorbidity was defined.[265,270]

In summary, there were a number of limitations in the literature surrounding the association between comorbidities and prescribing of EBTs in CHD. There was also a wide range in the quality of reporting of studies as assessed by the STROBE guidelines. Although Vehok *et al.*[269] is not the best reported study, this study obtained data from a national social insurance database and it examined a wide range of EBTs, using adjusted analyses to report the results. This study demonstrated that patients with diabetes generally are more commonly prescribed EBTs than those without diabetes.

Table 5 Inequalities in prescribing of EBTs for CHD by comorbidities

Study	Design/year/ subject	Reference	Prescribing	Medications	Prescribing percentage	OR, 95% CI	Adjustment	P values / statistical significance	STROBE Score (%)
Vehok et al[269]	Cross-sectional	DM vs. Not	Obtained from data after discharge	ACEI ARBs β-blockers LLD	Not reported	1.10 (1.04-1.17)* 1.10 (0.99-1.23)* 1.02 (1.00-1.05)* 0.94 (0.90-0.98)*	Age, income, myocardial infarction and previous use of drugs.	Not reported	14.5/22 (66%)
	Men (N)=43501		1st diagnosis						
Finland	1997-2002								
	Women (N)=31125	DM vs. Not		ACEI ARBs β-blockers LLD	Not reported	1.17(1.09-1.26)* 1.13(1.01-1.26)* 1.02(0.99-1.05)* 0.97(0.92-1.02)*		Not reported	
Han et al[267]	Cross-sectional	RF vs. Not (in patients with non-ST segment elevation)	At discharge	ACEI Aspirin β-blockers LLD	59.8 vs. 61.1 86.9 vs. 90.7 84.7 vs. 83.8 79.1 vs. 80.6	0.76 (0.69-0.83)‡ 0.82 (0.75-0.89) 1.01 (0.93-1.10) 0.93 (0.84-1.04)	Age, sex, BMI, race, family history of CAD, HTN, DM, smoking status, prior MI, PCI, CABG, CHF, positive cardiac markers,	Not reported	14/22 (61.3%)
	N=6560 with RF								
USA	Jan 2001-Dec 2003								
Ye Xin et al[247]	Retrospective cohort study	HTN vs. Not	Post discharge within 6 months,	Statins	Not reported	0.69 (0.90-1.02)¶	Age, sex, dyslipidaemia, hypertension, diabetes, psychosis, comorbidity index, count of medication , non-statins LLD, CHD type, enrol type, plan type, copayment, cardiologist visit and year of CHD hospitalisation	0.16	15.5/22 (70.5%)
		DM vs. Not				0.99 (0.91-1.08)		0.80	
	Men (N)=11145 Women(N)=6486	RF vs. Not	1st CHD			0.79 (0.62-1.00)		0.053	
USA	2000-03								
Mathur et al[222]	Cross-sectional N=10933	DM vs. Not	Collect the last drug record in the GP	ACEI/ARBs Aspirin β-blockers LLD	Not reported	2.92 (2.60-3.28) 1.43 (1.25-1.63) 1.90 (1.06-1.33) 2.84 (2.25-3.58)	Sex, age, ethnicity, deprivation, comorbidity, drug exclusion	Not reported	15.7/22 (73%)
UK	2009-10								
Reid F D A et al[228]	Cross-sectional N=760	DM vs. Not HTN vs. Not	Confirmed by patients	Statins	Not reported	1.23 (0.72-2.12) 1.09 (0.74-1.59)	Sex and age	Not reported	11/22 (50%)
UK	1998								
Kassab et al[225]	Cross-sectional	RF vs. Not	Clinical records for discharge medications	ACEI/ARBs statins	Not reported	0.55 (0.3-1.002) 4.85 (1.5-15.50)	Age group, sex, CHD subtype, diabetes, hypertension, hyperlipidaemia, current smoking, previous MI, CABG, PCI	0.049 0.008	13.5/22 (60%)
Malaysia	N=380	Asthma/COPD vs. Not		β-blockers		0.07 (0.018-0.27)		<0.001	
	2009-10								

Salomaa et al[224] **Finland**	Cross-sectional N=53353 1995-2003	DM vs. Not	Within 3 months post discharge, 1st CHD	ACEI β-blocker LLD	Not reported	1.89 (1.81-1.99) 0.83 (0.79-0.88) 0.82 (0.78-0.86)	Age, sex, study year, and university hospital district	Not reported	13.5/22 (61%)
Opotowsky et al[219] **USA**	Cross-sectional N=1869 2000-02	DM vs. Not Asthma vs. not HTN vs. Not	Confirmed by patients	Aspirin	72.1 vs. 69.8 61.2 vs. 71.9 72.1 vs. 66.1	1.15 (0.87-1.52)[I] 0.72 (0.52-1.00)[I] 1.50 (1.16-1.95)[I]	Age, socioeconomic, demographic, diabetes, MI, asthma, hypertension	Not reported	17/22 (77.7%)
Bennett et al[265] **Ireland**	Cross-sectional N=14826 1999-2000	DM vs. Not	National primary care data base GMC	ACEI ARBs Aspirin β-blockers statins	Not reported	3.09 (1.30-1.61) 1.47 (1.13-1.87) 1.23 (1.09-1.38) 0.82 (0.74-0.91) 1.44 (1.30-1.61)	Unadjusted	<0.0001 <0.05 <0.001 <0.001 <0.0001	13.5/22 (61.3%)
Pyorala et al[266] (EUROASPIREII) **15 Countries**	Cross-sectional N=5556 1999-2000	DM vs. Not Patients with diabetes=1086	Medical records and patients	ACEI ARBs Antiplatelet CCB β-blockers statins	49.2 vs. 35.3 5.20 vs. 3.20 83.4 vs. 86.4 31.4 vs. 24.8 62.1 vs. 63.0 54.0 vs. 55.6	Not reported	Age, sex, diagnostic category and centre	<0.001 0.08 0.008 0.005 0.84 0.92	12.5/22 (57.0%)
EUROASPIREII) **9 Countries**	N=3374	Patients with diabetes=740		ACEI Antiplatelet CCB β-blockers statins	52.0 vs. 40.0 82.2 vs. 84.3 32.0 vs. 24.2 66.0 vs. 66.5 56.8 vs. 57.9	Not reported	Unadjusted	Not reported	
EUROASPIRE I **9 Countries**	N=3569 1995-96	DM vs. Not Patients with diabetes=641	Medical records and patients	ACEI Antiplatelet CCB β-blockers statins	43.2 vs. 26.5 81.8 vs. 81.0 40.1 vs. 35.5 52.0 vs. 54.0 14.0 vs. 19.5	Not reported	Unadjusted	Not reported	
Maggioni et al[218] **Italy**	Cross-sectional N=3078 Jan-June 2007	DM vs. Not HTN vs. Not PAD vs. Not	Discharge records	Statins	Not reported	1.20 (0.95-1.51) 2.30 (1.76-3.02) 1.06 (0.48-2.35)	Unadjusted	Not reported	14/22 (64%)
Mostaza-Prieto et al[263] 	Cross-sectional N=6568	DM vs. Not[§] Patients with RF=2130	After discharge from case note	ACEI/ARBs Antiplatelet/ anticoagulant β-blocker	73.8 vs. 61.5 90.4 vs. 89.2 49.2 vs. 49.4	Not reported	Unadjusted	<0.001 NS NS	14/22 (63.3%)

Spain	2004 (6 months)			LLD	88.4 vs. 86.2			<0.001	
	N=8817	Patients with RF=2884		CEI/ARBs	73.5 vs. 61.0			<0.001	
				Antiplatelet	80.2 vs. 80.2				
				Aspirin	62.5 vs. 62.3				
				β-blocker	45.4 vs. 47.7			0.048	
				CCB	29.8 vs. 21.9			<0.001	
				LLD	81.1 vs. 80.3				
				Statins	79.5 vs. 78.9				
Lahoz et al[261]	Cross-sectional	RF vs. Not	Clinical case note at discharge time	ACEI	44.8 vs. 38.5	Not reported	Unadjusted	Not reported	12/22
				ARBs	73.3 vs. 63.5				
Spain	RF=1766			Aspirin	58.7 vs. 63.9				(54.5%)
				CCB	29.3 vs. 23.2				
	July-Sep 2004			β-blockers	41.3 vs. 49.0				
				nitrates	53.5 vs. 50.6				
				statins	77.2 vs. 80.6				
Sharma et al[264]	Audit	DM vs. Not	Case record form	ACEI/ARBs	86.4 vs. 82.1	Not reported	Unadjusted	Not reported	
				Aspirin	88.7 vs. 88.3				
India				β-blockers	59.4 vs. 69.2				
	2007-08			nitrates	38.8 vs. 41.5				
				statins	67.1 vs. 59.7				

*Result for year 2001-2002, and value are risk ratio. ‡Unadjusted OR 0.92 (0.84-1.00), 0.66 (0.61-0.73), 1.00 (0.92-1.09), 0.87 (0.79-0.96). ¶ Univariate OR 0.89 (0.84-.94; 0.001), 0.79 (0.74-0.85), 0.48 (0.39-0.58) p=0.001, ‖ After excluding patients with contraindication 1.45 (0.97-2.16), 0.78 (0.52-1.18), 2.08 (1.48-2.93). §=Exclude patients with contraindication to any of these drugs or patients with adverse effect.

2.5 Inequalities in prescribing of EBTs for MI

After experiencing a MI a number of medications have been shown to improve outcomes. Unless contraindicated, patients should be discharged from hospital with these medications including an antiplatelet agent (aspirin or clopidogrel), an ACEI or ARB, a β-blocker and a statin.

2.5.1 Inequalities by age in prescribing of EBTs for MI

Unadjusted analyses

Older patients with MI less commonly undergo cardiac procedures and they receive suboptimal treatment with EBTs compared to younger patients.[271,272] Older patients are less commonly treated with β-blockers[273,274] and aspirin,[275] despite evidence that secondary prevention reduces mortality post-MI.[124,127,276] However, older patients are more likely to be prescribed ACEI than younger patients,[277-279] though some have showed no difference (Table 6, unadjusted studies).[280] In one study,[279] age was stratified by sex and there was no difference in prescribing of ACEI by age in either sex. β-blockers were less often prescribed in older compared to younger patients,[277,279-281] whereas the opposite was reported for the prescription of CCBs.[277,279,281] Prescribing of statins was lower in older compared to younger patients,[277,279,280] although one study reported that older patients were more likely to be prescribed lipid lowering drugs (LLD) than younger patients.[278]

Adjusted analyses

In adjusted studies older patients were significantly less likely to be prescribed aspirin.[282-284] Studies of prescribing of ACEIs or ARBs are conflicting. Some studies reported that older patients were more likely to be prescribed an ACEI or ARB,[284-286] while others reported that older patients were less likely to receive an ACEI or ARB.[282,283,287] The studies by Marandi *et al*[285] and Winkelmayer *et al*[288] are the only two studies to report that older patients were more likely to receive β-blockers though the difference was not statistically significant. Prescribing of statins was significantly lower among older patients in all studies that carried out multivariable adjustment.[282-284,289]

There are clearly differences in prescribing of EBTs by age, however, studies were limited by presenting unadjusted results or only adjusting for a few variables. Other studies grouped drugs into less specific groups such as lipid lowering drugs, or examined the relationship in patients with a narrow age range. Small sample size may influence some studies, as well as short period of follow-up. Limited age grouping in some studies would

not show what is the effective age for prescribing medication. The most recent study was conducted between 2007 and 2008, however an earlier one was in 1984.

A number of studies examined the relationship between age and the prescribing of evidence based therapies following a diagnosis of CHD. The majority of previous studies demonstrated that older age groups were less likely to receive EBTs compared to younger age groups (Table 6). However, studies were limited by a number of factors including study design, data collection methods, and/or statistical methods.

Limitations in the reporting of the literature

The score for literature describing the association between age and prescribing EBTs after MI ranged from 45% to the highest score 70.4% (Table 6). The study design indicated using common terms such as cross-sectional, in the majority of the studies, however, five studies did not state the study design either in the title or abstract. [284,286,290,291,292] Four studies failed to clearly state their objectives. [293,288,289,294] The study design was clearly presented in most studies, though three studies did not describe it clearly in the methods.[283,284,295] The eligibility criteria of individuals included in the study was not mentioned in one study. [296] A number of studies did not clearly define and describe how their variables were handled. [293,284,285,290,296] Although bias is common in the observational studies, none of the studies addressed or discussed potential biases in their methods. All studies described their statistical methods with the exception of one study. [293] Rathore *et al.*[283] discussed and explained how missing data were handled, however other studies did not. None of the studies described any sensitivity analysis.

A number of studies did not define the study cohort clearly, for example, reporting the number of potentially eligible individuals, only reporting the number of those who survived after discharge.[277,279,280,284,289,290,296,292] The characteristics of patients included were not described in two studies. [284,294] Only two studies indicated the number of missing data in their results. [294,281] Five studies did not report the number of outcome events. [293,284, 288, 292, 297] A clear and full presentation of outcomes including unadjusted results and results adjusted for potential confounders can help the reader to compare and judge the magnitude and direction of the influence of the confounders. However, only six studies presented these results.[293,278,283,288,296,291] Only three studies discussed their limitations, including the potential sources of bias.

Limitations in the design and analysis of studies included in the literature review

A number of gaps were also identified in the previous literature. There are clear differences in prescribing of EBTs by age after MI, however, a number of studies were unable to adjust the results for confounders or only able to adjust for a few confounders. [277,279,280,281,285,286,290,294,297] The majority of American and Canadian studies used prescription data between 1987 and 1997, which may not be relevant to current clinical practice. Also, these studies were limited to patients in the age group over 64 years old. Macchia *et al.*[282] and Winkelmayer *et al.*[288] overcame that by using a large sample size, adjusted result for a wide range of confounders, and examined prescribing of a wide range of EBTs, however, their studies only included patients who survived at least 1 and ≥ 120 days in the year after diagnosis, i.e. both studies suffered from a selection bias. A number of studies were able to avoid selection bias, however, they were limited to a few EBTs, [287,289, 296, 294] or grouped drugs into less specific groups such as lipid lowering drugs, or examined the relationship in patients within a narrow age range.

In summary, there were a number of limitations in the literature surrounding the association between sex and prescribing of EBTs in CHD. There was also a wide range in the quality of reporting of studies as assessed by the STROBE guidelines. Although some studies were well reported, they associated with some limitations such as Rathore *et al.*[283] which was exposed to the selection bias. Furthermore, the study by Ohlesson *et al.*[278] is a well reported study but used unadjusted analyses and was limited to few drug groups. The study by Gislason *et al.*[287] benefited from a high quality of reporting and had a number of strengths over other studies. The authors adjusted for a wide range of confounders, but not socioeconomic status, but they did use a nationwide population data set for all hospitals in Denmark. This study demonstrated that older patients are less commonly prescribed EBTs compared to younger patients.

Table 6 Inequalities by age in prescribing of EBTs after myocardial infarction

Study	Design /subject/year	Age range/	Prescribing	Medications	Prescribing percentage Eldest vs. youngest age group	OR, 95% CI Old vs. young	Adjustment	P values / statistical significance	STROBE Score (%)
Martinez et al[297]	Retrospective cross-sectional	< 51 51-60 61-70 71-90	At time of discharge from hospital discharge form	ACEI β-blockers	Not available	1.12 (0.37-3.38) 0.2 0 (0.10-0.38)	Unadjusted	Not reported	11/22 (50%)
Spain	N=324 and 190 (514) 1989-91/ 1994								
Excoffier et al[281]	Cross-sectional	≤ 65, 62-75, > 75	At discharge from the medical chart	ACEI β-blockers CCB	Not available	1.20 (1.11-1.30) 0.65 (0.59-0.70) 1.17 (1.08-1.27)	Unadjusted	Not reported	15/22 (68%)
France	N=2102 Sep 1993-Jan 95								
Austin et al[280]	Retrospective longitudinal cohort	65-69, 70-74, 75-79, ≥ 80	Within 90 days post-discharge	ACEI β-blockers Statins	74.6 vs. 81.0 75.0 vs. 81.5 71.3 vs. 87.9	Not reported	Unadjusted	Not reported	12/22 (54.5%)
Canada	N=8706 2005-06		Used linked administrative database						
Kvan et al[277]	Retrospective cohort A three months period	≥ 80 vs. < 80	After 6 months post discharge treatment obtained from the hospital records	ACEI Aspirin CCB β-blockers Statins	48 vs. 32 72 vs. 86 15 vs. 13 67 vs. 85 9.0 vs. 72	Not available	Unadjusted	Not reported	11/22 (50%)
Norway	N=901 1999/2000								
Ohlesson et al[278]	Retrospective longitudinal cohort	17-59, 60-69 70-79	Within three months post discharge 1st MI	ACEI LLD	65 vs. 70 78 vs. 92	Not reported	Unadjusted	Not reported	15.5/22 (70%)
Sweden	N=1364 2006								
Pilote et al[279]	Cross sectional	65-74, 75-84 >85	Within 90 days post-discharge	ACEI β-blockers CCB Statins	58.0 vs. 57.0 48.0 vs. 71.0 33.0 vs. 29.0 10.0 vs. 44.0	Not reported	Unadjusted	Not reported	12.5/22 (57%)
	N=28647	Men							
Canada (Ontario)	1997-2000	Women		ACEI β-blockers CCB	59.0 vs. 59.0 49.0 vs. 68.0 32.0 vs. 34.0				

				Statins	9.00 vs. 46.0				
Rathore et al[283]	Cross-sectional	65-69, 70-74, 75-79,80-84, ≥ 85	At discharge	ACEI Aspirin	57.1 vs. 61.6 73.6 vs. 76.0	0.90 (0.86-0.95)* 0.96 (0.95-0.98)	Demographic characteristic, medical history, admission findings, and comorbidities	0.05 <0.0001	15.5/22
	N=96364		1st MI	β-blockers	61.8 vs. 55.3	0.88 (0.85-0.92)		0.02	(70.4%)
USA	1994-96								
Macchia et al[282]	Three longitudinal cohorts	>75 vs. ≤ 75‡	Post-discharge follow for one year	ACEI/ARBs Aspirin β-blockers	79.1 vs. 79.3 78.5 vs. 87.0	0.75 (0.67-0.83) 0.60 (0.54-0.67)	Sex, previous CHD, diabetes, stroke, TIA, atrial fibrillation, COPD, depression and malignancy	NA	15/22
	N=21423	Men		Statins	54.6 vs. 73.1 63.2 vs. 85.6	0.46 (0.42-0.50) 0.31 (0.28-0.34)			(68%)
Italy	2003-04 2005-06 2007-08	Women		ACEI/ARBs Aspirin β-blockers Statins	77.3 vs. 81.3 73.4 vs. 83.2 54.6 vs. 73.9 55.1 vs. 81.1	0.59 (0.53-0.65) 0.45 (0.40-0.49) 0.43 (0.39-0.46) 0.22 (0.20-0.24)			
Marandi et al[285]	Retrospective longitudinal Cohort	20-39, 40-59, 60-79, 80-99	One year post discharge follow up,	ACEI β-blockers Statins	Not reported	5.69 (3.66-8.82)+ 1.93 (0.58-6.47) 0.17 (0.02-1.37)+	Sex	0.05 NS NS	13/22 (59%)
	N=4025		1st MI, Survived more than 30 days						
Estonia	2004-05								
Tran et al[286]	Retrospective Cohort study	≥ 65 vs. <65	At discharge	ACEI	Not reported	1.46 (1.22-1.74)	Contraindications to therapy	Not reported	12.5/22
	N=4524								(57%)
Canada	1994-96								
Heller et al[290]	Retrospective longitudinal Cohort	65-69, 70-74, 75-79,	Outpatients prescription database within 90 days	β-blockers	Not reported	1.00 1.09 (0.91-1.30) 1.07 (0.90-1.27)	Demographic and year of MI	------- 0.3 0.4	11.5/22 (52%)
	N=9534	80-84,	post discharge			1.01 (0.85-1.21)		0.8	
USA	1994-1997	≥ 85				0.84 (0.69-1.01)		0.06	
Rasmussen et al[289]	Retrospective longitudinal cohort	30-44 45-54 55-64	Within 6 months post discharge	Statins	Not reported	0.89 (0.77-1.03) 1.22 (1.09-1.37) 1.00	Sex, concomitant medications, hospital type	Not reported	15/22 (68%)
	N=17875	64-74 75-84	Follow statins purchased after			0.55 (0.50-0.61) 0.19 (0.17-0.21)			
Denmark	1995-2002	≥ 85	1st MI			0.02 (0.02-0.03)			

Winkelmayer et al[288] **Austria**	Cross-sectional N=4105 2004	70-89 vs. < 50 ≥ 90 vs. < 50	Within 120 days post discharge 1st MI	ACEI/ARBs β-blockers statins ACEI/ARBs β-blockers statins	Not reported	1.48 (1.19-1.85) 1.05 (0.83-1.33) 1.08 (0.86-1.36) 0.73 (0.59-0.90) 0.62 (0.51-0.76) 0.39 (0.32-0.47)	Sex, length of stay at hospital, concomitant medications	Not reported	12.5/22 (57%)
Krumholz et al[295] **USA**	Retrospective cross-sectional N=45308 1994/1995	65-74, 75-84, ≥ 85	At discharge	β-blockers		1.00 0.92 (0.90-0.94) 0.76 (0.73-0.79)	Sex, race, medical history, hospital and discharge medications, clinical status, hospital complications, hospital procedures, length of stay	Not reported	14/22 (63%)
Gislason et al[287] **Denmark**	Retrospective longitudinal cohort N=55315 1995-2002	30-59 60-69 70-79 ≥ 80	Within 30 days post discharge 1st MI	ACEI β-blockers	27.1 vs. 25.3 41.9 vs. 71.9	0.61 (0.57-0.65) 0.31 (0.29-0.33)	Sex, calendar year, concomitant treatment (loop diuretic & antidiabetic drugs)	Not reported	15/22 (68%)
Spencer et al[284] **USA**	Cross-sectional N=5739 1986-1997	<55, 55-64, 65-74, ≥ 75	At time of discharge	ACEI Aspirin β-blockers LLD	Not reported	1.37 (1.07-1.75) 0.70 (0.57-0.85) 0.42 (0.35-0.52) 0.24 (017-0.34)	Sex, medical history and clinical characteristic	Not reported	10.5/22 (48%)
Barakat et al[296] **England**	Prospective longitudinal cohort N=1225 1988-1994	< 60, 60-69 ≥ 75	At time of discharge	Aspirin β-blockers	Not reported	0.88 (0.51-1.50) 0.25 (0.16-0.37)	Sex, diabetes, previous MI. Q wave infarction, left ventricular failure	0.6 <0.001	10/22 (45%)
Rochon et al[291] **Canada**	Retrospective longitudinal cohort N=15542 1993-1995	66-74, 75-84, ≥ 85	Within a year after hospital discharge (administrative database)	β-blockers		1.00 1.5 (1.4-1.6)± 2.8 (2.5-3.2) ±	Sex, Charlson comorbidity score, contraindication, residence of long term facilities	Not reported	14.5/22 (66%)
Carey et al[294,] **UK**	Retrospective longitudinal cohort N=9367 1997-2006	30-49 50-59 60-64 65-69 70-74 75-79 80-84	Within 6 months post discharge, obtained from primary care database 1st MI	Statins	81.1 84.3 79.0 78.6 72.6 66.3 57.7	0.96 (0.93-1.00)* 1.00 0.94 (0.90-0.94) 0.93 (0.90-0.96) 0.86 (0.83-0.89) 0.78 (0.75-0.82) 0.68 (0.64-0.72)	Sex and practice	Not reported	14.5/22 (66%)

Avanzini et al[292]	Retrospective longitudinal cohort	>70 vs. ≤ 70	Post discharge, data from	β-blockers	Not reported	----------	Sex, comorbidities, AMI characteristic at admission, procedure complications, treatment at discharge	----------	11.5/22
		GISSI-1				0.25 (0.18-0.35)		< 0.01	(52%)
	N=9452	GISSI-2				0.50 (0.42-0.59)		< 0.01	
	N=10407	GISSI-3				0.45 (0.40-0.50)		< 0.01	
	N=16958								
Italy	1984-1993								
Whincup et al[293]	Cross-sectional survey N=286	< 60, 60-69, ≥ 70	Post discharge, general practice records and patients questionnaire	LLD	7.00 vs. 49.0	0.18 (0.05-0.62)	Previous revascularisation, age at last diagnosis, year of last diagnosis, manual social classes, smoking and geographical residence	0.06	10/22 (45%)
Britain	1998-2000								

***** Risk ratio, ‡ OR Reference is men ≤ 75 (younger) for both men and women age >75, + Reference is age group (40-59). ± Indicated that older patients at higher risk of not receiving a β-blocker.

2.5.2 Inequalities by sex in prescribing of EBTs for MI

Unadjusted analyses

Prescribing rates of EBTs for secondary prevention following a MI vary by sex, with women being prescribed EBTs at a lower rate than men. In unadjusted analyses women were less likely to receive a prescription for aspirin after a MI than men (Table 7, unadjusted).[298-302] Only one study suggested an opposite trend with women aged less than 65 years being more likely to be prescribed aspirin than men of the same age.[303] Studies of prescribing rates of ACEI conflicted, some reporting no difference by sex, however [280,298,300,302] others reported that men received ACEIs more often than women.[278,299,301,303] One study reported that women were more likely to be prescribed an ACEI.[297] Women were less commonly prescribed β-blockers,[298-301,304] however, two studies reported a non-significant trend towards women being more likely to be prescribed a β-blocker than men,[302,303] and one reported no difference.[280] Three studies examined the sex differences in prescribing of CCBs. In a Scottish study,[304] women were more likely to be prescribed a CCB than men (30.8% vs. 26.4%), a finding replicated in two studies from Japan.[301,303] The proportion of women prescribed a statin was lower than men in two studies.[280,302] Conversely, women were more likely to be prescribed a lipid lowering drug in studies from Japan,[301,303] but not in studies from Canada[300] and Sweden.[278]

Adjusted analyses

In multivariable analyses (Table 7, adjusted studies), women were less likely to receive aspirin compared to men. One age adjusted study reported that women and men were almost equally likely to be prescribed an ACEI,[305] though all other studies reported that women were less likely to be prescribed an ACEI or ARBs than men.[282,284,287,305-308] Most studies reported that women were less likely to be prescribed β-blockers.[282-284,287,289,305-310] However, a study by Rathore *et al.*[311] included patients diagnosed with MI between 1994 and 1996 and examined the difference in those older than 64 years. This study showed no difference in the prescribing of β-blockers by sex. Heller *et al*.[290] reported that after adjustment for demographics and year of MI, women were significantly more likely to receive β-blockers than men (OR 1.12; 95%CI 1.01-1.24, p=0.03). In Scotland, Weir *et al.*[310] examined 865 patients with a first MI and found that men were significantly more likely to be prescribed a β-blocker than women (OR 1.59; 95%CI 1.21-2.10) but the difference disappeared after adjustment (OR 0.98; 95% CI 0.70-1.37). Griffith *et al.*[306] reported that after adjusting for confounders, women were significantly (p=0.05) more likely to be prescribed β-blockers than men. In the GISSI trials[312] women were more likely

to receive β-blockers, however, the difference was attenuated with time. Two studies reported that women were more likely to be prescribed CCBs than men, though this did not reach statistical significance.[284,305] In general, statins were less likely to be prescribed for women compared to men, however, two studies reported that women were more likely to be prescribed a statin.[305,306]

Limitations in the reporting of the literature

The quality of the reporting of these studies was assessed by using STROBE checklist and ranged from 41% to 70%. In this section I will discuss the studies that examined sex inequalities in prescribing of EBTs which I did not discuss in the previous section 2.4.1.[298-303,305-307,309-311] The quality of reporting for these studies ranged from 41% to the highest score 63.6%. Three studies did not indicate the study design in their study title or abstract.[299,301,302] The study background was described clearly in almost all studies but one study did not explain the scientific background clearly.[301] Specific study objectives were not stated in three studies.[298,299,302] Criteria of eligibility was not described and discussed in four studies.[299,300, 302,310] Four studies did not define the variables included in their study clearly, including outcome variables and confounding variables.[301,302,305,307] No study adequately described or discussed potential sources of bias. All studies described the statistical methods used for analyses.

All studies reported the number of potential and eligible participants in their studies with the exception of one.[311] Only one study discussed and described the reasons for patient exclusions.[306] Two studies did not described the cohort characteristic.[302,311]Three studies described the missing data of included participants.[300,307,309] The number of outcome events was summarised clearly in the majority of studies, though it was not reported in three studies.[307,309,311] Six studies presented the unadjusted and adjusted analyses in their results, however, other studies either presented unadjusted or adjusted results. One study discussed the limitations including potential sources of bias.[305] Four studies did not interpret their results clearly.[300, 305, 307, 311]

Limitations in the design and analysis of studies included in the literature review

A number of gaps and limitations were also identified in the previous literature. Since the prescribing of EBTs is the main focus in these studies, many of the studies were limited to one or two drugs. [298,309-311] A number of studies used data for patients diagnosed between 1988 and 1997 and therefore prescribing may not represent current clinical practice. [298,305,309,310] The study by Griffith *et al*.[306] conducted in the Southwest of Scotland, had a number of strengths including the study design, a prospective cohort, which enabled EBTs to be collected at time of discharge, examined prescribing inequalities for almost all recommended EBTs and adjusted for a wide range of confounders that were included in the analyses. Its only weakness was its relatively small sample size though this is inevitable in a study that collects such detail. Unfortunately, they did not clearly describe whether they excluded patients who did not survive 30 days. A number of conducted studies used primary or secondary care data sets making the generalisability of results difficult. The age of patients included in the study was not mentioned in two studies. Finally, one study was subject to selection bias as they did not include patients who did not survive more than 30 days.[307]

In summary, there were a number of limitations in the literature surrounding the association between sex and prescribing of EBTs in MI. There was also a wide range in the quality of reporting of studies as assessed by the STROBE guidelines. Few studies achieved a quality score of over 63.6%, however, these studies were associated with a number of limitations that have already has discussed above such as selection bias and a small sample size. The study by Gislason *et al.*[287] had a number of strengths over other studies. This study adjusted for a wide range of confounders, although not socioeconomic status, and used nationwide population data sets for all hospitals in Denmark, making results generalisable. In general women were less likely to receive appropriate EBTs following MI than men.

Table 7 Inequalities by sex in prescribing of EBTs after myocardial infarction

Study	Design/year	subject	Prescribing	Medications	Prescribing percentage Women vs. men	OR, 95% CI Women vs. men	Adjustment	P values / statistical significance	STROBE Score (%)
Martinez et al[297]	Retrospective cross-sectional	324 and 190	At time of discharge from hospital chart	ACEI	Not reported	4.45 (2.16-9.14)	Unadjusted	Not reported	11/22
		N=514							(50%)
Spain	1989-91/ 1994								
Austin et al[280]	Retrospective population cohort	Age ≥ 65	Within 90 days post-discharge	ACEI	78.5 vs. 78.5	Not reported	Unadjusted	Not reported	12/22
				β-blockers	78.1 vs. 78.4				
		N=8706		Statins	76.7 vs. 82.0				(54.5%)
Canada	2005-06								
Sadowska et al[302]	Retrospective cross-sectional	N=420	At time of discharge from data centre	ACEI	90.4 vs. 90.9	Not reported	Unadjusted	0.84	8.5/22
				Aspirin	89.2 vs. 94.1			0.06	
		(Cardiology centre)		Clopidogrel	16.9 vs. 28.7			0.005	(39%)
				β-blockers	81.9 vs. 77.6			0.28	
				Statins Nitrates	78.9 vs. 85.8			0.06	
Poland	2005-06				54.8 vs. 49.2			0.26	
Hirakawa et al[301]	Prospective cross-sectional	< 65	At time of discharge Detailed chart review & questionnaire	ACEI	42.6 vs. 46.6	Not reported	Unadjusted	NS	11/22
				Aspirin	80.5 vs. 89.6			< 0.01	
		Women= 169		CCB	14.8 vs. 18.6			NS‡	(50%)
		Men= 1246		β-blockers	4.14 vs. 7.7			NS	
Japan	2001-2003			LLD	43.2 vs. 35.8			NS	
				Nitrates	46.7 vs. 49.8			NS	
		≥ 65		ACEI	34.7 vs. 41.7			< 0.01	
				Aspirin	72.4 vs. 81.2			< 0.01	
		Women=616		CCB	14.3 vs. 16.5			NS	
		Men=1240		β-blockers	5.40 vs. 5.97			NS	
				LLD	26.6 vs. 22.4			< 0.05	
				Nitrates	44.8 vs. 49.8			< 0.05	
Barakat et al[298]	Retrospective cohort study	Women=463	At time of discharge	ACEI	34.3 vs. 32.9	Not reported	Unadjusted	NS	12/22
		Men=1274		Aspirin	90.0 vs. 92.9			0.08	
England				β-blockers	31.6 vs. 44.9			< 0.001	(54.5%)
	1988-97								
Di Cecco et al[300]	Audit	≥ 60	Chart review	ACEI	57.0 vs. 56.0	Not reported	Unadjusted	Not reported	11.5/22
				Anticoagulant	17.0 vs. 11.0				
		Women=81		Aspirin	77.0 vs. 82.0				(52%)
				β-blockers	72.0 vs. 75.0				
Canada		Men= 142		LLD	33.0 vs. 48.0				

	2000			Nitrates	77.0 vs. 66.0				
Clarke et al[299]	Retrospective cross-sectional	Women=424	At time of discharge	Aspirin	75.0 vs. 79.7 28.7 vs. 42.2	Not reported	Unadjusted	< 0.01	11.5/22
UK		Men= 997		β-blockers				< 0.01	(52%)
	1998-90								
Hirakawa et al[303]	Retrospective cross-sectional	< 65	At time of discharge Detailed chart	ACEI Aspirin	33.5 vs. 40.1 71.3 vs. 64.1	Not reported	Unadjusted	NS NS	11/22
		Women= 143	review & questionnaire	CCB β-blockers	51.1 vs. 46.8 7.70 vs. 5.23			NS NS	(50%)
		Men= 822		LLD	17.5 vs. 12.4			NS	
Japan	1995-97			Nitrates	39.8 vs. 38.2			NS	
		≥ 65		ACEI	31.7 vs. 30.5			< 0.01	
				Aspirin	68.5 vs. 67.7			< 0.01	
		Women=319		CCB	35.3 vs. 38.4			NS	
				β-blockers	3.60 vs. 2.72			NS	
		Men=661		LLD	8.95 vs. 5.57			< 0.05	
				Nitrates	31.4 vs. 32.5			< 0.05	
Ohlesson et al[278]	Retrospective cohort	N=1364	Within three months post discharge 1st MI	ACEI LLD	63.0 vs. 72.0 82.0 vs. 87.0	Not reported	Unadjusted	Not reported	15.5/22
Sweden	2006		Income						(70%)
Macchia et al[282]	Three cohorts	Age ≤ 75	Post-discharge follow for one year	ACEI/ARBs Aspirin	81.3 vs. 79.3 83.2 vs. 87.0	0.94 (0.84-1.04) 0.72 (0.65-0.81)	Age, previous CHD, diabetes, stroke, TIA, atrial fibrillation,	Not reported	15/22
	2003-04			β-blockers	73.9 vs. 73.1	0.99 (0.90-1.08)	COPD, depression and		(68%)
Italy	2005-06 2007-08	N=21423		Statins	81.1 vs. 85.6	0.70 (0.63-0.78)	malignancy		
Heller et al[290]	Retrospective Cohort study	≥ 65	Outpatients prescription database with 90 days post discharge	β-blockers	Not available	1.12 (1.01-1.24)	Demographic and year of MI	0.03	11.5/22
		N=9534							(52%)
USA	1994-1997								
Rasmussen et al[289]	Retrospective cohort	1995-97	Within 6 months post discharge	Statins	Not reported	1.29 (1.18-1.45)	Age, concomitant medications, hospital type	Not reported	15/22
		1998-99	Follow statins purchased			1.26 (1.18-1.38)			(68%)
		2000-02				0.95 (0.88-1.03)			
	1995-2002		1st MI						
Denmark		N=17875							
Winkelmayer et al[288]	Retrospective cohort	N=4105	Within 120 days post discharge	ACEI/ARBs β-blockers	Not reported	0.93 (0.80-1.09) 0.87 (0.74-1.03)	Age, length of stay at hospital, concomitant medications	Not reported	12.5/22
	2004			statins		0.90 (0.77-1.06)			(57%)

Austria			1st MI						
Gislason et al[287]	Retrospective cohort	Men vs. women	Within 30 days post discharge	ACEI β-blockers	28.8 vs. 29.8 52.2 vs. 62.6	0.85 (0.82-0.89) 0.80 (1.21-1.30)	Age, calendar year, concomitant treatment (loop diuretic & antidiabetic drugs)	<0.001	15/22
Denmark	1995-2002	N=55315	1st MI						(68%)
Spencer et al[284]	Cross-sectional	N=5739	At time of discharge	ACEI Aspirin CCB β-blockers LLD*	Not reported	0.86 (0.74-1.01) 0.86 (0.78-1.01) 1.06 (0.92-1.20) 0.83 (0.73-0.94) 0.92 (0.73-1.16)	Age, medical history and clinical characteristic	Not reported	10.5/22
USA	1986-1997								(48%)
Griffith et al[306]	Prospective cohort	Women= 458	At time of discharge	ACEI Aspirin β-blockers Statins	49.6 vs. 52.0 86.7 vs. 90.3 38.0 vs. 48.8 23.8 vs. 23.8	0.85 (0.66- 1.08)+ 0.90 (0.62- 1.32) 0.78 (0.60- 1.00) 1.48 (1.10- 1.98)	Age, smoking, comorbidity, previous angina, revascularisation PAD, DM, HTN, and social deprivation	0.18 0.60 0.05 0.001	9/22
Southwest Scotland	1994-2000 follow up to end of 2001	Men= 821	1st MI						(41%)
Sial et al[309]	Retrospective cross-sectional	N=444	At time of discharge from medical records	β-blockers	Not reported	0.52 (0.30- 0.88)	Age, race, comorbidities, other medications, MI characteristic, physician	Not reported	13.7/22
USA	1990-1991								(62%)
Rathore et al[311]	Retrospective cross-sectional	≥ 65	At time of discharge from medical records	Aspirin β-blockers	Not reported	0.98 (0.96-0.99) 1.00 (0.97-1.02)	Age, illness severity, doctor speciality, live rural area, US census region of residency	Not reported	12.5/22
USA	1994-96	N=169079	database 1st MI						(57%)
Hanrratty et al[305]	Prospective cohort study	Women=850	At time of discharge	ACEI Anticoagulant Aspirin CCB β-blockers Nitrates Statins	Not reported	1.01 (0.82-1.26) 1.40 (0.97-2.03) 0.91 (0.68-1.23) 1.25 (0.96-1.63) 0.84 (0.67-1.07) 0.85 (0.69-1.06) 1.37 (0.92-2.03)	Age	0.91 0.07 0.55 0.09 0.15 0.15 0.12	11/22
		Men=1303							(50%)
England	Sep-Nov 1995								
Williams et al[307]	Retrospective cross-sectional	Women=438	Case notes	ACEI Aspirin	Not reported	0.83 (0.63-1.10) 0.93 (0.65-1.32)	Age	Not reported	10/22
		Men= 819	Exclude patients	β-blockers		0.97 (0.73-1.28)			(45.5%)
Wales	Jan, Feb, July and Aug 1999		died within 30 days	Statins		0.98 (0.74-1.30)			
Carey et al[294]	Retrospective cohort	Women=3107	Within 6 months post discharge,	Statins	72.0 vs. 75.9	1.01 (0.98-10.3)‖	Age, and practice	Not reported	14.5/22
	N=9367	Men=6210	obtained from primary care database						(66%)
UK	1997-2006		1st MI						

Avanzini et al[312] **Italy**	Retrospective cohort 1984-1993	GISSI-1 (N=9452) GISSI-2 (N=10,407) GISSI-3 (N=16,958)	Post discharge, data from	β-blockers	Not reported	1.15 (0.93-1.24) 1.06 (0.92-1.22) 1.03 (0.93-1.14)	Age, comorbidities, AMI characteristic at admission, procedure complications, treatment at discharge	No significant	11.5/22 (52%)
Weir et al[310] **Scotland**	Retrospective cohort 1994-1995	Age 30 -93 N=865	Post discharge, use record linkage database 1st MI	β-blockers	Not reported	1.02 (073-1.42)¶	Age, deprivation, obstructive airway disease, diabetes mellitus, PAD, prior beta blockers, prior of CCB, ACEI, alpha blockers, thiazide diuretic, loop diuretic, nitrates, antiplatelet drug, lipid lowering drug, steroid.	Not reported	14/22 (63.5%)

*LLD=Lipid lowering drug, ‡ Not significant, ǁ Risk ratio, ¶ Unadjusted OR 0.62 (0.48-0.82), + Unadjusted ACEI (OR 0.91, 0.72-1.14), aspirin (OR 0.70, 0.49-1.00), blockers (OR 0.64, 0.51-0.81), statins (OR 1.00, 0.76-1.30).

2.5.3 Inequalities by socioeconomic status in prescribing of EBTs for MI

The association between the prescribing of EBTs and socioeconomic status has only been examined in a few studies (Table 8).

Unadjusted analyses

In an unadjusted analyses Hawkins *et al.*[313] reported that the most deprived were more likely to be prescribed aspirin, though this difference became non-significant over time (RR 1.28; 95% CI 1.08-1.53) in 1999 and (RR 1.01; 95% CI 0.76-1.34) in 2007. In the same study ACEI/ARBs were prescribed similarly for the most and least deprived.[313] Although this study was not adjusted, it has a number of strengths such as large sample size obtained from the general practice database, including all EBTs, and it used a deprivation measurement based on different domains. In contrast, a Swedish study[278] using routinely collected regional data reported that the least deprived were more likely to be prescribed an ACEI than the most deprived (66.0 vs. 74.0). No studies reported a significant difference in prescribing rates of β-blockers between the most and least deprived groups.[278,313] Hawkins *et al.*[313] reported that statins were less commonly prescribed for the most versus the least deprived patients post-MI but this was not statistically significant (RR 0.67; 95% CI 0.45-1.01).

Adjusted analyses and limitations of the published literature

In the multivariable adjusted analyses examining the relationship between socioeconomic status and the prescription of aspirin, more deprived patients were not significantly less likely to be prescribed aspirin (OR 0.98; 95% CI 0.96-1.00). However, this study used a single deprivation measurement and only included patients aged ≥ 65 years in the study.[311] Reid *et al.*[314] reported that the least deprived were more likely to be prescribed an ACEI. Conversely, prescribing of β-blockers was higher among the least deprived patients after adjustment.[311,314] Although these studies adjusted their results for a wide range of confounders and examined prescribing inequalities for more than one drug, they were subject to a number of limitations such as limiting the study to patients aged ≥ 65 years,[311] excluding patients who did not survive more than 120 days leading to selection bias, [314] and using one measure to determine socioeconomic deprivation.[311,314] Carey *et al.*'s[294] study avoided these limitations using a measurement based on different domains of deprivation, though it was adjusted for only a few confounders. This study reported no difference in statin prescribing rates by socioeconomic status.[294] Reid *et al.*[314] reported that

statins were significantly more likely to be prescribed for men with high income than those with lower income.

Limitations in the reporting of the literature

The quality of the reporting of these studies was assessed by using STROBE checklist and ranged from 45% to 70%. All studies indicated their study design using common terms either in the title or in the abstract. Three studies did not state their objectives.[293,294,314] The study design was not described clearly in the methods for one study. [311] One study did not report the eligibility criteria for patients included in their analyses.[313] Two studies did not describe the statistical methods included in the analyses.[293,313] All studies reported the number of individuals included in the study and those included in the analyses, however one study did not.[313] Three of the six studies did not describe the demographic characteristics of the patients. [294,311,313] Only one study described and discussed the potential sources of bias in the limitation section. [278]

In summary, there were a number of limitations in the literature surrounding the association between socioeconomic and prescribing of EBTs in MI. There was also a wide range in the quality of reporting of studies as assessed by the STROBE guidelines. One study achieved a quality score of over 70%. In those studies that did adjust their analyses the most deprived individuals were less likely to receive appropriate EBTs following a MI.

Table 8 Inequalities by socioeconomic status in prescribing of EBTs after myocardial infarction

Study	Design /year/	Reference/ subject	Prescribing/ Deprivation measure	Medications	Prescribing percentage Affluent vs. deprived	OR, 95% CI Affluent vs. deprived	Adjustment	P values / statistical significance	STROBE Score (%)
Ohlesson et al[278]	Retrospective cohort	high income vs. Low income	Within three months post discharge	ACEI LLD	74.0 vs. 66.0 91.0 vs. 82.0	Not reported	Unadjusted	Not reported	15.5/22
		Age 40-100	1st MI						(70%)
	2006	N=1364	Income						
Sweden									
Hawkins et al[313]	Cross-sectional	Less deprived vs. Most deprived	General practice research database	ACEI/ARBs Aspirin β-blockers	17.5 vs. 18.8 33.7 vs. 43.3 32.1 vs. 32.9	0.92 (0.73-1.19)‡ 1.28 (1.08-1.53) 0.98 (0.52-1.82)	Unadjusted	Not reported	13.5/22
	1999	N=32976		statins	45.2 vs. 30.3	1.49 (0.99-2.22)			(61%)
UK									
	2007		IMD*	ACEI/ARBs Aspirin β-blockers statins	56.1 vs. 57.3 63.5 vs. 64.3 49.7 vs. 52.7 74.6 vs. 67.8	0.98 (0.76-1.26) 1.01 (0.76-1.34) 0.94 (0.72-1.25) 1.10 (0.85-1.41)			
Rathore et al[311]	Retrospective cross-sectional	Affluent vs. deprived	At time of discharge	Aspirin β-blockers	Not reported	1.02 (1.00-1.04) 1.05 (1.01-1.09)	Age, illness severity, doctor speciality, live rural area, US census region of residency	Not reported	12.5/22
		≥ 65							(57%)
USA	1994-96	N=169079	Household income						
Whincup et al[293]	Cross-sectional survey	Non-manual vs. Manual	Post discharge, general practice records and patients questionnaire	LLD	49.0 vs. 49.0	1.45 (0.82-2.56)	Previous revascularisation, age at last diagnosis, year of last diagnosis, manual social classes, smoking and geographical residence	0.2	10/22
		N=286							(45%)
	1998-2000	Men	*Occupation*						
UK									
Carey et al[294]	Retrospective cohort	Least deprived vs. Most deprived	Within 6 months post discharge, primary care database	Statins	72.0 vs. 75.9	1.01 (0.98-1.03)‖	Age, sex and practice	Not reported	14.5/22
		Women=3107	1st MI						(66%)
UK	1997-2006	Men=6210	IMD*						
Reid RJ et al[314]	Cross-sectional	High income vs. low income	Within 120 days post discharge	ACEI β-blockers Statins	Not reported	1.37 (1.24-1.51) 1.50 (1.35-1.68) 1.71 (1.53-1.90)	Age using 5 years age bands, urban residence and general health status	Not reported	15.2/22 (69%)

Canada	1999-2006	Men N=28216	administrative database		
		Women	Income	ACEI	1.04 (0.89-1.20)
				β-blockers	1.25 (1.06-1.47)
				Statins	1.32 (1.12-1.54)

* Index of Multiple deprivation, ‡ Rate ratio, ǁ Risk ratio

2.5.4 Trends in prescribing of EBTs for MI

Several studies have reported that the use of EBTs for secondary prevention post-MI has improved over the last decade (Table 9). Prescribing of EBTs at discharge or shortly after discharge has been examined in a number of studies.

Unadjusted analyses

Prescribing of aspirin or any antiplatelet agent at any time point post discharge increased over time in the studies.[282,284,315-319] Only one study reported that prescribing of aspirin declined at time of discharge, though the sample size was very small in this study compared to other studies.[297] Prescribing of ACEI/ARBs similarly improved over time. Since the 1990s the prescribing of β-blockers has improved.[282,284,297,315-320] The largest increases in prescribing were seen with statins.[282,284,315,316,319] Although all above studies were unadjusted, they have a number of strengths. Almost all of these studies included all recommended EBTs after MI, however, a few did not. Long time periods of the trend were examined in the majority of these studies, which helps to demonstrate how far prescribing EBTs has improved. A recent report published in 2014 by British Heart Foundation (BHF), reported that the prescription used in the prevention and treatment of cardiovascular diseases in England, Wales and Scotland increased over the time.[321]

Adjusted analyses

Few studies used multivariable analyses to examine the prescribing trends for EBTs after MI. Of the studies that did adjust for other confounders they all reported that prescribing rates improved over time for all of the above drugs. However, they only adjusted for a limited number of covariates or were limited to one or two drugs. One study[322] with a large sample size, included all patients diagnosed with MI from age 35 years and above, and examined prescribing trends for all recommended EBTs. This study, however, adjusted for limited confounders and was not specific for statins examining all lipid lowering drugs. This study showed that prescribing EBTs increased significantly from 1991 to 2002 for all secondary prevention therapies.

Limitations in the reporting of the literature

A number of studies were identified that examined the trends in prescribing after diagnosis with MI. In this section, I will focus my discussion on the studies that explicitly examined trends in prescribing of EBTs after MI.[315-320, 322-323] The quality of the reporting of studies describing the prescribing trends over the time was assessed using the STROBE checklist

and ranged from 36% to 74%. Two studies did not indicate the study design using common terms in the title or abstract.[318,320] The majority of studies provided a clear summary in the abstract including background, methods, results and conclusion.[315-319,322-323] Study objectives were not described clearly in three studies.[315,320,323] Study design was not clearly described in one study.[323] The eligibility criteria of patients for inclusion in the study was not described in three studies.[317,318,320] The outcome, exposure and potential predictors were not described clearly in one study.[320]

Statistical methods were described in all but one study not. [320] Furthermore, none of the studies described any further analyses or explained how missing data were addressed. All studies reported the number of eligible patients included in the study. Four studies did not describe the reasons for those who were excluded from the analyses. [315-317,320] The number of outcome events was not indicated in five studies.[315,319,324,323] Three studies presented the unadjusted and adjusted analyses in their results.[318,319,324] Other studies, however, either presented unadjusted or adjusted results. Two studies failed to discuss the source of the potential bias in their limitations.[322,324]

Limitations in the design and analysis of studies included in the literature review

A number of gaps and limitations were identified in the literature. Few studies examined prescribing trends using all EBTs and most limited their analyses to select groups of drugs. The majority of previous studies reported unadjusted analyses and therefore results were not adjusted for potential confounders. The results of some studies may not represent current clinical practice as they measured the trends using older data sets. De Ruijter *et al.*[320] did not explain how the practices included in the study were selected. In addition, this study examined prescribing at three different points but did not clarify whether they avoided double counting of individuals between periods. Selection bias was identified in two studies.[322,324]

In summary, a number of limitations were identified in the previous studies of trends in prescribing EBTs after MI. There was variation in the quality of reporting of studies as assessed using STROBE guidelines. There was, however, a general consensus in the literature that the prescribing of EBTs has improved over time.

Table 9 Trends in prescribing of EBTs after myocardial infarction

Study	Design/year	Reference/ Subject	Prescribing	Medications	Prescribing percentage	OR, 95% CI	Adjustment	P values / statistical significance	STROBE Score (%)
Spencer et al[284]	Cross-sectional	1986 vs. 1997	At time of discharge	ACEI Aspirin	0.00 vs. 40.0‡ 15.0 vs. 77.0	Not reported	Unadjusted	Not reported	10.5/22
		N=5739		β-blockers CCB	35.0 vs. 70.0 50.0 vs. 15.0				(48%)
USA	1986-1997			LLD*	1.00 vs. 20.0				
Perschbacher et al[318]	Cross-sectional	1979 vs. 1998	At time of discharge, medical records database	ACEI Aspirin	0.00 vs. 39.0 10.0 vs. 88.0	Not reported	Unadjusted	Not reported	13/22
	1979-1998	N= 2093		β-blockers	25.0 vs. 73.0				(59%)
USA									
De Ruijter et al[320]	Cross-sectional	2000 vs. 2007	Post discharge, obtained from medical records of GP	ACEI β-blockers	30.0 vs. 47.0 40.0 vs. 58.0	Not reported	Unadjusted	Not reported	8/22
	2000-2007	N=800		Statins	44.0 vs. 71.0				(36%)
Netherlands									
Gasse et al[316]	Retrospective longitudinal cohort	1997 vs. 2003	Within 6 months post discharge	ACEI/ARBs Aspirin	35.0 vs. 52.7 38.0 vs. 83.0	Not reported	Unadjusted	Not reported	15/22
		N=11927		β-blockers Statins	74.0 vs. 76.2 17.0 vs. 70.5				(68%)
Denmark	1997-2003								
Masoudi et al[317]	Retrospective cohort	1992 vs. 2001	At time of discharge, used patients Medical records	ACEI Aspirin	47.3 vs. 64.6 66.0 vs. 79.4	Not reported	Unadjusted	< 0.001 < 0.001	11.5/22
		N=20550		β-blockers	33.1 vs. 71.4			< 0.001	(52%)
USA	1992-2001								
Macchia et al[282]	Three cohorts	2003 vs. 2007	Within 1 year after discharge	ACEI/ARBs Aspirin	73.1 vs. 82.1 76.4 vs. 85.7	Not reported	Unadjusted	Not reported	15/22
	2003-04 2005-06 2007-08	N=21423		β-blockers Statins	59.3 vs. 71.2 67.0 vs. 80.6				(68%)
Italy									
Setoguchi et al[324]	Retrospective cohort study	1995 vs. 2004	Within 30 days post discharge	ACEI/ARBs Antiplatelet	39.2 vs. 50.0 2.60 vs. 50.9	Not reported	Unadjusted	<0.0001 <0.0001	13.7/22
		N=21484		β-blocker Statins	41.5 vs. 71.6 7.60 vs. 50.7			<0.0001 <0.0001	
USA	1995-2004								(62%)
Austin et al[315]	Cross-sectional	1992 vs. 2005 Age ≥ 65 years	Within 90 days post discharge from Ontario MI database,1st MI	ACEI/ARBs β-blocker	42.0 vs. 78.4 42.6 vs. 78.1	Not reported	Unadjusted	< 0.001	12.5/22
				statins	4.20 vs. 79.2				(57%)
Canada	1992-2005	N=132778							

Barron et al[323] **USA**	Cross-sectional 1994-1996	1994 vs. 1996 N=190015	At discharge, from national registry for MI2	ACEI	25.0 vs. 30.7	Not reported	Unadjusted	Not reported	12/22 (54.5%)
Setguchi et al[319] **USA**	Retrospective cohort 1995-2004	1995 vs. 2004 N=19368	Within 90 days post discharge	ACEI/ARBs β-blockers Statins	46.0 vs. 58.0 47.0 vs. 80.0 11.0 vs. 61.0	Not reported	Unadjusted	<0.001 <0.001 <0.001	13/22 (59%)
Martinez et al[297] **Spain**	Retrospective cross-sectional 1989-91/ 1994	1989 vs. 1994 324 and 190	At discharge	ACEI β-blocker Aspirin CCB	14.0 vs. 23.0 62.0 vs. 63.0 75.0 vs. 71.0 20.0 vs. 17.0	Not reported	Unadjusted	Not reported	11/22 (50%)
Aventine et al[292] **Italy**	Retrospective cohort 1984-1993	1984 vs. 1993 N=36817	Post discharge, data from GISSI-1 GISSI-2 GISSI-3	β-blockers	8.50 vs. 31.4	5.73 (5.23-6.26)	Age, sex, comorbidities, AMI characteristic at admission, procedure complications, treatment at discharge	Not reported	11.5/22 (52%)
Heller et al[290] **USA**	Retrospective Cohort study 1994-1997	1994 1995 1996 1997 N=9534 (≥ 65)	Outpatients prescription database with 90 days post discharge	β-blockers	Not reported	1.00 1.36 (1.20-1.53) 1.72 (1.50-1.97) 2.33 (2.03-2.67)	Demographic and year of MI	--------- 0.0001 0.0001 0.0001	11.5/22 (52%)
Gislason et al[287] **Denmark**	Retrospective cohort 1995-2002	1995 vs. 2002 N=55315	Within 30 days post discharge 1st MI	ACEI β-blockers	24.5 vs. 35.5 38.1 vs. 67.9	1.86 (1.73-2.01) 3.84 (3.58-4.13)	Age, sex, calendar year, concomitant treatment (loop diuretic & antidiabetic drugs)	<0.001	15/22 (68%)
Carey et al[294] **UK**	Retrospective cohort N=9367 1997-2006	1997-1998 1999-2000 2001-2002 2003-2004 2005-2006	Within 6 months post discharge, from primary care database, 1st MI	Statins		1.00 1.34 (1.31-1.47)* 1.68 (1.58-1.79) 1.93 (1.81-2.07) 1.97 (1.84-2.11)	Age, sex and practice	Not reported	14.5/22 (66%)
Hardoon et al[322] **UK**	Retrospective cohort N=10,352 1991-2002	1991 vs. 2002 ≥ 35 years	Within 90 days post discharge, general practice (GP) database	ACEI Antiplatelet β-blocker LLD	11.0 vs. 71.0 46.0 vs. 86.0 26.0 vs. 68.0 3.00 vs. 79.0	1.28 (1.26-1.30) 1.20 (1.17-1.23) 1.23 (1.20-1.26) 1.79 (1.73-1.85)	Age, sex, and GP	Not reported	16/22 (74%)
		Men=6586		ACEI Antiplatelet β-blocker LLD	11.6 vs. 72 .7 47.7 vs. 87.1 32.9 vs. 73.3 3.90 vs. 83.1	1.30 (1.27-1.32) 1.20 (1.18-1.22) 1.22 (1.20-1.24) 1.83 (1.78-1.89)		< 0.001 < 0.001 < 0.001 < 0.001	

		Women=3766		ACEI	10.2 vs. 67.1	1.25 (1.22-1.28)	< 0.001	
				Antiplatelet	42.3 vs. 83.5	1.20 (1.17-1.23)	< 0.001	
				β-blocker	12.8 vs. 59.7	1.24 (1.21-1.27)	< 0.001	
				LLD	1.28 vs. 71.7	1.72 (1.66-1.79)	< 0.001	
Gale C et al[325]	Cross-sectional	2003 vs. 2010	At time of				Not reported	16/22
		<55	discharge, obtained	Aspirin	95.8 vs. 82.5	0.20 (0.19-0.22)*		
England and Wales	N=612995	>85	from electronic data base		81.1 vs. 71.6	0.59 (0.55-0.63)		(74%)
		<55		ACEI	81.4 vs. 76.5	1.35 (1.27-1.42)		
		>85			57.4 vs. 55.9	1.06 (1.01-1.12)		
		<55		β-blockers	85.5 vs. 75.3	0.52 (0.49-0.55)		
		>85			49.1 vs. 56.7	1.35 (1.29-1.43)		
		<55		Clopidogrel	56.1 vs. 97.3	28.48 (20.64-39.69)		
		>85			28.1 vs. 89.1	81.31 (59.06-112.26)		
		<55		Statins	94.2 vs. 82.4	0.29 (0.26-0.31)		
		>85			61.3 vs. 68.6	1.38 (1.31-1.46)		

*Relative risk, ‡ result approximated from a figure.

2.5.5 Prescribing of EBTs for MI by comorbidities

Prescribing of EBTs post-MI may be influenced by the presence of concomitant disease. One study reported that aspirin was less commonly prescribed in patients with end stage renal disease (ESRD) post MI.[326] Prescribing rates of ACEIs were lower among patients with the comorbidities of diabetes mellitus, HF, cancer, stroke, chronic kidney disease (CKD) and RF.[280] Similar trends have been reported for β-blockers and statins.[280,326,327]

A number of studies examined the effect of comorbidities using adjusted multivariable analyses and reported that the presence of concomitant disease was associated with a lower rate of prescribing of EBTs (Table 10). Aspirin was prescribed less commonly among patients with diabetes than without.[328] ACEI/ARBs were prescribed more commonly in patients with respiratory disease, diabetes and HF.[287,288,328] However, rates of prescribing of ACEI/ARBs were lower in those with CKD and RF.[308] The most widely studied group of drugs was β-blockers. The presence of a number of comorbidities (asthma, COPD, diabetes, PAD, HF and atrial fibrillation) was associated with lower rates of prescribing of β-blockers.[287,288,290,309,310,328] Two comorbidities were associated with higher rates of prescribing of β-blockers, these were hypertension[309] and CKD.[308] One study,[308] reported that statins were more commonly prescribed in patients with CKD. Other studies, however, reported that statins were less likely to be prescribed in the presence of comorbidities.[288,308,328]

Limitations in the reporting of the literature

Few studies examined the relationship between comorbidities and the prescribing of EBTs following a diagnosis of MI. The STROBE scores for literature that described the association between comorbidities and prescribing of EBTs after MI ranged from 45% to 68% (Table 10). Four studies did not mention their study design either in the title or in the abstract.[290,326,327,328] Four authors did not state their study objectives.[287,288,308,328] One study did not report the eligibility criteria for patients included in their analyses.[310] The outcome, exposure, predictors and potential confounders variables were not defined clearly in one study.[310] No studies discussed or identified potential sources of bias, though all studies reported how the statistical analysis was conducted. One study described a subgroup analysis.[308] Four studies did not report the number of individuals included in the study and the patient population was not clearly described in other studies.[280,326,327,290, 309,328]

The rationale of excluding participants from a study was explained in four studies.[287,288,326,328] Two studies did not describe the baseline characteristics of the included population.[326,328] Missing variables were only reported in one study.[309] Four studies presented the unadjusted and adjusted analyses in their results.[288,308, 309,310.] Other studies, however, either presented unadjusted or adjusted results. Three studies discussed the limitations including the source of potential biases.[288,308,326]

Limitations in the design and analysis of studies included in the literature review

A number of gaps and limitations were also identified in the previous literature. Three studies were subject to bias. Norhammar *et al.*[328] obtained comorbidity diagnosis from patients and is therefore subject to "recall bias". They also excluded patients aged 80 years and older. Winkelmayer *et al.*[308] excluded patients who did not survive more than 30 days after diagnosis "survivor bias" and Berger *et al.*[326] excluded patients younger than 65 years selection bias. Limiting the study sample to one area, or one hospital will limit the generalisability of the results to the whole population. Younis *et al.*[327] examined the association between comorbidities and prescribing EBTs after MI in a small sample recruited from one hospital. A number of studies were limited to one disease such as RF or diabetes.[326-328]

In summary, there were a number of limitations in the literature surrounding the association between comorbidities and prescribing of EBTs in MI. There was also a wide range in the quality of reporting of studies as assessed by the STROBE guidelines. Only a few studies achieved a quality score of over 70%. The presence of comorbidities was generally associated with lower rates of prescribing of EBTs.

Table 10 Inequalities in prescribing of EBTs after MI by comorbidities

Study	Design/year/ Subject	Reference/	Prescribing	Medications	Prescribing percentage	OR, 95% CI	Adjustment	P values / statistical significance	STROBE Score (%)
Berger et al[326] **USA**	Retrospective cohort N=146765 1994-1996	ESRD vs. No ESRD=1025 ≥ 65	Not reported	ACEI Aspirin β-blockers	27.6 vs. 37.2 62.0 vs. 78.9 37.7 vs. 45.8	Not reported	Unadjusted	Not reported	
Austin et al[280] **Canada**	Retrospective population cohort N=8706 2005-06	DM vs. No DM Age ≥ 65 HF vs. No HF Cancer vs. No cancer Stroke CKD	Within 90 days post-discharge Used linked administrative database	ACEI β-blockers Statins ACEI β-blockers Statins ACEI β-blockers Statins ACEI β-blockers Statins ACEI β-blockers Statins	69.7 vs. 79.0 79.4 vs. 78.2 77.9 vs. 79.6 77.0 vs. 79.0 75.5 vs. 79.2 71.8 vs. 82.1 64.9 vs. 78.9 72.1 vs. 78.5 64.1 vs. 80.0 75.0 vs. 78.6 75.4 vs. 78.4 75.8 vs. 79.6 59.7 vs. 80.3 75.8 vs. 78.5 74.6 vs. 80.0	Not reported	Unadjusted	Not reported	12/22 (54.5%)
Younis et al[327]	Retrospective cross-sectional N=400 1995-1999	DM vs. not DM=201	At discharge obtained from the case sheet 1st MI	β-blockers	23.4 vs. 52.3	Not reported	Unadjusted	Not reported	10/22 (45.5%)
Norhammar et al[328] **Sweden**	Retrospective longitudinal cohort N=25633 1995-1998	DM vs. Not DM=5193 < 80 years	At discharge, Medical records database (RIKS-HIA)	ACEI Aspirin β-blockers Statins	50.0 vs. 34.0 80.0 vs. 84.0 75.0 vs. 80.0 25.0 vs. 28.0	1.45 (1.33-1.58) 0.97 (0.87-1.08) 0.97 (0.87-1.07) 0.88 (0.80-0.97)	Adjusted different confounders, however not particularly mentioned	Not reported	10/22 (45.5%)
Heller et al[290]	Retrospective longitudinal cohort study	AF vs. No AF HF vs. No HF	Outpatients prescription database with 90 days post discharge	β-blockers	Not reported	0.86 (0.76-0.97) 0.52 (0.47-0.58)	Demographic and year of MI	0.01 <0.01 <0.01 <0.01	11.5/22 (52%)

		COPD vs. No				0.49 (0.44-0.56)			
	N=9534								
		Asthma vs. No				0.32 (0.22-0.47)			
USA									
	1994-1997	≥ 65							
Winkelmayer et al[288]	Retrospective cohort	Asthma/COPD vs. No	Within 120 days post discharge	ACEI/ARBs	Not reported	1.07 (0.86-1.34)	Age, sex, length of stay at hospital, concomitant medications	Not reported	12.5/22
				β-blockers		0.67 (0.55-0.83)			
	N=4105		1st MI	statins		0.87 (0.71-1.07)			(57%)
Austria	2004								
Gislason et al[287]	Retrospective longitudinal cohort	DM vs. No DM	Within 30 days post discharge	ACEI	Not reported	1.48 (1.40-1.58)	Age, sex, calendar year, concomitant treatment (loop diuretic & antidiabetic drugs)	Not reported	15/22
				β-blockers		0.79 (0.74-0.84)			
	N=55315	HF vs. No HF	1st MI	ACEI		3.32 (3.19-3.47)			(68%)
				β-blockers		0.71 (0.68-0.74)			
Denmark	1995-2002								
Sial et al[309]	Cross-sectional	COPD vs. Non	At time of discharge from medical records	β-blockers	Not reported	0.21 (0.07- 0.60)	Gender, age, race, comorbidities, other medications, MI characteristic, physician	Not reported	13.7/22
	N=444	HTN vs. Non				1.86 (1.11- 3.12)			(62%)
USA	1990-1991	HF vs. Non				0.46 (0.27-0.79)			
Wei et al[310]	Retrospective longitudinal cohort	OAD vs. Not	Post discharge, use record linkage database 1st MI	β-blockers	Not reported	0.30 (0.15-0.60)*	Age, sex, deprivation, obstructive airway disease, diabetes mellitus, PAD, prior beta blockers, prior use of CCB, ACEI, alpha blockers, thiazide diuretic, loop diuretic, nitrates, antiplatelet drug, lipid lowering drug, steroid.	Not reported	14/22
		DM vs. Not				0.93 (0.57-1.65)			(63.5%)
	N=865	HF vs. Not				0.33 (0.19-0.60)			
		PAD vs. Not				0.64 (0.31-1.32)			
Scotland	1994-1995	Age 30 -93							
Winkelmayer et al[308]	Retrospective longitudinal cohort	CKD vs. Not	Within 30 days post discharge	ACEI/ARBs	38.0 vs. 45.0	0.78 (0.75-0.82)+	Demographic, discharge year, comorbidities, health service measure, in-hospital procedures		15/22
				β-blockers	55.0 vs. 58.0	1.00 (0.96-1.03)			
		CKD=3645		Statins	28.0 vs. 26.0	1.02 (0.96-1.08)			(68%)
	N=21484								
USA	1995-2004	≥ 65							
		ESRD vs. Not		ACEI/ARBs	28.0 vs. 45.0	0.57 (0.49-0.66)			
				β-blockers	57.0 vs. 58.0	0.94 (0.86-1.04)			
		ESRD=436		Statins	22.0 vs. 26.0	0.83 (0.70-0.99)			

* Unadjusted OR: OAD 0.24 (0.15-0.39), DM 0.83 (0.51-1.35), HF 0.27 (0.16-0.46), PAD 0.52 (0.28-0.94), + Risk ratio,

OAD=obstructive airway disease, HF=heart failure, PAD=peripheral vascular disease, DM=diabetes mellitus,

RIKS-HIA= Register of information and knowledge about Swedish heart intensive care admissions, ESRD=End stage renal disease, CKD=chronic kidney disease

2.6 Inequality in prescribing of EBTs for Angina

Patients who are diagnosed with angina usually have frequent episodes of chest pain which can be treated using nitrate sublingually or nitrate spray such as glyceryl trinitrate (GTN). Other treatments that are recommended by the guidelines include β-blockers, CCBs, ACEIs, aspirin and statins. The literature surrounding the prescribing of these medications in patients with angina will be discussed here.

2.6.1 Inequalities by age in prescribing of EBTs for angina

Unadjusted analysis

Two unadjusted studies (Table 11) reported the association between age and prescribing of EBTs in patients with angina. Murphy *et al.*[329] reported that the proportion of patients prescribed aspirin, ACEI/ARBs, CCBs and nitrates was higher among older patients compared to younger patients. In contrast, prescribing of β-blockers was higher among younger patients.[329] This study included a wide range of EBTs, age grouping, large sample size and datasets that represent the Scottish population. Beaulieu *et al.*[330] in a study from Canada with a large sample size, wide range of ages (although limited to a few EBTs and to older ages) reported that older patients were less commonly prescribed β-blockers or any lipid lowering drugs.[330] This study used an out-patient pharmaceutical database. Clopidogrel was more often prescribed in young patients although prescription rates were very low in all ages.[329] Statins were less likely to be prescribed in older patients.[329]

Adjusted analysis

Bennett et al.[238] identified a cohort of patients who were prescribed a nitrate (as a proxy for a diagnosis of angina) and reported that older age was significantly associated with lower rates of prescribing of aspirin, β-blockers and statins but higher rates of ACEI prescriptions (OR 1.65; 95% 1.35-1.79, p <0.001). This study has a number of strengths such as including most recommended EBTs, a large sample size and wide range of age groups, and included all patients diagnosed with angina at any point during their life (i.e. no age specificity), although this was adjusted for fewer confounders. Whincup *et al.*[293] examined the difference in prescribing of all lipid lowering drugs (LLD i.e. not specific for statins) in very limited sample and again reported that older patients were less likely to be prescribed a LLD than younger patients.

Only a small number of studies examined the relationship between age and the prescribing of EBTs following a diagnosis of angina. The majority of studies demonstrated that older

age groups were less likely to receive most EBTs compared to younger age groups (Table 11). However, studies were limited by a number of factors such as study design, data collection methods, and/or statistical methods.

Limitations in the reporting of the literature

The STROBE checklist score for the literature describing the association between age and prescribing EBTs ranged from 45% to 63.5% (Table 11). The study design was indicated using common terms such as cross-sectional in all studies. Two studies did not describe their study objectives.[293,329] All authors described their study design clearly in the methods. The eligibility criteria were described in all studies. Variables included in the analyses were not described clearly in one study. [293] Although, all studies described how their sample was collected, one study failed to describe the statistical methods. [293]

One study did not define the study cohort clearly.[238] Though all studies did not explain the reason for non-participation. The participant characteristics were not described in one study.[238] . No studies reported the degree of missing data in their results. Two studies did not report the number of outcome events.[293,238] A clear and full presentation of outcomes including unadjusted results and results adjusted for potential confounders was only presented by one study.[293] Two studies discussed their limitations.[329,330]

Limitations in the design and analysis of studies included in the literature review

A number of gaps were also identified in the previous literature as have been already discussed in part above. There are clear differences in prescribing of EBTs by age after angina diagnosis. Two studies, however, were unable to adjust the results for confounders.[329,330] Even though many studies did adjust for confounders, the biggest limitation was that they did not adjust for a wide range of confounders that may explain the unadjusted association between prescribing and age. All studies used single resources for data, i.e. primary care or secondary care data sets.

In summary, there were a number of limitations in the literature surrounding the association between age and prescribing of EBTs in angina. There was also a wide range in the quality of reporting of studies as assessed by the STROBE guidelines. Although Beaulieu *et al.*[330] adjusted for a few confounders, it included the most recommended EBTs, had a large sample size and wide range of age groups. The study by Murphy *et al.*[329] although unadjusted examined a wide range of EBTs, over broad ages in fairly big sample

size and in datasets that represent the Scottish population. Both studies demonstrated that older patients were less commonly prescribed β-blockers and statins.

Table 11 Inequalities by age in prescribing of EBTs for angina

Study	Design /year	Age range/ subject	Prescribing	Medications	Prescribing percentage Eldest vs. youngest age group	OR, 95% CI Old vs. young	Adjustment	P values / statistical significance	STROBE Score (%)
Murphy et al[329]	Cross-sectional	< 45, 45-54, 55-64, 65-74, 75-84, ≥ 85	Primary care practice database	ACEI/ARBs	26.2 vs. 20.9	Not reported	Unadjusted	Not reported	14/22
				Aspirin	65.6 vs. 50.5				
	N=9508		CMR	β-blockers	34.1 vs. 46.1				(63.5%)
				CCB	36.2 vs. 22.3				
Scotland	2001-2002			Clopidogrel	2.60 vs. 3.40				
				Nitrates	59.1 vs. 43.7				
				Statins	9.30 vs. 38.3				
Beaulieu et al[330]	Cross-sectional	65-69, 70-74, ≥ 75	Outpatients pharmaceutical database	Antiplatelet	Not reported	Not significant	Unadjusted	Not reported	14/22
				β-blockers		0.71 (0.64-0.79)			
	N=11141			LLD		0.28 (0.25-0.31)			(63.5%)
Canada	1996-1997								
Bennett et al[238]	Retrospective cross-sectional	44-45, 55-64, 65-69, 70-74, ≥ 75	Post discharge, GP prescription database	ACEI	Not reported	1.65 (1.35-1.79)	Age, sex, health region	< 0.001	13
				Aspirin		0.79 (0.72-0.85)		< 0.001	
	N=47275			β-blockers		0.42 (0.39-0.46)		0.02	(59%)
				Statins		0.24 (0.22-0.25)			
Ireland	1999-2000								
Whincup et al[293]	Cross-sectional survey	< 60, 60-69, ≥ 70	Post discharge, general practice records and patients questionnaire	LLD*	7.00 vs. 49.0	0.18 (0.05-0.62)	Previous revascularisation, age at last diagnosis, year of last diagnosis, manual social classes, smoking and geographical residence	0.04	10
	N=286								(45%)
UK	1998-2000								

*One third of prescriptions were statins, LLD= not specific lipid lowering drug including statins and fibrate.

2.6.2 Inequalities by sex in prescribing of EBTs for angina

Unadjusted analyses

A number of studies examined the association between sex and prescribing of EBTs for angina (Table 12). Use of aspirin was higher among men than women,[331-333] however, one unadjusted study reported that women were significantly more likely to be prescribed an antiplatelet agent.[330] Two studies reported that the likelihood of being prescribed a β-blocker was higher among men than women.[332,333] Beaulieu *et al.*[330] reported that the odds of being prescribed a β-blocker was significantly higher among women compared to men. One study examined the difference in prescribing CCBs and reported that men were more likely than women to be prescribed a CCB.[333] Daly *et al.*[332] reported that the proportion of men to be prescribed a statin was higher than women.

Adjusted analyses

Bennett *et al.*[238] reported that aspirin was significantly more likely to be prescribed for men compared to women. Crilly *et al.*[334] found that there were no sex differences in prescribing aspirin, however, this study included a relatively small sample size, and was adjusted for few confounders. Patients selection in this study was based on nitrate prescription, leading to potential selection bias. Murphy *et al.*[329] in a large study and adjusting for more confounders including socioeconomic status reported that women were significantly less likely to receive antiplatelet agents (aspirin and clopidogrel) compared to men. Two studies examined the prescribing of ACEI/ARBs and reported that men were significantly more likely to receive these drugs than women.[238,329] Similar results were reported for β-blockers and statins.[238,329] Furthermore, women were significantly less likely to receive a CCB. Women were also less likely to be prescribed a nitrate though this was not significant after adjustment.[329]

Limitations in the reporting of the literature

Only a few studies examined the relationship between sex and the prescribing of evidence based therapies following a diagnosis of angina. The majority of studies demonstrated that women were less likely to receive most EBTs compared to men (Table 12). The STROBE checklist used to assess the reporting qualities for the studies examined the prescribing inequalities based on sex difference. The score for literature described the association between sex and prescribing EBTs in those with angina ranged from 41% to the highest score 66% (Table 12). A balanced summary including background, aims, methods and

results was provided in all studies except one.[331] Two studies failed to explain the scientific background[331,333] and three studies did not describe their objectives.[329,332,333] All authors described their study design, eligibility criteria, and cohort setting clearly in the methods. Variables included in the analyses were not described clearly in one study.[331] The potential source of bias was only discussed in one study.[333] However, all studies described how the sample was collected. All studies described the statistical methods. None of the studies described further analyses including sensitivity tests.

One study did not define the study cohort clearly,[238] and only one study explained the reason for non-participation.[334] One study did not describe the characteristics of the cohort,[238] and none described the missing data. Two studies did not report the number of outcome events.[238,333] Only two studies accounted for confounders.[332,334] Three studies discussed their limitations[329,330,333] and two studies included potential sources of bias in the limitations and discussion. [332,334]

Limitations in the design and analysis of studies included in the literature review

The main limitation of the literature was the failure to adjust for confounders in most studies.[330-333] In one of the studies that did adjust, selection bias (due to the definition of a case in the cohort) potentially limits the generalisability of results. [334]

In summary, there were a number of limitations in the literature surrounding the association between sex and prescribing of EBTs in angina. There was also a wide range in the quality of reporting of studies as assessed by the STROBE guidelines. A few studies achieved a quality score of over 66%. These studies demonstrated that women patients are generally less commonly prescribed most EBTs than men.

Table 12 Inequalities by sex in prescribing of EBTs for angina

Study	Design/year	Reference/ subject	Prescribing	Medications	Prescribing percentage Women vs. men	OR, 95% CI Women vs. Men	Adjustment	P values / statistical significance	STROBE Score (%)
Beaulieu et al[330]	Cross-sectional	N=11141	Outpatients pharmaceutical database	Antiplatelet β-blockers LLD	Not reported	1.43 (1.32-1.55) 1.15 (1.06-1.25) Not significant	Unadjusted	Not reported	14/22
Canada	1996-1997								(63.5%)
Scirica et al[333]	Cross-sectional	Women=1160	At time of discharge	Aspirin β-blockers	63.0 vs. 72.0 42.0 vs. 43.0	Not reported	Unadjusted	Not reported	12/22
		Men=1788		CCB Nitrates	35.0 vs. 31.0 45.0 vs. 47.0				(54.5%)
USA	1995-96								
Daly et al[332]	Cross-sectional	N=3379	At time attending physician from electronic case record forms	Aspirin β-blockers Statins	73.0 vs. 81.0 65.0 vs. 67.0 45.0 vs. 51.0	Not reported	Unadjusted	< 0.001 < 0.001 0.021	13.5/22 (61%)
Europe	March-Dec 2000								
Bouvy et al[331]	Retrospective cross-sectional	N=346	General practice	Aspirin	33.0 vs. 66.1	Not reported	Unadjusted	Not reported	9/22 (41%)
Netherland	1996								
Bennett et al[238]	Retrospective cross-sectional	Women=22524	Post discharge, GP prescription database	ACEI Aspirin	Not reported	0.82 (0.79-0.85) 0.74 (0.71-0.77)	Age, health region	Not reported	13/22
		Men=24751		β-blockers Statins		0.87 (0.83-0.90) 1.01 (0.97-1.05)			(59%)
	N=47275								
Ireland	1999-2000								
Crilly et al[334]	Retrospective Cross-sectional	Women=552	Primary care, Liverpool primary care data project	Aspirin β-blockers	81.0 vs. 86.0 28.0 vs. 38.0	0.75 (0.53-1.03) 0.69 (0.53-0.90)	Age, duration of angina, and previous MI	Not reported	14.5/22
		Men=610		Statins	53.0 vs. 56.0	1.08 (0.85-1.38)			(66%)
England	Sep-Dec 2001								

Murphy et al[329]	Cross-sectional	Women vs. men	Primary care practice database	ACEI/ARBs	Not reported	0.69 (0.63-0.76)	Practice, age, deprivation category, comorbidity,	<0.001	14/22
				Antiplatelet*		0.82 (0.74-0.90)		<0.001	
	N=9508			β-blockers		0.86 (0.78-0.93)		<0.001	(63.5%)
				CCB		0.85 (0.78-0.93)		<0.001	
Scotland	2001-2002			Nitrates		0.96 (0.88-1.04)		0.31	
				Statins		0.83 (0.76-0.91)		<0.001	

*Aspirin and clopidogrel

LLD= Not specific lipid lowering drug including statins and fibrate.

2.6.3 Inequalities by socioeconomic status in prescribing of EBTs for angina

Two cross-sectional studies examined the association between socioeconomic status and prescribing of EBTs for angina.[293,329] In a cross-sectional study conducted in Scotland between 2001 and 2002, Murphy *et al.*[329] investigated prescribing EBTs for those diagnosed with angina in a primary care setting. In adjusted analyses (for practice, age, deprivation category, comorbidity), the same study reported that patients residing in more deprived areas were significantly more likely to be prescribed ACEI/ARBs (OR 1.51; 95%CI 1.23-1.85, p<0.001), CCB (OR 1.25; 95%CI 1.04-1.48, p=0.015), or nitrates (OR 1.25; 95%CI 1.05-1.50, p<0.012) than those from the least deprived areas. However, there were no differences in prescribing β-blockers, statins, or antiplatelet agent. Whincup *et al.*'s[293] study was conducted between 1998 and 2000, and used general practice records in Britain. This study was limited to one therapeutic group (LLD) and recruited a small sample size of men aged between 60 and 75 years. This study used an occupation-based measure of deprivation. Patients in the non-manual class received more prescriptions of LLD compared to patients in the manual class (28% vs. 21%). After adjustment for covariates (previous revascularisation, age, year of last diagnosis, smoking status and geographic residence), manual social class was associated with lower odds of prescribing LLD (OR 0.75; 95% CI 0.42-1.32, p=0.32) compared to non-manual social class. The limitations of these studies and quality of reporting of these studies have been discussed previously.

2.6.4 Trends over time in prescribing of EBTs for angina

Trends over time in the prescribing of EBTs for angina have not been well studied. Smith *et al.*[335] examined the prescribing rate of EBTs for a small sample (885) of patients hospitalised due to unstable angina from 1990 to 1995, which may not be relevant to current clinical practices and patients with stable chronic angina. Out-patient pharmacy records were used to identify elderly patients who filled a prescription within 90 days after hospital discharge, however, those who did not were excluded leading to selection bias. Furthermore, they only included the first diagnosis of unstable angina. Prescribing rates over time showed modest increases for aspirin (from 73.0% to 74.1%) and for β-blockers (33.3% to 36.4%). However, prescribing of ACEI/ARBs increased from 18.4% to 29.0% (p <0.01) and from 12.1% to 26.5% (p >0.01) for dihydropyridine CCBs, respectively. Conversely, the prescribing of nitrates declined significantly over the study period (81.0%

to 72.2%, $p < 0.05$), and declined for non-dihydropyridine CCBs mainly diltiazem (from 56.9% to 40.1%, $p < 0.01$).

The quality of reporting for this study was assessed using the STROBE checklist and it scored 12/22 (54.5%). This study did not describe a clear background, statistical methods, and interpretations.

2.6.5 Prescribing of EBTs for angina by comorbidities

The influence of concomitant comorbidities on the prescribing of EBTs for angina was examined in one study. Beaulieu *et al.*[330] described the association of comorbidities (COPD, HF and DM) in prescribing EBTs for patients with stable angina aged ≥ 65 years. Prescribing of EBTs was obtained from an out-patient pharmaceutical database for all prescriptions prescribed by either a general practitioner or cardiologist. The study only reported the significant results for each of the studied medications. Furthermore, it examined general groups of therapies (antiplatelet agents and LLD) instead of specific effective known drugs, e.g. aspirin, clopidogrel and statins. In a multivariable analyses, prescribing of EBTs was significantly lower among patients with COPD for β-blockers (OR 0.20; 95% CI 0.16-0.24), for antiplatelet agents (OR 0.73; 95% CI 0.62-0.86) and for LLD (OR 0.69; 95% CI 0.57-0.84). Patients with HF were less likely to receive β-blockers (OR 0.58; 95% CI 0.51-0.65), antiplatelet agents (OR 0.86; 95% CI 0.77-0.97) and LLDs (OR 0.60; 95% CI 0.52-0.70). Patients with diabetes, however, were more likely to be prescribed an antiplatelet agent (OR 1.13; 95% CI 1.01-1.26). The limitations of this study have been discussed previously.

2.7 Inequalities in prescribing of EBTs for PAD

2.7.1 Inequalities by age in prescribing of EBTs for PAD

Two studies described age differences in the prescribing of EBTs for patients diagnosed with PAD. Paquet *et al.*,[336] a Canadian study that had a fairly large sample (n=5062) between 1997 and 2007 and included a population-based cohort of patients ≥ 50 years with PAD, reported that age did not influence the prescribing of antiplatelet agents within 90 days following discharge. However, the proportion of patients prescribed an ACEI was higher among younger patients (50-64 years) compared to older patients aged ≥ 80 years (44.0% vs. 40%, p <0.05). Furthermore, the proportion of patients prescribed statins was higher in younger patients (57% vs. 33%, p< 0.005). In a cross-sectional study that was conducted in China, Jing *et al.*[337] examined the association between age and the prescribing of statins in patients with a history of atherosclerotic disease including PAD. In the same study, only 89 patients with PAD were included and interviewed. Using an unadjusted analysis, they reported that increasing age was associated with higher rates of being prescribed a statin. For example, 38% of patients aged between 70 to 80 years were prescribed a statin compared to 13% of those patients aged between 50 and 59 years.

The quality of reporting for these studies was assessed using the STROBE checklist and was found to be 14.5/22 (66%) for Paquet *et al.*[336] and 11/22 (50%) for the Jing *et al.*[337] study. Neither of these studies stated the study design either in the title or abstract. Jing *et al.*[337] did not mention their study objectives and did not describe clearly the variables included in the study. Although recall bias was evident in the Jing *et al.*[337] study, sources of potential bias were not described in either study. These studies described the statistical methods used in the analyses, however, they did not describe any further analyses. The number of eligible patients included in the study was indicated in both studies. In their study, Jing *et al.*,[337] however, did not explain the reasons for those who were excluded from the analyses. Finally, both studies failed to discuss their study limitations and give an explicit overall interpretation of results.

2.7.2 Inequalities by sex in prescribing of EBTs for PAD

A few studies described sex inequalities in prescribing of EBTs for patients with PAD (Table 13). All studies only reported the proportional differences in prescribing medication. Furthermore, three studies were small in sample size.[337,338,339] Antiplatelet agents were prescribed more frequently for women compared to men though the difference was not statistically significant.[336] Klein-Weigel *et al.*[338] examined the use of aspirin and clopidogrel separately and reported that the rate of prescribing clopidogrel was significantly greater for women compared to men (p=0.03), but no significant difference in aspirin use was observed. Also, it was reported that women were more frequently prescribed ACEI and slightly less frequently ARBs than men. In another study, the prescription of ACEIs was significantly ($p < 0.005$) higher in men compared to women.[336] Men were also more likely to be prescribed a β-blocker than women. Moreover, a large study reported that men were more likely to be prescribed statins,[336] though two small studies found the opposite.

Four studies examined the relationship between sex and the prescribing of EBTs following a diagnosis of PAD. Generally, women were less likely to receive most EBTs compared to men (Table 13). The STROBE score for literature ranged from 45% to 66% (Table 13). The study design was not indicated in all studies. Only one study described their study objectives.[336] All authors described their study design, eligibility criteria and cohort setting clearly in the methods. Variables included in the analyses were not described clearly in three studies.[337,338,339] The potential sources of bias were not discussed in all studies, although one study was clearly subject to influence by recall bias. [337] All studies described the statistical methods, however, none of them described further analyses including sensitivity tests. All studies defined the study cohort clearly, however, only one study explained the reason for non-participation.[336] The participants' characteristics were described in all studies but none indicated the number of missing data in their results. One study did not report the number of outcome events.[339] No studies presented an adjusted analysis. Two studies discussed their general limitations, though all failed to discuss the sources of potential bias.

In summary, there were a number of limitations in the literature surrounding the association between sex and prescribing of EBTs in PAD. The most important limitation

was the lack of adjustment of the results. In general women were less likely to be prescribed EBTs.

Table 13 Inequalities by sex in prescribing of EBTs for PAD

Study	Design/year	Reference/ subject	Prescribing	Medications	Prescribing percentage Women vs. men	OR, 95% CI Women vs. men	Adjustment	P values / statistical significance	STROBE Score (%)
Paquet et al[336]	Retrospective cohort	Women=2610	Post discharge within 90 days	ACEI Antiplatelet	39.3 vs. 44.5 72.3 vs. 71.1	Not reported	Unadjusted	< 0.005 Not	14.5/22
		Men=3352		Statins	39.3 vs. 44.5			significant < 0.005	(66%)
Canada	1997-2007								
Klein-Weigel et al[338]	Retrospective cross-sectional	Women=143	Discharge medications documented in case records forms	ACEI ARBs	54.5 vs. 52.9 11.9 vs. 13.2	Not reported	Unadjusted	0.80 0.80	11/22
		Men=121		Aspirin Anticoagulant β-blockers Clopidogrel Statins	89.5 vs. 91.7 4.90 vs. 9.10 33.6 vs. 44.6 74.1 vs. 61.2 72.0 vs. 71.2			0.60 0.20 0.07 0.03 0.70	(50%)
Germany	Jan 2007-June 2008								
Jing et al[337]	Retrospective cross-sectional	N=89	Post discharge/ Diagnosis	Statins	40.0 vs. 16.0	Not reported	Unadjusted	Not reported	11/22
									(50%)
China	June 2007-Oct 09								
McDermott et al[339]	Randomised control trial	N=311	Not reported	LLD	73.7 vs. 79.5	Not reported	Unadjusted	Not reported	10/22
									(45%)
USA	Feb2006-Sep 09								

2.7.3 Inequalities by socioeconomic status in prescribing of EBTs for PAD

One study examined the association of socioeconomic status with prescribing of EBTs in patients with PAD.[340] This study defined the socioeconomic status according to the median income of the patients. This study used the zip code of the residence to categorise participants into five quintiles. In the unadjusted analysis, patients in the lowest socioeconomic quintile were significantly less commonly prescribed statins (risk ratio [RR] 0.84, 95% CI 0.83-0.86; p< 0.0001). However, the difference between socioeconomic status and prescribing of statins was attenuated (RR 0.99, 95% CI 0.99-1.01; p=0.77) after adjustment for practice, age, sex, history of MI, revascularisation in the previous 12 months, insurance, HF, diabetes, stroke, tobacco use and dyslipidaemia. Similarly, prescribing of an antiplatelet agent (aspirin and/or clopidogrel), was less likely in the lowest socioeconomic quintile (unadjusted RR 0.93; 95% CI 0.91-0.94; p< 0.0001). After adjustment, the difference was not significant (RR 0.99; 95% CI 0.99-1.01, p=0.87). The quality of reporting for this study was assessed using the STROBE checklist and it scored 13/22 (59%). This study did not state a specific study's objectives, did not describe the potential source of bias, and did not give the reasons for non-participation at each stage.

2.7.4 Trends over time in prescribing of EBTs for PAD

A few studies examined the trends over time in prescribing of EBTs after a diagnosis with PAD. All of these studies reported the proportional difference in prescribing EBTs (Table 14). Two studies included the four main drugs used as secondary prevention after PAD diagnosis, however, these studies did not report a significance test for their results.[316,341] Prescribing of antiplatelet agents significantly improved in two studies.[336,342] Prescribing of ACEI and β-blockers also significantly improved over time in two studies. The degree of significance, however, was not reported in the other studies. The main limitation for these studies was that they all used unadjusted analyses to report prescribing improvements after diagnosis with PAD. One study used population cohort patients over 64 years, and limited their analysis to statins.[343]

Limitations in the reporting of the literature

The quality of the reporting of studies described the prescribing trends over the time was assessed by using the STROBE checklist and ranged from 50% to 73% (Table 14). Two studies did not indicate the design of the study.[336,342] All authors described their study eligibility criteria, and cohort setting clearly in the methods. Variables included in the analyses were not described clearly in one study.[343] The potential source of bias was discussed in one study.[341] All studies described the statistical methods and only one study described further analyses including a sensitivity test.[342]

The study cohort was described clearly in all studies. Two studies explained the reasons for non-participation.[336,342] The participants characteristics were described in all studies. However, none of the studies indicated the extent of missing data in their results. Two studies did not report the number of outcome events.[343,342] A clear and full presentation of outcomes including unadjusted results and results adjusted for potential confounders were not discussed in three studies.[336,343,342] Three studies discussed the general limitations but only one study discussed the sources of potential bias. Two studies discussed and gave explicit explanations for the results. [342,341]

In summary, there were a number of limitations in the literature surrounding the trends over time and prescribing of EBTs in PAD. There was also a wide range in the quality of reporting of studies as assessed by the STROBE guidelines. Two studies achieved a quality score of over 73%.[341,342]

Table 14 Trends in prescribing of EBTs for PAD

Study	Design/year	Reference/ Subject	Prescribing	Medications	Prescribing percentage	OR, 95% CI	Adjustment	P values / statistical significance	STROBE Score (%)
Gasse et al[316]	Retrospective cohort	1997 vs. 2003	Within 6 months post diagnosis	ACEI/ARBs Aspirin β-blockers Statins	14.0 vs. 28.0 23.0 vs. 41.0 9.00 vs. 15.0 3.00 vs. 22.0	Not reported	Unadjusted	Not reported	15/22 (68%)
Denmark	N=3424 1997-2003								
Subherwal et al[342]	Retrospective cohort	2000 vs. 2007	Within 3 months post diagnosis	ACEI Antiplatelet Statins	11.0 vs. 17.0 29.0 vs. 59.0 9.00 vs. 56.0	Not reported	Unadjusted	<0.0001 <0.0001 <0.0001	16/22 (73%)
Denmark	N=34160 2000-2007	≥ 40							
Paquet et al[336]	Retrospective cohort	1997 vs. 2006	Post discharge within 90 days	ACEI Antiplatelet Statins	38.0 vs. 49.0 67.0 vs. 80.0 38.0 vs. 67.0	Not reported	Unadjusted	< 0.005 < 0.005 < 0.005	10/22 (45%)
Canada	N=5962 1997-2007								
Al-Omran et al[343]	Retrospective cross-sectional	1995 vs. 2004	Post discharge, obtained from ODB*	Statins	6.80 vs. 43.3	Not reported	Unadjusted	< 0.01	14.5/22 (66%)
Canada	N=23886 1995-2004	≥ 65							
Feringa et al[341]	Prospective cohort	1983-89 vs. 2000-04	Post discharge/ diagnosis, obtained from hospital records and patients	ACEI Aspirin β-blockers Statins	12.0 vs. 30.0 15.0 vs. 27.0 17.0 vs. 40.0 13.0 vs. 32.0	Not reported	Unadjusted	Not reported	16/22 (73%)
Netherland	N=2420 Jan 1983-Jan2005								

*ODB= Ontario Drug Benefit database.

2.7.5 Prescribing of EBTs for PAD by comorbidities

Jing *et al.*[337] examined the influence of concomitant hypertension and diabetes mellitus on the prescribing of statins for patients with PAD. They reported that compared to patients without hypertension, those with hypertension were less likely to receive a statin (13% hypertension vs. 28% no hypertension). Similarly, patients with diabetes were less likely to receive a statin (20% vs. 24%).

Summary

This literature review showed that inequality in prescribing of evidence based therapies for CHD (including MI and angina), MI separately, angina separately and PAD may exist for age, sex and socioeconomic groups and be influenced by other chronic concomitant disease. Furthermore, prescribing of EBTs has improved over time. In general, older age and female sex were associated with less prescribing of evidence EBTs. Most of the previous studies, however, focused on CHD and MI. Most studies focused on inequality in prescribing EBTs for age and sex. But different methods and designs have been used in the previous studies making comparison difficult.

The majority of prior studies examined prescribing inequalities using either a primary or secondary care database, which may mean that the results do not generalise to the other populations. Administrative databases were used in a number of studies allowing large sample sizes but not all studies were of sufficient size to make firm conclusions. A major limitation that was common to many of the studies was a lack of adjustment for confounders. This was the consistent limitation in the studies. Furthermore, of the studies that did adjust, a number did not adjust their results for socioeconomic status.

A number of studies only examined one or a few select drugs. This was evident for all conditions. This makes comparison of the relative prescribing inequalities between drugs difficult, e.g. are statins less likely to be prescribed in the elderly than aspirin in the elderly.

In this thesis, I will fill these gaps using a linked database of primary and secondary care records to identify patients, whether the first diagnosis was in hospital or by their GP records, and examine their prescription history. I will also examine various confounding variables including age, sex, socioeconomic status, comorbidities and calendar year, which will be studied in a consistent manner using one population-based data set. I will also examine a wide range of EBTs recommended for the treatment of MI, angina and PAD.

3.0 Aims and objectives

Aims

1. To describe the evidence based pharmacological therapies prescribed to patients diagnosed with MI, angina and PAD in Scotland.
2. To describe the factors associated with rates of prescribing of evidence based therapies including age, sex, socioeconomic status, and comorbidities after first presentation of MI, angina and PAD.
3. To describe trends over time in the prescribing of evidence based therapies for MI, angina and PAD over the period of the study.

Objectives

Multiple cardiovascular diseases will be identified. Each of the following objectives will be examined in relation to CHD (including angina and MI) and PAD.

- To describe the baseline characteristics and incidence rate for patients diagnosed with MI, angina, PAD and PAD/CHD
- To describe the rate of prescribing EBTs before, within 30 days and at any time after first diagnosis of MI, angina, PAD and PAD/CHD
- To describe the effect of age, sex, socioeconomic status and comorbidities on prescribing rate of EBTs within 30 days after first diagnosis of MI, angina, PAD and PAD/CHD
- To examine the independent effect of age, sex, socioeconomic status and comorbidities in prescribing EBTs within 30 days after first diagnosis of MI, angina, PAD and PAD/CHD
- To describe trends over time of prescribing EBTs within 30 days after first diagnosis of MI

- To examine whether the trends in prescribing differ by age, sex, socioeconomic status and comorbidities.

4.0 Methods

4.1 Data sources

The data used for analysis were extracted from a primary care database (The Continuous Morbidity Record) and a secondary care database (The Scottish Morbidity Records).

4.1.1 Electronic health records

Electronic health record (EHR) is a systematic digital format records system that can be shared across different health care settings adopting a longitudinal collection of electronic health information about an individual patient or population.[344] A wide range of data can be shared using EHR across different health care settings. These data may include demographics, medical history, medication and allergies, immunization status, laboratory test results, radiology images, vital signs, personal statistics such as age and weight, and billing information.[345] Generally, health care system is organised in different ways in different countries, however, generally it split into different settings including primary, secondary and tertiary care. Different health care professionals including physicians, nurses, radiologists, pharmacists, laboratory technicians and radiographers use EHR as well as administrative staff.[345] One of the advantages of electronic records over paper records is the decrease of errors due to handwriting problems and ease of physical storage requirements. Moreover, electronic records simultaneously affect other error-reducing technologies by rendering them coherent. Another significant additional advantage of delivering a longitudinal record by EHR models is the ability to track all medical interactions by a particular patient and provide comprehensive data across populations.[346,347] Many potential benefits for patients and providers of EHRs can be gained, including reduction in medical errors, delivery of more efficient health care, reduced costs, streamlined clinical workflow, better disease management, improved quality, and improved data tracking and accessibility.[270] Furthermore, health care researchers can potentially benefit from widespread EHR adoption. Observational data from clinical practice, obtained by EHR data "observational data from clinical practice" have implications in many aspects of research. Understanding practice patterns, assessing outcomes, evaluating quality indicators, and developing effective quality improvement interventions are some examples of these implications.[348] Furthermore, EHRs can serve care organizations, insurance companies and other payers. This is particularly important with the growing

concern over the cost and quality of medical care.[349] Moreover, accessing records by patients reviewing lab results, scheduling appointments online, referring back to their discharge and follow-up instructions and even communicating with their physician or nurse practitioner via e-mail are all made possible with the use of EHRs. Consequently, these capabilities would enhance the ability for patients to become actively involved in managing their own care. Furthermore, the use of EHRs would result in improving efficiency within health care as well as decreasing costs. This is mainly due to preventing duplicate tests from being ordered as well as the ability of accessing a complete medical record.[350]

Continuous Mortality Records database (CMR), which collects data from the primary care setting, and Scottish Morbidity Records (SMR) which collect data from the secondary care setting, are the two main data sets in Scotland. They are mainly handled by the information service division (ISD). These databases are comprised of a range of data including patients' demography and treatments (which will be discussed in detail in the method chapter).

4.1.2 The General Practice Administration System for Scotland

Based on a software that was originally developed by Dr David Ferguson, The General Practice Administration System for Scotland (GPASS) was introduced in 1984 as a clinical record and practice administration software package. This relatively simple system was initially based on the routine administrative functions of the practice. After a year and a half 85 general practices with approximately 750,000 patients in Scotland had installed the system. It was a practical system, requiring little knowledge of computing, other than elementary keyboard skills. Furthermore, within ten years (between 1988 and 1999) 80% of general practices, covering some 4,133,000 of the 5,102,400 registered patients in Scotland, had used the GPASS system.[351,352] The routine information included in the GPASS are: details of patient registration and identification, details regarding repeat prescription which recorded the interval between review consultations as well as some details with regard to up to 9 authorised drugs per patient, some data related to generic drug preparations (unless commanded during data entry to authorise a specific proprietary preparation for an individual patient), additional morbidity factors including smoking and blood pressure. A system that

enables patients to be flagged for drug trials using seven markers for each practice, dates related to routine major procedures such as most recent cervical smear test, records of blood pressure measurements, health visitor markers, e.g. for immunisations, and nurse markers such as injection therapies.[351,353,354]

GPASS Data Evaluation Project (GDEP) was introduced in 1988 at the Department of General Practice and Primary Care, the University of Aberdeen. This project approached those responsible for GPASS with the concept of the Electronic Questionnaire (EQ). It aimed at interrogating the GPASS patient data files and store anonymised and aggregated data on floppy disc. These data can be returned by participating practices for analysis and feedback. In June 1988, the first version of EQ was released and it enabled each practising GP to obtain information that reflected a practice level summary of clinical, prescribing and administrative data. This data is available on the practice computer and it goes beyond specific information about individual patients.[351,355]

By April 1991, the EQ system had attracted, 328 GPASS general practices with 1,954,759 patients that were receiving feedback.[351,356] The number had increased to 460 practices with 2,400,000 patients by 1998.

Further development enabled collecting anonymous morbidity and drug data at patient and postcode level so that at the time of each diagnosis or prescription for individual patients the data was collected from the entire practice database. By doing this, the geographical, locality and regional analysis of data and linkage of morbidity and prescribing information have been achieved.[351,357]

4.1.3 Continuous Morbidity Record (CMR)

Almost all residents in Scotland are registered with a primary care practitioner and health care is provided free of charge. Individuals of any age can register and attend a primary health care practice at any point in time. Access to secondary care services is obtained through referral from primary care or by emergency admission. In the initial CMR dataset, patients' information was collected by GPs, i.e. in participating general practices.

The conception of CMR came about in 1995 as a reply for the recommendations for recording more detailed morbidity data for every GP consultation. These

recommendations were suggested by the University Department of General Practice in Aberdeen and the Information and Statistics Division (ISD) of the Scottish Office. This conception of CMR was introduced as a result of refinements made to GPASS software which was increasingly used by GPs as noted above. Data collected by this system was comprehensive and included symptoms, diagnoses, health promotion, illness prevention, and screening and administration activity.[351,352] Using 'Read Codes', each doctor/patient contact was coded and recorded in GPASS. As patient records used with the consultation were largely paper based, data operators supported by ISD, funded by the CMR project and employed within each participating CMR practice, coded and entered data directly into the clinical system after the patient contact had been completed. These data operators meant that potential drawbacks existed, however, as data collected by CMR practices lacked standardised criteria and this was largely discussed through internal validation.

In general, the CMR project aimed to support existing data collection systems that already existed within primary care (EQ) and secondary care (SMR). In 1998, CMR was recognised as a national dataset.[329,358,359] In 2002, 55 practices were participating. In 1999, the introduction of New GPASS' software (a Microsoft Windows™ based version of GPASS) enabled the CMR database to be carried out centrally by the data collection systems of ISD.

A positive feature of CMR is that clinicians recorded an additional code for every morbidity contact that identified whether the presenting condition is a first occurrence, a persistent problem with previous recent contacts, or a re-occurrence (defined as a subsequent presentation after a quiescent interval). This 'modifier' code can be used to separate disease workload from period prevalence and incidence.

In April 2003, CMR was superseded by Practice Team Information (PTI). By February 2010, 62 practices contributed in PTI which covered around 6% of the Scottish population (Appendix 3). Between 2003 and 2006, PTI information was collected by GPs, practice nurses, district nurses and health visitors in a general practice or a patient's home. However, by 2007 data were only collected by GPs and practice nurses.[360,361] These primary care data are representative of the Scottish primary care population in terms of age, sex, deprivation and urban/rural mix. Information from primary care obtained by practitioners at patients' face-to-face consultations are entered in the CMR record, including: unique Patient identifier, modifier (described below),

date of birth, date of consultation, sex, type of encounter, post code, clinician ID and diagnosis.

Each diagnosis is given a modifier that indicates whether the condition is new (first time diagnosis), recurrent or persistent. A diagnosis is recorded using a Read code, which was developed as a medical term thesaurus.[362] It is used as a national coding system in primary care. Read codes comprise five alphanumeric characters. They start with broad classification and then narrow to become more specific. For example, 'G….' denotes circulatory system disease, 'G3…' denotes ischaemic heart disease, 'G30..' denotes acute MI, 'G301.' denotes acute MI not otherwise specified and 'G3011' denotes acute anteroseptal infarction. The encounter type identifies whether the contact took place at a home visit, in out of hours or a surgery/clinic.[358,361,362]

Prescribed medications are also recorded in the CMR by general practitioners. Entering a new prescription or a repeat prescription is freely inputted without guidance and as a consequence the prescribed drug can be recorded automatically as various trade or generic names that are registered in the British National formulary (BNF). Recorded information for a drug includes drug name, dose, date of prescription, date of first time prescribed (start date) and date of discontinuation (end date).[358,363]

The included practices were located throughout Scotland (Appendix 3) with the highest concentration of practices and population in the central area of Scotland. Between April 1996 and April 1999 the number of practices increased from 47 (267,146 registered patients) to 60 (364,346 registered patients).[358,361] The decline in the recruitment of CMR practices was largely due to the release of several new GPASS versions.

4.1.3.1 Data Quality

ISD operates a continuous quality assurance system for completeness and accuracy of data entry into the CMR database. Completeness is assessed quarterly and it is measured by comparing the number of consultations on the CMR database in a week to the recorded contacts for the same week. Accuracy is assessed by comparing the clinical notes with the Read codes held on the CMR database for a random sample for 80 contacts in each practice. In 1999-2000 the completeness of capture of contacts was 91% and the accuracy of Read coding was 91%. Sensitivity of the CMR database has been tested in a survey that compared electronic data of chronic diseases with the paper records of 50 patients in each CMR practice. This survey demonstrated that

approximately 100% sensitivity was achieved. Furthermore, the sensitivity of repeat prescribing was found to be nearly 100%.[361,364]

4.1.3.2 Validity of the CMR datasets

Although no sensitivity analysis has been carried out specifically on CMR practices, a study by Whitelaw *et al.*[365] showed that, in a sample of 5,567 patients who were registered in 41 out of the 410 GPASS practices that contributed to the EQ dataset in April 1992, a 75% sensitivity over 19 conditions was observed when comparing data recorded on the computer with patient notes. A sensitivity of nearly 100% was found for repeat prescriptions. A series of quality assurance exercises undertaken more recently by ISD in 2001 have been reassuring in terms of data accuracy.[351]

The practices included in the CMR are broadly representative of the Scottish population in relation to age, sex and socioeconomic status.[366] The age and sex structure of the cohort population matches the age and sex structure of the Scottish population. The distribution of socioeconomic status is similar to the Scottish population. In an assessment of the dataset, 91.5% were not in deprived areas versus 88.5% of the whole population of Scotland. Therefore deprived patients were slightly under-represented in the cohort but not significantly so. The CMR practices reflect the rural and urban mix of Scotland. They are located across Scotland including the islands (Appendix 3) and are therefore representative of the geographical distribution of the population of Scotland. For example 10.8% of patients are in rural communities compared to 8.5% of the whole Scottish population.[366] There were no specific criteria required to become a CMR practice. There was no specific requirement to be of a certain standard to join the CMR. Experience in coding was not necessary as a coder was employed by the Information and Statistics Division (ISD) to provide coding support to the practice. The training of the coders was undertaken and maintained by ISD.

A number of factors may influence the performance of the practice and lead to a potential source of bias. Single-handed practices did not participate in CMR (Dr Colin Simpson, ISD Custodian of datasets, personal communication) therefore the inability to account for this is not a potential source of bias in the analysis though the results may not be applicable to single-handed practices. However, prior studies have shown that there is no difference in standards between single-handed practices and other practices with multiple partners, therefore the lack of single-handed practices is unlikely to make

the results of these analyses biased.[367,368] Indicators of quality of a practice are the Practices Accreditation (PA) and Quality Practice Award (QPA) standards as well as being a training practice; however, data on these characteristics are not recorded in CMR. (James McNally, Health and Social care pathway, ISD NHS National Services Scotland, and Paula L McClements, ISD NHS National Services Scotland, personal communication). Therefore analyses will be corrected for clustering to account for these potential differences in the absence of practice level data on quality indicators.

4.1.3.3 Organisation and extraction of the CMR data

Information extraction from the CMR is carried out through the use of an electronic questioner (EQ) software programme and data stored in Rich Text Formatted files. These are converted and stored in a Microsoft Access™ database, which is a relational database system. Microsoft Access™ uses Standard Query Language (SQL) queries to extract data from long lists of information into smaller and easier understandable tables. These are the patient table, the clinical events table and the prescribing table. All tables include the unique practice and patient identifiers. The patient table includes date of birth, sex, registration status (i.e. whether temporary, full registered or deregistered), and post code of residence. The clinical events table includes Read codes for every identified diagnosis, date of diagnosis, modifier code (to discriminate whether first, recurrent or persistent), and encounter number. The prescribing table includes information of the name, dose, quantity and frequency on every drug prescribed, start and end dates, and whether the drug was prescribed as repeat or acute script (Script type).[358,361]

4.1.4 Scottish Morbidity Record (SMR)

Secondary care data in Scotland is collected as a series of records at the individual level. The main record type denotes the general type of healthcare received during a hospital episode. They include outpatient attendances (SMR00), all discharges from acute hospitals (SMR01), maternity units (SMR02), psychiatric units (SMR04), neonatal units (SMR11) and geriatric long stay inpatients (SMR50). This study covers the analysis of SMR01 data.

The SMR01 is a scheme of episode-based patient records which relate to all inpatient or day case discharges from non-obstetric and non-psychiatric wards across Scotland's hospitals. A stay in hospital (continuous inpatient stay) can consist of one or more episodes. A new episode is generated if a patient changes specialty within a hospital or

moves between hospitals. The SMR01 record contains data from the case notes. These data include patients' principal diagnosis and up to five comorbidities or secondary diagnoses, up to four operations, identifiable information, administrative details including hospital and consultant in charge, demographic information. These comorbidities are recorded if they affect the management of the patient or are associated with the main condition or are chronic conditions. At discharge from each episode, principal diagnosis and comorbidities are assigned using codes from the World Health Organisation (WHO) International Classification of Diseases (ICD) system. The ICD coding system is a standard diagnostic tool for epidemiology, health management and clinical purposes. It is divided into several chapters and each disease given a numeric code comprised of three or four digits. Three digits are used to define major headings and the fourth digit to give more specificity of the diagnosis. For example, for MI the ICD-9 code is 410 (three digits) and more specifically 410.0 is MI of the anterior wall. In the tenth revision the coding system was revised using alphanumeric codes so that MI is I21 (three "digits") and anterior wall infarction is I21.1 (four "digits"). Up to five digits are used in ICD coding but for practical purposes up to four are used commonly. All linkages with SMR data include as many digits as are coded in the database, be that 3 or 4 or 5. Diseases were coded using the ninth revision (ICD-9) up to March 31st 1996 and the tenth revision (ICD-10) thereafter.

The General Register Office for Scotland records the causes of death (GROS) for all Scottish residents.[361,369] The codes used to classify deaths are allocated using ICD system. Classification of the cause of death is based on information collected on the medical certificate of cause of death which contains information on the underlying cause of death and up to three other causes considered to have contributed to the death.

Linking individual patients records together was first demonstrated in 1968.[361] In Scotland, secondary care records and death registration records belonging to the same patients have been linked together in the Scottish Record linkage system since 1970.[370,371] This system aimed to bring all records centrally stored in ISD into one dataset. Since 1980, the linked dataset holds hospital discharge records for non-psychiatric, non-obstetric specialist (SMR01) together with Scottish Cancer Registry records (SMR06) and Registrar General's death records.

To provide profiles for each individual patient the probability matching record was used to link records from individual hospital episodes from different SMR schemes together with records from the Registrar General. Methods of probability matching

have been developed and refined in Oxford, Scotland and Canada since the early 1970s, and are used by the Record Linkage System to allow for inaccuracies in identifying information. After linking records together, two records are compared using identifying items such as surname, first initial, sex, month and day of birth, and postcode. The decision is made as to whether they belong to the same patient. A computer algorithm calculates a score for each pair of records that is proportional to the likelihood that they belong to the same patients. The huge volume of data would mean that it would be impossible to compare every record with all the other records and blocking is used to cut down the number of comparisons required. Only those records that have a minimum level of agreement in identifying items are compared. Probability matching then allows mathematically precise assessment of the implications of the levels of agreement and disagreement between records.[361,372,373]

The process of linkage is complex and more details can be found in an overview by Jaro.[372] The mathematical basis of the linking algorithms is outside of the scope of this thesis. However these are detailed by Jaro. In essence however, firstly blocks are formed for matching as described above. Weights and computed probabilities are then computed so that the two records match. A matrix of all matching variables, age, sex, postcode etc. is made and a linear sum made, above which a match is deemed to have been made. This process also looks for duplicates using the same algorithm.

4.1.4.1 Quality of the data

The linkage process is largely automatic as a threshold score based on probability matching dictates the decision as to whether the records belong together. Clerical checking has shown that the accuracy of probability matching is 98%.[361,374] In ISD the Quality Assessment and Accreditation (QAA) unit monitor the quality of SMR data, by assessing accuracy, completeness, consistency and fitness for purpose. QAA performs routine validation of a sample of SMR01 records where data held on the sampled records are compared with information contained in the medical case notes. Between 2000 and 2002, assessment and accuracy of a 2% sample of SMR01 data demonstrated that the accuracy for recording of clinical data at the three-digit level was 88% for the main diagnosis, falling to 81% at the four-digit level.[375] A recent assessment report (May 2012) of SMR01 data showed a similar accuracy of recording clinical data regarding the main condition at the three-digit level and four-digit level (described above 4.1.3).[376] The accuracy of AMI, angina and chest pain coded as a principal diagnosis was shown to be 86%, 88% and 93% respectively. The accuracy of AMI

coded as a principal diagnosis had been shown to be 97% in the1996/97 audit.[377] The accuracy of coding when the PAD is the main diagnosed condition is from 90 to 100%.[378]

4.1.4.2 Quality outcome framework

General practice scheme has an essential public health role to improve the population health care.[379] A number of countries introduced pay-for-performance to approach better care for chronic disease in the primary care.[380] In the United kingdom (UK), a new contract for general practice known as Quality and Outcome Framework (QOF) was established in 2004, which includes the pay-for-performance elements.[379] The QOF is a voluntary incentive program for general practices in the UK.[381] The QOF measures a general practice's achievement against a number of evidence-based indicators that are designed to encourage good practice.[382] The QOF comprised of five main components "domains" including: clinical, public health, public health additional services, patient experience, quality and productivity. Each of these domains consists of a number of measures "indicator", and payment for the general practice based on their level of achievement against those indicators. In the 2013/14 revision, the QOF measured achievement against 121 indicators, practices scored points on the basis of achievement against each indicator, up to a maximum of 900 points.[383] Indicators are distributed on the main five domains as follow:

- Clinical domain, comprised of 93 indicators across 20 clinical areas (e.g. chronic kidney disease, HF, hypertension) worth up to a maximum of 610 points,

- Public health domain, comprised of 9 indicators (worth up to 113 points) across four clinical areas – blood pressure, CVD (primary prevention), obesity and smoking,

- Public health additional services domain, comprised of 9 indicators (worth up to 44 points) across four service areas – cervical screening, child health surveillance, contraception and maternity services,

- Quality and productivity domain, comprised of 9 indicators (worth up to 100 points) as a service area in its own right (previously part of the now retired organisational domain),

- Patient experience domain, comprised of one indicator (worth up to 33 points) that relates to length of consultations.

A study used data collected from the first two years of QOF. This study showed an increase in pre-target improvements in the quality of care for asthma and diabetes.[379,384] Campbell *et al.*[379,385] reported that the rate of improvement for heart disease has significantly declined below the improvement rates of the years before introducing the QOF (p= 0.02).

Furthermore, this study found that the total quality score for year 2007 was similar to that in year 2005. A systematic review of the literature demonstrated that a modest improvement in diabetes care has been indicated since the introduction of the QOF.[386] For those conditions covered by the QOF, there is evidence of excessive or inappropriate prescriptions or referrals.[387,388] In a study of 147 practices in the UK, diabetes care was found to be steadily improving, but it was not possible to associate this with the QOF, however, this could be due to other factors such as the implementation of guidelines and the National Service Framework which may also contribute to improvements.[389] Financial encouragement has shown that the rate of cervical cancer screening in general practices has improved after implementation of the pay-for-performance scheme.[390]

4.1.4.3 Organisation and extraction of the data

The linked data is stored as a conventional flat file of records. The records for each individual are stored adjacently in chronological order and marked with a unique personal identifier. Different types of record are stored in their original unlinked format and are preceded by several fields of linkage information. The dataset is complex and requires tailored FORTRAN programs to access the data. The staff in ISD use FORTAN programming to produce specific datasets.[351]

4.1.5 Measurement of Socioeconomic Deprivation

Socioeconomic Deprivation (SED) can be measured by a variety of available methods including the use of a single measurement such as income, education and occupation. Occupation based indicators of socioeconomic status are commonly used. They can represent the socioeconomic status by demonstrating a person's place in society related to their social standing, income and intellect. Furthermore, occupation can characterise working relationships between employers and employees.[391] In the Registrar's General social class scheme occupations are classified into six categories and ranked from highest "professional I class" which includes doctors, lawyers, to "intermediate II",

"skilled non-manual III-N", "skilled manual III-M", "partly skilled IV" to the lowest social class, "unskilled V" which includes jobs such as porters and labourers. This classification can also be narrowed to two categories, non-manual and manual, I-IIIN vs. IIIM-V.[392,393] The most important strength of occupational measurements is their availability in different routine data such as the census and death registration. However, they cannot be used for those who are not currently employed and as the head of the household occupation is used to decide on the classification for a household it may not reflect the occupational class of all members of the house such as women.[392,393]

Income is another indicator that can be used to measure socioeconomic status. Income is the best single indicator to determine an individual's living standards.[391] However, income is relative and can be influenced by the education attainment and occupation. Furthermore, it is a sensitive question that many participants may refuse to provide information on when asked and is therefore prone to bias.[391] The policy of a health care system may limit the use of income as a socioeconomic status measure, for example in countries with free access to health care it may not be as good a determinant of health care use as in countries with no free health care system.[393] Furthermore, income (as obtained from a job) may not fully encapsulate the income of a house or individual as other sources of income such as state benefits are not usually taken into account.

Education is a commonly used measure of socioeconomic status in epidemiological studies.[391,393] Education level is not such a sensitive question, so a higher proportion of participants are likely to respond to this question compared with questions on income. Education is easy to measure as years to complete education, or categorised by education level such as primary or high school, low or higher education. Level of education can be influenced by birth cohorts and access to free education. Therefore, the social and behavioural correlates of education may be influenced by age.[391,393]

More complex measurements based on different domains can be used to measure socioeconomic status. The UK has a long history in constructing this type of measurements including: the Townsend Scale,[394] Carstairs Index,[395] the Index of multiple deprivation (IMD),[396] and Scottish index of multiple deprivation (SIMD).[397,398] The Townsend and Carstairs measures are based on data collected by census, however the IMD and SIMD, using the routinely collected data, are regularly updated.[398] For the purpose of this thesis I will discuss the Scottish index of multiple deprivation below.

Scottish Index of Multiple Deprivation

The Scottish Index of Multiple Deprivation (SIMD) is an area based measurement that is used in Scotland to identify small area concentrations of multiple deprivation across Scotland.[399] In August 2003, a report from the Scottish Centre for Research on Social Justice called "Measuring Deprivation in Scotland: Developing a Long-Term Strategy" was published by the Scottish Executive.[400,401] A wide range of recommendations for the short, medium and long term measurement of deprivation were established. The recommendations in the long term strategy report to build on the Scottish Indices of Deprivation (SID) 2003 were executed by the Scottish Executive in order to deliver the Scottish Index of Multiple Deprivation (SIMD) 2004.[400,402]

In the first published SIMD in 2004, all Scotland is divided into 6,505 small areas, which are known as data zones.[403] In each data zone, the median population is 769 individuals. The most deprived 976 data zones are the 15% most deprived in Scotland which tend to be the focus of policies and funding. A range of administrative systems and the Scottish Census of Population have been used as the source of the data for the SIMD 2004. Six domains including current income, employment, health, education, skills and training, and telecommunication formed the SIMD 2004. The relative weight and number of indicators for each domain are:

- Income (7 indicators, given 28% of the total weighting),
- Employment (3 indicators, 28%),
- Health (7 indicators, 14%),
- Education, skills and training (5 indicators, 14%),
- Geographic Access to Services (8 indicators, 9%),
- Crime (6 indicators, 5%) and
- Housing (2 indicators, 2%).

All together, they provide a comprehensive picture of deprivation within each data zone across Scotland, measuring both individual and area characteristics.[403,404] Each domain is comprised of and measured using different indicators. For example the housing deprivation domain is measured by two indicators obtained from the 2001 census: 1) Persons in households which are overcrowded and 2) Persons in households without central heating. Scores from each domain are combined into an overall score using weights. This is further expressed as a rank, where 1 is the most deprived data zone in Scotland and 6505 is the least deprived data zone. These scores are then grouped into quintiles or deciles. A final score is ultimately produced by adding together the

household populations that experience each type of deprivation represented by the indicators.[403,404] Because the SIMD is based on census data it can be applied to older data such as that used in this thesis.

In 2006, the second version of SIMD was published.[405] The new 2006 SIMD included a new public transport sub-domain in the geographic access to services domain and a new crime domain, which is a collection of selected recorded crimes linked to deprivation. The SIMD 2006 is therefore based on 37 indicators in seven domains as well as data from 2004 or 2005 with their relevant denominators. Furthermore, two SIMD versions were published in 2009 and 2012 and both used the same domains as 2006.

The degree of deprivation in one data zone compared to another cannot be determined by the SIMD. However, Scotland's most deprived small areas on the overall index and each individual domain can be identified by the SIMD. This can be commonly achieved by applying a cut off such as 10%, 15% or 20%. This cut off should, however, be informed by whether it aims to target areas with the very highest concentrations of deprivation or to be wider ranging. The figure provided by SIMD is a relative measure of deprivation. This means that the main output from SIMD – the SIMD ranks – can be used to compare data zones by providing a relative ranking from the most deprived (rank 1) to the least deprived (rank 6,505).

One theoretical criticism of SIMD is that because it includes a health domain, its use in studying deprivation patterns in health is invalid because the SIMD and the health indicator being studied are not independent of each other. However, the health domain is weighted to account for a relatively small part of the overall SIMD (14% of SIMD 2009 and 2012), and analyses of health inequalities using SIMD 2004 were found to give similar results whether the health domain was included or excluded, because that domain was so highly correlated with the overall index (Catherine Dickie, Office of the Chief Statistician and Performance, Scottish Executive, personal communication). Therefore on the advice of the Scottish Executive Office of the Chief Statistician and Performance, the health domain was not removed from the SIMD score.

4.2 Permission, governance, security and extraction of data for present study

The Privacy Advisory Committee (PAC) was established in 1990 to provide ISD and Registrar General with independent advice on the processing of the personal data for which these organisations are responsible. It also advises other divisions of NHS National Services Scotland (NNS) as required. PAC was established as an advisory committee for NNS in 2007. PAC's views are particularly sought in relation to any request of process to information that would involve the release of data that are, or have the potential to be, person-identifiable, and in respect of any new record linkage.

PAC aims to advise on the protection of the privacy of patient information while at the same time recognising the need for legitimate access to information held in data sets by research workers and those involved in health administration for well-defined and bona fide purposes, subject to appropriate safeguards to maintain confidentiality.

An application to use personal health information was submitted to the PAC to get a data set for current research project and approved. This application included information about:

1- The team that will be involved in the study including all persons responsible for the design and analysis of the study, a principal contact person, information about the custodian, and the principal co-workers,
2- General description of the study including the study background, aims, objectives, and methods,
3- Requested data including all information that the researcher needs in the study such as age, sex and diagnosis,
4- Information governance during the study.

In collaboration with Dr Colin Simpson (ISD custodian of datasets) the datasets were extracted for the purposes of this study. Each patient record contains information on date of birth, sex, general practice identifier, patient identifier, date of diagnosis, ICD code or Read code, prescribed drug, date of prescription, SIMD score, comorbidities, date of deaths. Patients' personal information was fully anonymised (i.e. no name, address, postcode, practice identifier). The data was stored on a password protected, encrypted computer in a locked room in the university of the Glasgow.

4.3 Organizing data for analyses

4.3.1 Prior to data analysis

Prior to starting the data analysis many steps were conducted including manipulation of the datasets and merging dataset files together. The datasets are patients diagnosed in primary care, patients diagnosed in secondary care, prescriptions, deaths and SIMD scores. SIMD is categorised from one (least deprived quintile) to ten (most deprived quintile). Manipulating data includes creation of new variables for disease (MI, angina, isolated PAD and PAD/CHD), variables for medications used in the management of these diseases and which are recommended by guidelines, variables to identify first date of a disease diagnosis either at the hospital or at the general practitioner clinic (GP), variables to identify every time point when each patient was prescribed an evidence based drug, and creating comorbidity variables. To identify first time of diagnosis the Read codes for primary care, and the ICD9 and ICD10 for secondary care were used. Age was stratified into five groups (< 55, 55-64, 65-74, 75-84, and ≥ 85 years). British national formulary (BNF) codes were used to identify the evidence based medications that are used in the management of MI, angina and PAD.

Linking the CMR to SMR

The data were extracted from the practices including Read codes, prescribing and demographics, and linked using probabilistic methods using the identifiers Community Health Index Number (CHI), date of birth, sex and postcode to the SMR01, which means that the linkage was of high quality. The same practices were included over time to minimise the effect of any changes in prescribing or expertise between practices or effect of entering or leaving the CMR which may have biased the results.

4.3.2 Identifying patients with disease

In this study all patients with a first diagnosis of MI, angina, isolated PAD and PAD/CHD from 1st January 1997 to 31st December 2005 were identified. A first diagnosis was defined as a first hospitalisation OR first recording of the diagnosis in primary OR secondary care during the time of study. This was achieved in the merged file of datasets that included all patients diagnosed in the primary or secondary care, by sorting the records by patient ID and then date of the record. The first date in which a diagnosis was recorded was considered the first diagnosis for each patient regardless of whether that was a record from primary or secondary care.

Data from primary care included 40 practices that contributed in the CMR project from 1997-2005. The number of these practices was consistent for all study years. Patients with a first diagnosis in primary care were identified using the Read codes. In this dataset, modifiers were ignored as their quality is variable (personal communication, Dr Colin Simpson, ISD custodian of the datasets). The information on the GP's consultation involved in the CMR project (including the diagnosis and modifier code), is handed to the data operator who enters the information immediately onto GPASS. It is not required that the data operator enter the previous diagnostic information into the datasets. Therefore prior diagnoses or problems are not always entered and therefore the modifier for code is not entered on every occasion leading to its variable quality. This does mean that some lifetime morbidity that a patient may have had, which is not an active disease during the study period, will not have been included in these analyses. However, in order to achieve best practice, GPs have been encouraged to enter summarised information of patients onto the GPASS system. Again this is variable in practice. This means that some information on chronic morbidity conditions may have been entered into the database with a modifier code. However, its use is not consistent enough to permit accurate use and therefore it was not used at any point in the analyses.

Patients diagnosed within secondary care were identified by ICD9 for cases prior to 2000, thereafter ICD10 (Appendix 4). In the secondary care diagnostic dataset, patients may have been admitted due to a different cause, but the condition of interest, i.e. MI, angina or PAD could be one of a patient's comorbidities. Therefore, these conditions were included in the analyses even if they were not the main cause for hospital admission. Furthermore, only the first diagnosis was included in the analyses which means that the case recurrence was excluded, i.e. individual cases were included just once in the analyses and there was no duplication. Comorbidities (coronary obstructive pulmonary disease (COPD), asthma, hypertension, atrial fibrillation, diabetes, cancer, HF, renal failure and stroke) were defined as any concomitant recorded diagnosis occurring within the previous five years. These comorbidities were considered if the date of diagnosis was identified within five years before the date index for the first diagnosis of MI, angina or PAD. The five years period was used for consistency. In the analyses of patients with PAD/CHD, PAD was considered as a principal disease and then patients were followed to identify whether they had complications with CHD.

Patient selection bias

Patients who were identified with MI, angina or PAD in the primary or secondary care and had survived 30 days after diagnosis were included in this study. However, those who did not survive 30 days were excluded which means that this study is exposed to selection bias. A sensitivity analysis was undertaken to identify the number/proportion of those who died within 30 days after first diagnosis and had at least one prescription of EBTs.

4.3.3 Identification of medications

Common clinical guidelines were reviewed to identify EBTs for each individual disease. These guidelines include the Scottish Intercollegiate Guidelines Network (SIGN) guideline which is the principal guideline for Scotland, the National Institute for Health and Clinical Excellence (NICE) guideline, the European Society of Cardiology (ESC) guideline and the American College of Cardiology foundation and American Heart Association (ACC/AHA) guideline. Recommended medications in these guidelines were defined as EBTs and used to examine inequalities in prescribing for age, sex, socioeconomic deprivation and comorbidities.

Patients diagnosed at hospital usually need to visit their GP to get a prescription within a month after hospital discharge. To establish the 30 days prescription, the times between first diagnosis in the primary care or date of discharge in the secondary care and prescription for EBTs were calculated. Prescribed medications within 30 days and at any time point were extracted from the primary care database. Any patients identified with a prescription for EBTs were introduced at one time in the study which means that there were no multiple observations for the same patients and there was no cumulative effect on the analysis. Medications were prescribed either in trade varied names or generic name therefore BNF and electronic medicines compendium (eMC) have been used to identify medications prescribed with trade name. All medications were then classified into their pharmacological groups according to the BNF coding system (Appendix 5), for example 2.5.5 including drugs affecting the renin-angiotensin system, 2.4 beta blockers. A medication was counted as having been prescribed if a prescription was issued within the 30 day period. As many general practitioners will supply a 30 day batch of medications it was assumed that patients who received a prescription before day 30 were still receiving it. While I cannot separate out those who

stopped medications, the aim was to document the intent to prescribe appropriate EBTs for each condition

4.4 Statistical analysis

The incidence of first diagnosis of MI, angina and PAD was calculated for sex, age and socioeconomic status. Incidence is the number of patients who present with illnesses for a first time (i.e. newly diagnosed) during a specified time. The rate of incidence was calculated per 1000 using the following formula:

$$\text{Incidence} = \frac{\text{new cases occurring during a given time period}}{\text{Population at risk during the same time period}} \times 1000$$

The population at risk was the total registered practices population for the years studied.

Percentage of prescribed EBTs was calculated for the first 30 days and at any time point after first diagnosis. Percentage of prescribed EBTs before first diagnosis was also calculated. Chi-square test was used to identify the association between prescribing an EBTs and other variables including age, sex, socioeconomic status and comorbidities.

Multivariable logistic regression for those subsets of patients who did not die within 30 days after first diagnosis was conducted to examine the independent effects of age, sex, socioeconomic status, years and comorbidities on prescribing EBTs within 30 days after first diagnosis. Adjustment was performed on the basis of available data. Unadjusted results were not presented as they would be confounded in this observational cohort. In this study a sensitivity test was conducted to identify the number of patients who died within 30 days and had a prescription of EBTs. A higher ratio of patients who died within 30 days before getting a prescription of EBTs has been identified compared to those who had a prescription and died within 30 days. Therefore, to avoid overestimation I decided to exclude patients who died within 30 days after first diagnosis.

The odds ratios were adjusted for age group, sex, socioeconomic status, year, comorbidities including diseases which may affect prescribing for MI, angina or PAD (COPD/asthma, AF, hypertension, diabetes, cancer, renal failure, HF, PAD, stroke, angina), a drug prescribed prior to the first diagnosis and clustering of practices.

A statistical test for interaction with study year was performed for associations with significant P values. The rationale for this was to assess whether any identified inequality was narrowing or widening over the study period.

4.4.1 Slope index of inequalities (SII) and relative index of inequalities (RII)

The slope index of inequality (SII) represents the linear regression coefficient that shows the relation between the level of health or the frequency of a health problem in each socioeconomic category and the hierarchical ranking of each socioeconomic category on the scale.[406-408] It is an absolute summary measure of inequality, and can be used to measure health inequalities based on socioeconomic status. The approach involves calculating the mean health status of each socioeconomic group and then ranking classes by their socioeconomic status (not by their health).[406] The SII is sensitive to the mean rate of health in the population, therefore, another useful index is the relative index of inequality (RII) which is not sensitive to the mean rate of health in the population. RII can be calculated by dividing the SII by the mean rate or frequency of population health or the health outcome in the population.[407-410]

4.4.2 Goodness of fit

Goodness of fit or "accuracy of the model" in statistics is a term used to describe how well the logistic regression model agrees with the observed data. There are two essential components for the accuracy of mode calibration and discrimination. The Hosmer and Lemeshow test evaluates whether the logistic regression model is well calibrated so that probability predictions from the model reflect the occurrence of events in the data. A significant p value, usually <0.05, indicates that the model is not well calibrated i.e. that the fit is not good. Discrimination is a measure to describe the ability of the model to separate subjects having the event from subjects not having the event. For this test from the logistic regression model I predicted the probability of being prescribed the EBT and the predictions were then ranked and split into fifths. Within each of the fifths the observed number prescribed EBT was compared to the predicted by multiplying the average probability in that group by the number of people in that group. If a model is well calibrated there should be good agreement between these numbers. The receiver operating characteristic (ROC) curve is the most commonly used measurement for discrimination. The minimum value for the ROC is 0.5 (no discrimination) and the maximum value is 1.0. The values of ROC from 0.7 to

0.8 are considered as acceptable discrimination, values of 0.8 to 0.9 to show excellent discrimination, and values ≥ 0.9 to show outstanding discrimination of the model.[411,412] In this thesis the Hosmer and Lemeshow test and ROC curves were used to examine the magnitude of the goodness of fit for the logistic regression models that examined the odds of being prescribed EBTs in patients who survived 30 days after first diagnosis of MI, angina, PAD and PAD/CHD.

The SII and the RII were conducted in this study and used to measure the relation between the prescribing of EBTs after 30 days of hospital discharge or diagnosis of MI, angina or PAD, also the ROC to examine the accuracy of the logistic regression model.

The presence of missing data was examined in this study, however there was no missing data for all of the variables included in the study.

4.4.3 Tests of linearity

Linear associations with age and year were tested using the contrast command in Stata. These are presented below for MI (Table 15), angina (Table 16), PAD (Table 17) and PAD with CHD (Table 18). As a non-linear trend was observed for many of the drugs the variables were categorised and treated as a categorical variable. Age was categorised into the groups <55, 55-64, 65-74, 75-85 and >=85 years. Year was categorised per year i.e. 1997-2005.

Table 15 Tests of linear trend by age and year in prescribing evidence based therapies for MI

	ACEI/ARBs	β-Blockers	CCB	Statins	aspirin	clopidogrel	oral anticoagulant
Age	<0.001	0.01	0.75	<0.001	0.03	0.35	0.04
Year	<0.001	<0.001	0.06	<0.001	0.01	<0.001	0.26

Table 16 Tests of linear trend by age and year in prescribing evidence based therapies for Angina

	ACEI/ARBs	β-Blockers	CCB	Nitrates	Statins	aspirin	clopidogrel	Other antianginal
Age	0.53	<0.001	0.83	0.78	<0.001	0.003	0.87	0.27
Year	<0.001	<0.001	0.005	<0.001	0.004	<0.001	<0.001	0.15

Table 17 Tests of linear trend by age and year in prescribing evidence based therapies for isolated PAD

	ACEI/ARBs	β-Blockers	CCB	PVD	Statins	aspirin	clopidogrel	oral anticoagulant
Age	0.73	0.003	0.21	<0.001	<0.001	0.01	0.05	0.94
Year	0.21	0.78	0.13	0.01	0.07	0.002	0.93	0.95

Table 18 Tests of linear trend by age and year in prescribing evidence based therapies for PAD with CHD

	ACEI/ARBs	β-Blockers	CCB	PVD	Statins	aspirin	clopidogrel	oral anticoagulant
Age	0.70	0.92	0.20	0.11	0.81	0.21	0.30	0.02
Year	0.67	0.37	0.05	0.23	0.02	0.01	0.06	0.63

4.4.4 Multiple testing and clustering

Multiple testing

To answer the research questions of this thesis many statistical analyses were conducted. A potential danger of carrying out multiple statistical tests is that the chance of detecting a spurious finding (i.e. finding $p<0.05$ when in fact the null hypothesis is true) is considerably increased. This is particularly the case when focusing on results of significant associations for hypotheses that were not pre-specified.[413] I will only look at those associations that directly address the research questions that were defined a priori.

The issue of preserving an overall significance level by using a multiple comparisons procedure such as Bonferroni is controversial in epidemiology. It is justified not to do such procedures because it can lead to a lack of power in detecting real associations and the null hypothesis becomes that all null hypotheses for each single test are simultaneously true, which is not of interest.[414] Therefore, in this study I will not conduct a formal multiple comparisons procedure but will mention in the discussion that there is a chance that any of the statistically significant associations found might be spurious because of multiple testing.

Clustering

In all regression models, cluster standard errors have been used (with the GP practice used as the clustering variable). This allows the standard errors, and therefore the confidence intervals, to be corrected for any lack of independence imposed by the hierarchical structure of the data.

Hierarchical model "multilevel analysis" is a statistical method of analysis which can be used to analyse hierarchical or multilevel data. The data in this model are organized into a tree like structure (my data would have two levels, patients (level 1) nested within practices (level 2). Hierarchical analysis models allow the variance seen at multiple levels to be quantified, while also allowing estimation of covariate effects at every level of the hierarchy. The aim of my thesis was not specifically to look at geographical variation in EBT prescribing and obtain practice specific estimates. Therefore, I decided to account for the hierarchical structure in the data using cluster standard errors in the regression models rather than with multilevel analysis methodology.

All analyses were undertaken using Stata (versions 12, Stata cooperation, College Station, Texas, USA). Statistical significance was assessed at the conventional level of 5% ($P<0.05$). Results are presented with SD for means, and 95% confidence intervals for proportions and ratios.

5.0 Results

The Scottish primary and secondary care database contained health care records for 238,064 individuals for the period 1997-2005 (approximately 6% of the Scottish population).

5.1 Myocardial Infarction (MI)

Baseline demographic characteristics

A total of 5162 individuals were identified as having a diagnosis of MI. In the study cohort, 1803 patients identified with first MI in the primary care and 3359 patients in the secondary care (Figure 1). Of these, 875 patients (261 from the primary care and 596 from the secondary care) did not survive 30 days after hospital discharge and were excluded. In this study, 4305 (83.4%) patients who survived 30 days after first diagnosis were eligible to be included in the study. Of these, 1542 (35.8%) patients were identified in the primary care and 2763 (64.2%) patients in the secondary care. Table 19 summarises the characteristics of these patients and the subset of patients who survived 30 days after the first recorded diagnosis. Approximately 60% of the MI patients are men and the largest proportion were aged between 65 and 74 years. Patients residing in the most deprived areas (quintile 10) made up a higher percentage of patients in the dataset than those residing in areas from the least deprived area (quintile 1). The most prevalent comorbidities were hypertension (33.1%), angina (22.7%) and HF (22.2%).

Table 20 shows the incidence of MI per 1000 population. The incidence rate was higher in men, 3.85 per 1000, than in women, 2.62 per 1000. The incidence of MI displays a clear age gradient, from 1.08 per 1000 in those aged less than 45 years compared to 19.78 per 1000 in patients aged 85 years and over. The incidence rate of MI also increased with increasing levels of socioeconomic deprivation from 2.08 per 1000 in the least deprived quintile to 3.87 per 1000 in the most deprived quintile. The most recent study year, 2005, had a lower incidence rate of MI than the first study year, 1999, incidence seemed to reach its peak in 2002/2003.

Figure 1 Flow diagram showing the selection of patients with a first diagnosis of MI

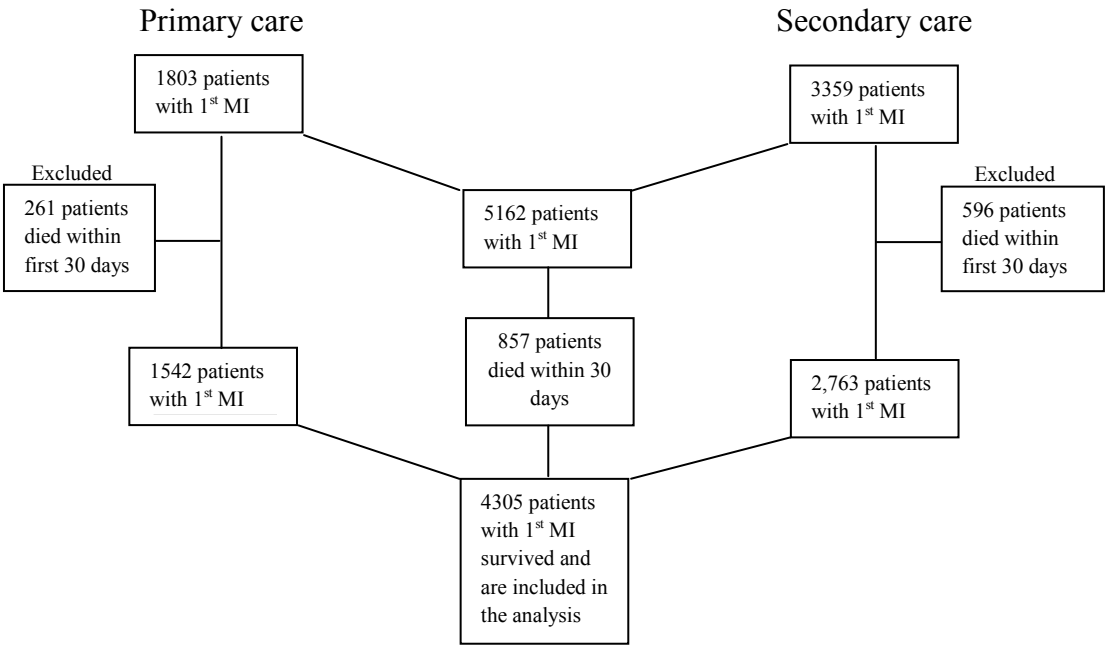


Table 19 Baseline demographic characteristics

	Survived 30 days (n=4305)§	Patients died within 30 days after 1st diagnosis (n=857)*	All patients (n=5162)
Male sex	2628 (61.0%)	420 (49.0%)	3048 (59.0%)
SD/variance	0.5/0.2	0.5/0.3	0.5/0.2
Age (years):			
< 55	977 (22.7%)	45 (5.2%)	1022 (19.8%)
55 – 64	979 (22.7%)	84 (9.8%)	1063 (20.6%)
65 – 74	1175 (27.3%)	200 (23.3%)	1375 (26.6%)
75 – 84	877 (20.4%)	323 (37.7%)	1200 (23.3%)
85+	297 (6.9%)	205 (23.9%)	502 (9.7%)
Socioeconomic deprivation			
Q1 Least deprived	309 (7.2%)	58 (6.7%)	367 (7.1%)
Q2	233 (5.4%)	31 (3.6%)	264 (5.1%)
Q3	427 (9.9%)	88 (10.2%)	515 (9.9%)
Q4	406 (9.4%)	88 (10.2%)	494 (9.5%)
Q5	453 (10.5%)	87 (10.1%)	540 (10.4%)
Q6	650 (15.1%)	150 (17.5%)	800 (15.5%)
Q7	501 (11.6%)	104 (12.1%)	605 (11.7%)
Q8	459 (10.6%)	87 (10.1%)	546 (10.5%)
Q9	513 (11.9%)	99 (11.5%)	612 (11.8%)
Q10 Most deprived	354 (8.2%)	65 (7.5%)	419 (8.1%)
Year			
1997	422 (9.8%)	89 (10.4%)	511 (9.9%)
1998	474 (11.0%)	97 (11.3%)	571 (11.1%)
1999	461 (10.7%)	104 (12.1%)	565 (10.9%)
2000	460 (10.7%)	106 (12.3%)	566 (11.0%)
2001	516 (12.0%)	93 (10.8%)	609 (11.8%)
2002	532 (12.4%)	98 (11.4%)	630 (12.2%)
2003	545 (12.7%)	103 (12.0%)	648 (12.6%)
2004	471 (10.9%)	96 (11.2%)	567 (11.0%)
2005	424 (9.8%)	71 (8.3%)	495 (9.6%)
Comorbidities			
COPD/Asthma	529 (12.3%)	145 (17.0%)	674 (13.1%)
Atrial fibrillation	424 (9.8%)	119 (14.0%)	543 (10.5%)
Hypertension	1401 (32.5%)	306 (35.7%)	1707 (33.1%)
Diabetes	426 (9.9%)	90 (10.5%)	516 (10.0%)
Cancer	250 (5.8%)	98 (11.4%)	348 (6.7%)
Renal failure	108 (2.5%)	89 (10.4%)	197 (3.8%)
Heart failure	863 (20.0%)	285 (33.2%)	1148 (22.2%)
PAD	331 (7.7%)	106 (12.3%)	437 (8.5%)
Stroke	373 (8.7%)	152 (17.7%)	525 (10.2%)
Angina	1002 (23.3%)	170 (19.8%)	1172 (22.7%)

* Only 34 (4.0%) patients died within 30 days and had a prescription, § No missing data

COPD=Chronic obstructive pulmonary disease, PAD=Peripheral arterial disease

Table 20 Rate per (1000) of incident myocardial infarction

	Total population registered with GPs	Patients with MI	Rate
Sex			
Men	792651	3048	3.85
Women	807959	2114	2.62
Age			
<45	950345	1022	1.08
45-64	410998	1063	2.59
65-74	133058	1375	10.33
75-84	80828	1200	14.85
85+	25381	502	19.78
Socioeconomic			
Q1	305557	637	2.08
Q2	358497	999	2.79
Q3	401492	1341	3.34
Q4	305760	1154	3.77
Q5	266735	1031	3.87
Years			
1999	227690	565	2.48
2000	226503	566	2.50
2001	225806	609	2.70
2002	227146	630	2.77
2003	228766	648	2.83
2004	232554	567	2.44
2005	232343	495	2.13

Prescribing of evidence based therapies before and after first recorded diagnosis

Table 21 shows prescribing of EBTs before and after the first recorded diagnosis of MI. Almost a third (30.3%) of patients were prescribed aspirin before first diagnosis of MI. After a first diagnosis, prescribing of aspirin increased to 42.8% (within 30 days) and to 83.1 % at any time after. A similar pattern was observed for ACEI/ARBs: 19.0% to 30.2% (within 30 days), β-blockers 24.1% to 35.5%, statins 15.6% to 36.1% and clopidogrel 2.6% to 11.6%. However, prescribing of calcium channel blockers (CCB) declined 22.1% to 9.0%.

Table 21 Evidence based therapies prescribing for patients with incident diagnosis of myocardial infarction

Medicine	Prescribed drug before 1st diagnosis	Prescribed drug after 1st diagnosis at any time	Prescribed drug within 30 days after 1st diagnosis*
ACEI/ARBs	19.0%	72.4%	30.2%
β-blocker	24.1%	72.4%	35.5%
CCB	22.1%	36.4%	9.0%
Statins	15.6%	83.5%	36.1%
Aspirin	30.3%	83.1%	42.8%
Clopidogrel	2.6%	29.3%	11.6%
Oral anticoagulant	3.9%	91.4%	3.3%

* This percentage is for patients alive 30 days after the 1st diagnosis, ACEI=Angiotensin converting enzyme inhibitor, ARBs=Angiotensin receptor blockers, CCB=calcium channel blockers.

5.1.1 Differences in prescribing of evidence based therapies for MI

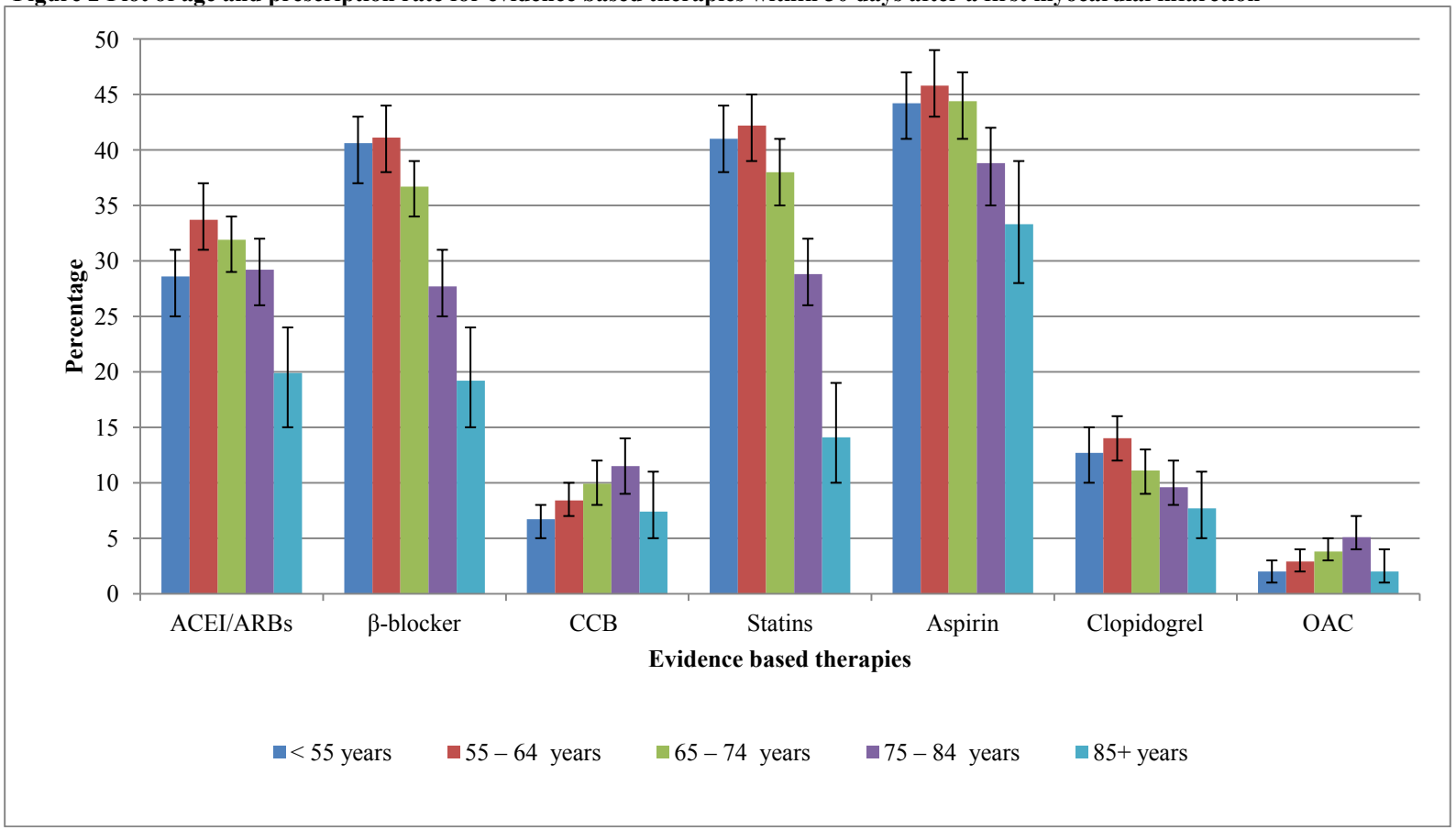
5.1.1.1 Age differences in prescribing of evidence based therapies

Patients aged between 55 and 64 years received proportionally more prescriptions of ACEI/ARBs, β-blockers, statins, aspirin and clopidogrel compared with the other age groups (Figure 2). Prescribing of oral anticoagulants and CCBs was highest for 75 to 84 year olds. In general the proportion prescribed a drug decreased as age increased. However, for CCBs and oral anticoagulants, prescribing increased as age increased (except in the oldest group). The percentages of prescribing EBTs for age group 55-64 were 45.8%, 42.2% and 41.1% for aspirin, statins and β-blockers, respectively (Table 25). After risk adjustment using multivariable analysis, there were statistically significant differences in the odds of prescribing between the age groups – ACEI/ARBs ($p<0.001$), β-blockers ($p<0.001$), statins ($p<0.001$), aspirin ($p=0.002$), and clopidogrel ($p=0.01$), (Table 1 appendix 6).

Compared to the youngest age group (<55 years), the eldest patient group (≥ 85 years) were significantly less likely to be prescribed ACEI/ARBs (OR 0.46; 95% CI 0.32-0.67), β-blockers (OR 0.38; 95% CI 0.26-0.54), statins (OR 0.21; 95% CI 0.11-0.32), aspirin (OR 0.66; 95% CI 0.47-0.92), clopidogrel (OR 0.51; 95% CI 0.31-0.85), and oral anticoagulants (OR 0.33; 95% CI 0.10-1.07). There were no significant differences

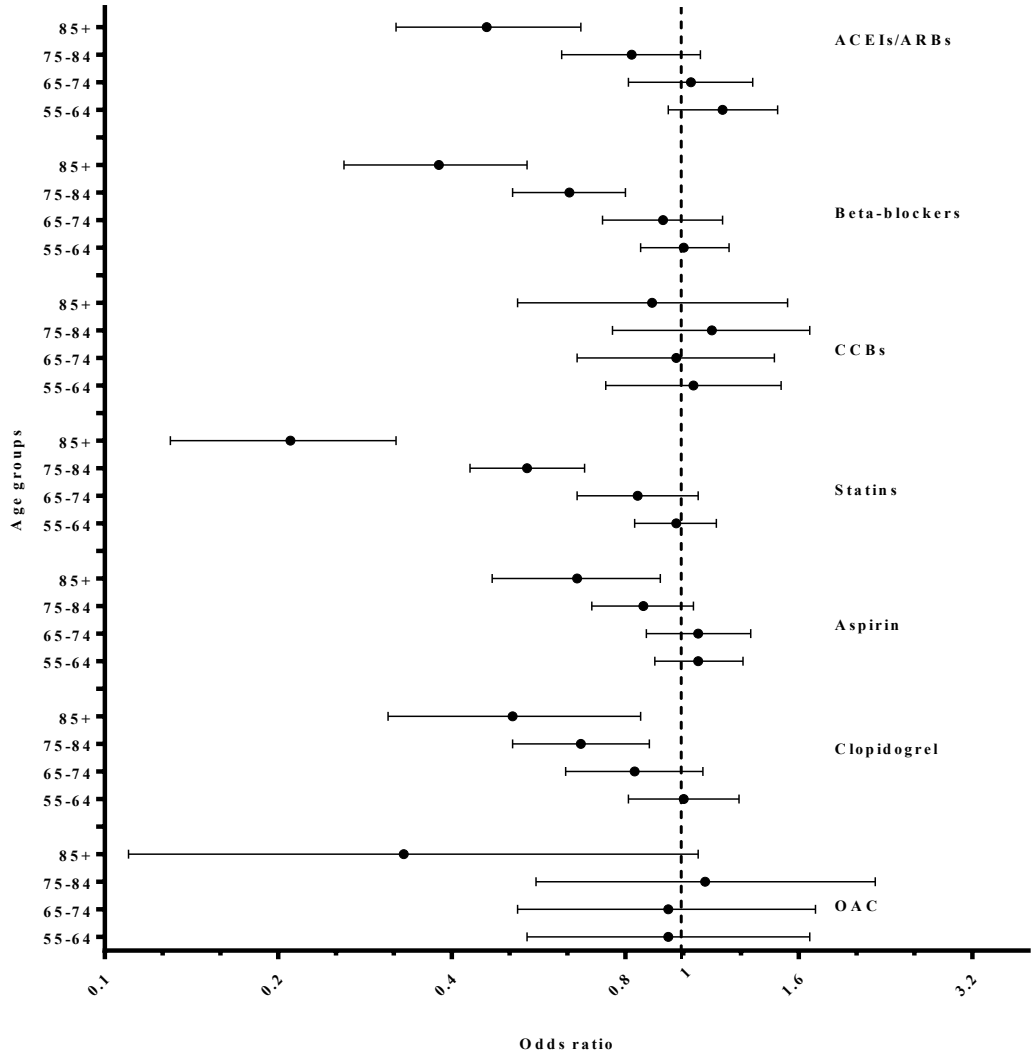
in prescribing EBTs between patients younger than 55 years and those aged between 55 years and 74 years. However, significant differences in prescribing EBTs were identified in age group 75 to 84 years compared to <55 years for β-blockers (OR 0.64; 95% CI 0.51-0.80), statins (OR 0.54; 95% CI 0.43-0.68), and clopidogrel (OR 0.67; 95% CI 0.51-0.88) (Figure 3).

Figure 2 Plot of age and prescription rate for evidence based therapies within 30 days after a first myocardial infarction



ACEI=Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, OAC= Oral anticoagulant

Figure 3 Forest plot of odds ratio of age and prescribing evidence based therapies within 30 days after first myocardial infarction



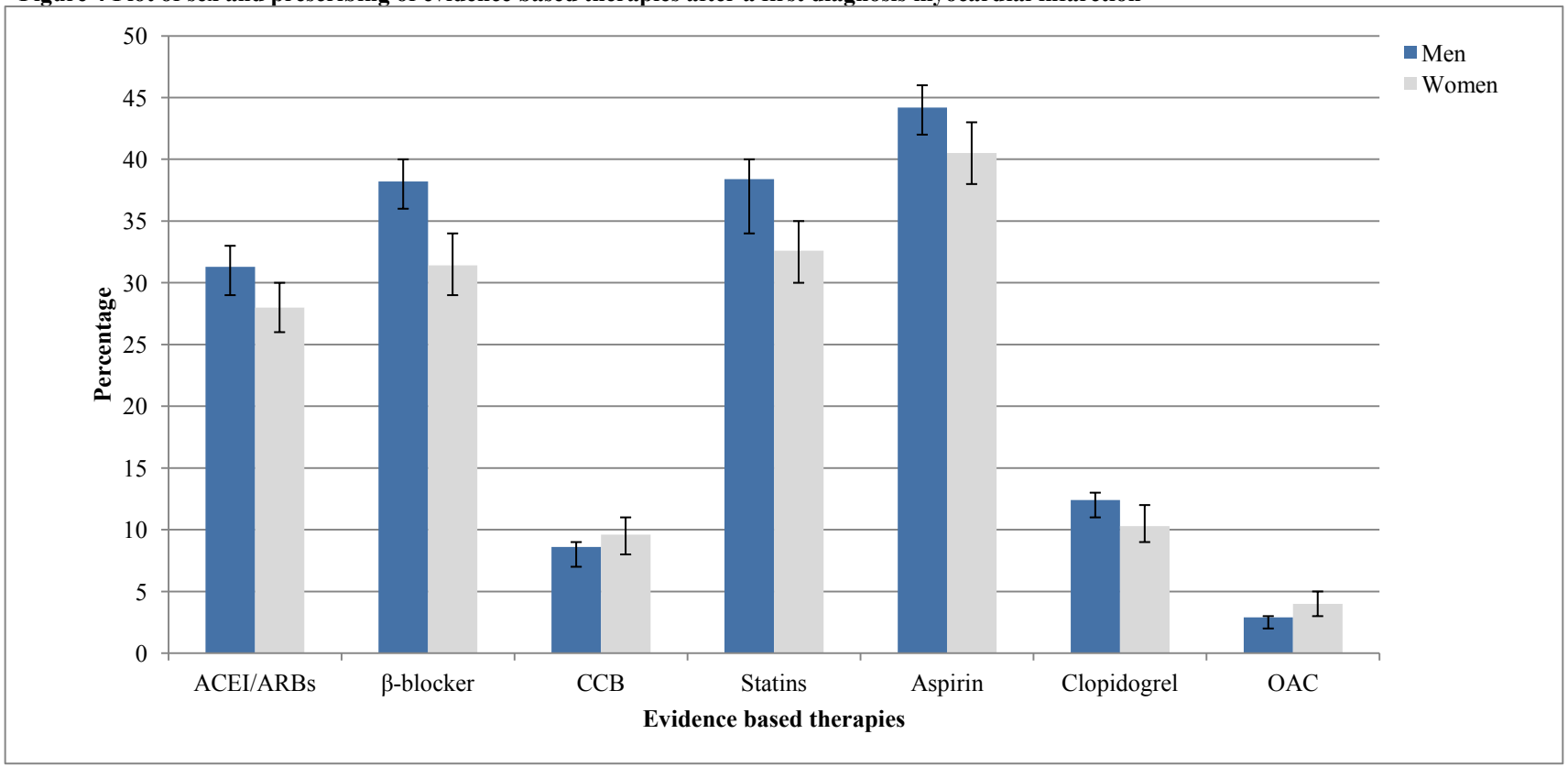
Patients aged <55 years are the reference category. Odds ratio adjusted for sex, socioeconomic status, year of diagnosis, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, peripheral arterial disease, angina, clustered practices, and whether the drug was previously prescribed.

ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, OAC=Oral anticoagulant

5.1.1.2 Sex differences in prescribing of evidence based therapies

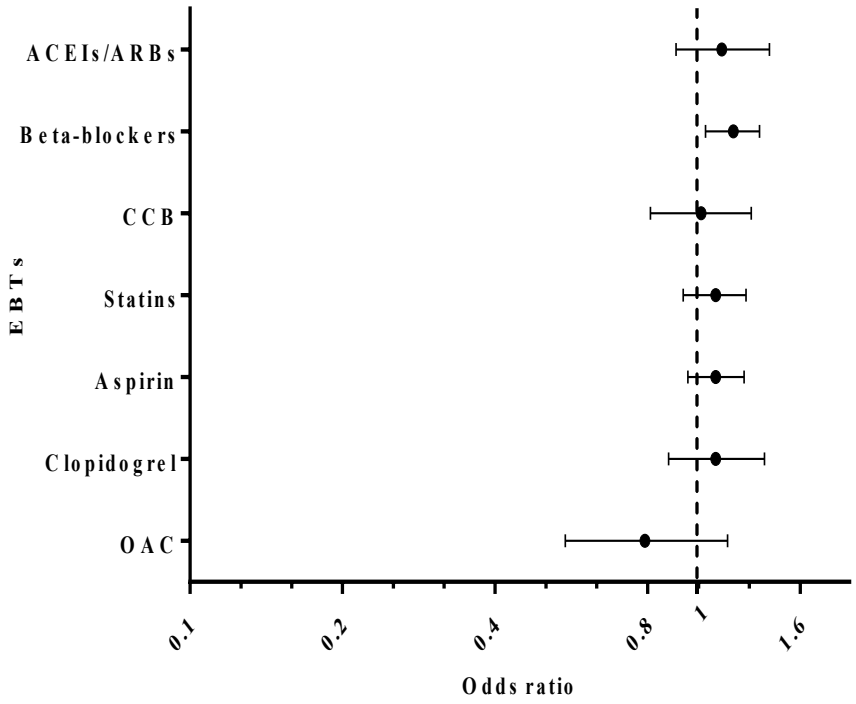
Prescribing of ACEI/ARBs, β-blockers, statins, aspirin and clopidogrel was higher in men compared with women, whereas women received more prescriptions for CCBs and oral anticoagulants than men (Figure 4). The values of the percentages shown in Figure 1 are in Table 25. β-blockers were prescribed for 38.2% of men versus 31.4% of women, statins 38.4% for men vs. 32.6% for women, aspirin 44.2% for men vs. 40.5% for women. As can be seen in Figure 5 (and Table 2 appendix 6), after adjustment using multivariable analysis compared to women, there was a trend towards men being more likely to be prescribed ACEI/ARBs (OR 1.12; 95% CI 0.91-1.39, p=0.27), CCB (OR 1.02; 95% CI 0.81-1.28, p=0.90), statins (OR 1.09; 95% CI 0.94-1.25, p=0.20), aspirin (OR 1.09; 95% CI 0.96-1.24, p=0.15), and clopidogrel (OR 1.09; 95% CI 0.88-1.36, p=0.41), although these were not statistically significant. Men were, however, statistically significantly more likely than women to receive β-blockers (OR 1.18; 95% CI 1.04-1.33, p=0.01). There was a trend towards men being less likely to be prescribed an oral anticoagulant than women (OR 0.79; 95% CI 0.55-1.15, p=0.29).

Figure 4 Plot of sex and prescribing of evidence based therapies after a first diagnosis myocardial infarction



ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, OAC= Oral anticoagulant

Figure 5 Forest plot of odds ratio of sex and prescribing evidence based therapies within 30 days after first myocardial infarction



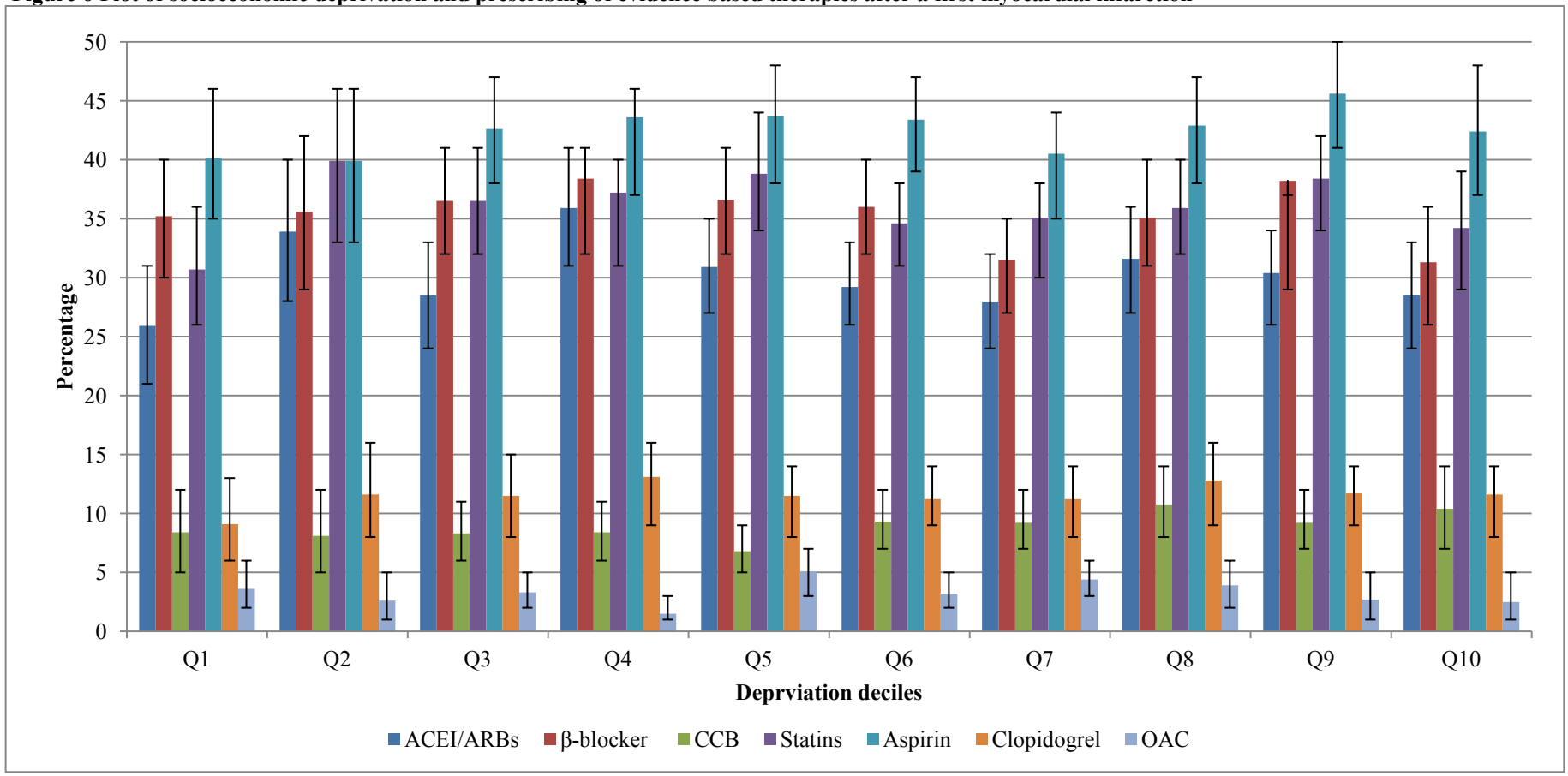
Women are the reference category. Odds ratio adjusted for age group, socioeconomic, year of diagnosis, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, stroke, peripheral arterial disease, angina, clustered practices, and whether the drug was previously prescribed.

ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, OAC=Oral anticoagulant

5.1.1.3 Socioeconomic differences in prescribing of evidence based therapies

There were only minor differences in the prescribing of EBTs between the socioeconomic groups (Figure 6). These were not consistent or statistically significantly different. The multivariable analyses showed that after adjustment clopidogrel was significantly more likely to be prescribed for patients in decile 4 than most deprived patients in decile 1 (OR 1.57; 95% CI 1.02-2.53; 0.04), however there was no evidence of differences in the odds of prescribing between the socioeconomic deprivation groups (Figure 7).

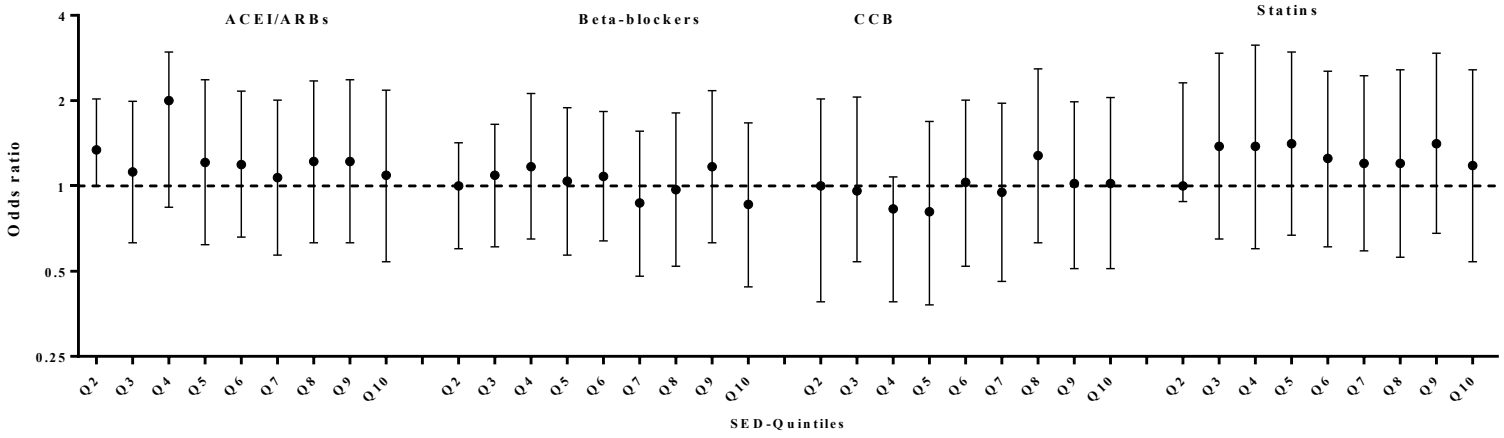
Figure 6 Plot of socioeconomic deprivation and prescribing of evidence based therapies after a first myocardial infarction



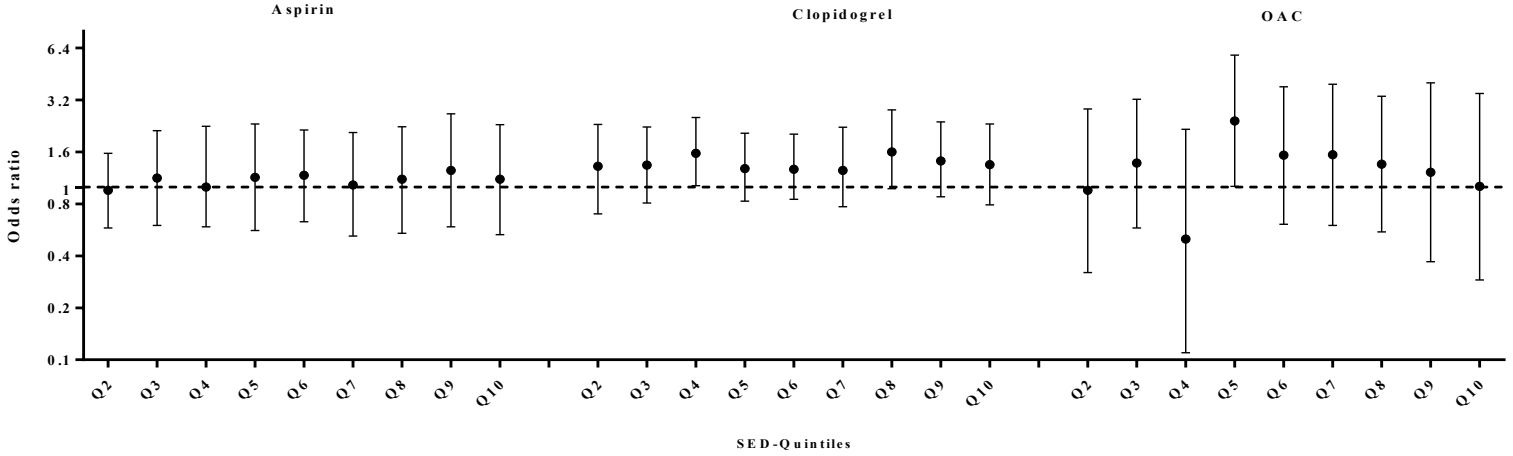
Q1= Least deprived, Q10=Most deprived, ACEI=Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, OAC= Oral anticoagulant

Figure 7 Forest plot of odds ratio of socioeconomic deprivation and prescribing evidence based therapies within 30 days after first myocardial infarction

A



B



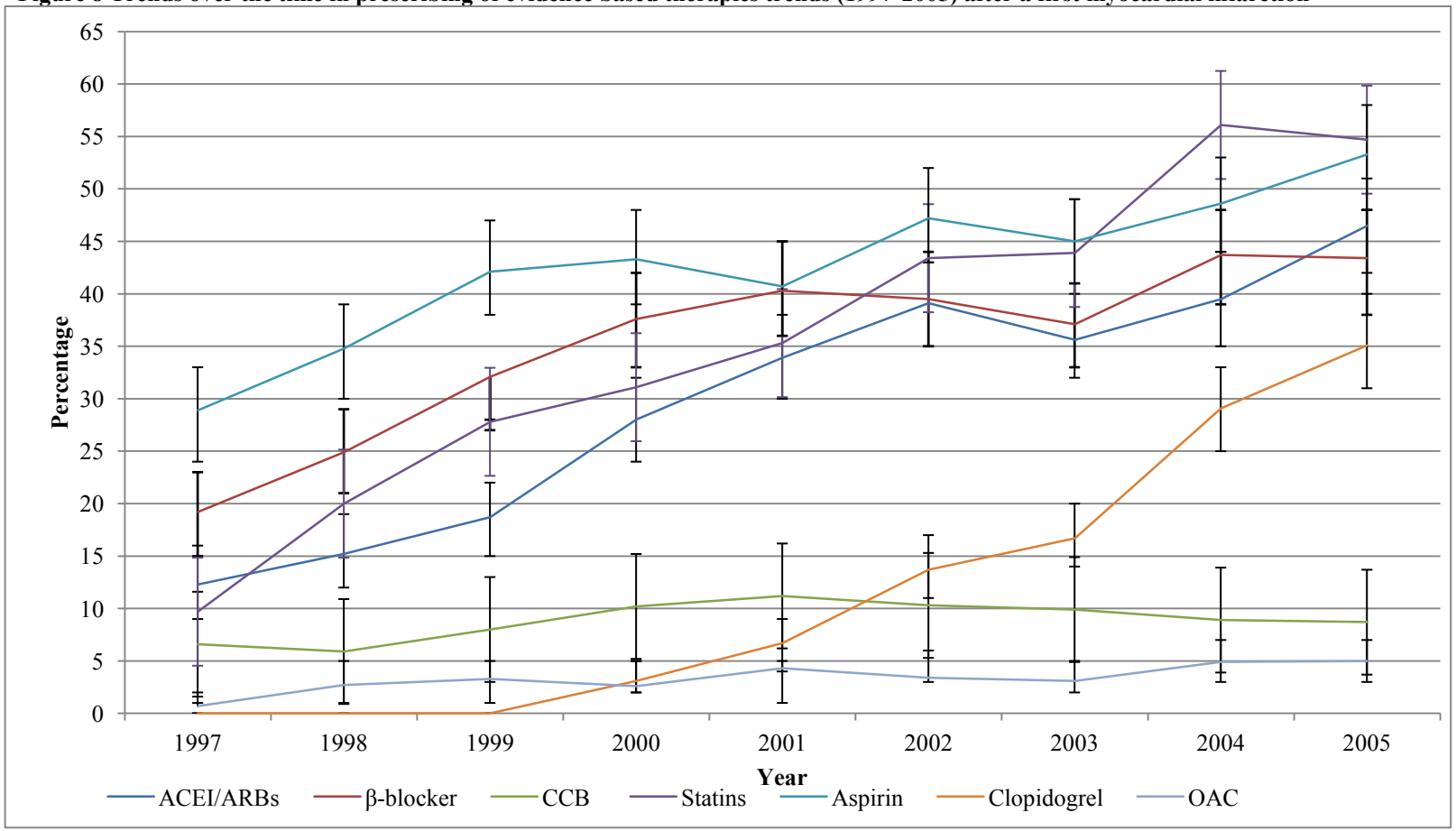
Quintile 1 (Q1) least deprived is a reference. Odds ratio adjusted for sex, age group, year of diagnosis, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, peripheral arterial disease, angina, clustered practices, and whether the drug was previously prescribed.

SED=Socioeconomic deprivation ACEI=Angiotensin converting enzyme inhibitors, ARBs=Angiotensin receptor blockers, CCB=Calcium channel blockers, OAC=Oral anticoagulants.

5.1.1.4 Trends of prescribing evidence based therapies from 1997 to 2005

Figure 8 shows the trends in prescribing of EBTs within 30 days after first diagnosis of MI over the 9 years of the study. Prescribing of most EBTs increased steadily over the period of study, by contrast, prescriptions of CCBs and oral anticoagulants changed little over time (Figure 8, Table 25). From 1997 to 2005, prescribing of EBTs within 30 days after a first diagnosis of MI increased for ACEI/ARBs (from 12.3% to 46.5%), β-blockers (from 19.2% to 43.4%), statins (from 9.7% to 54.7%), aspirin (from 28.9% to 53.3%), and clopidogrel (from 2000 to 2005, from 3.0% to 35.1%). There were no increases in prescribing of CCBs (from 6.6% to 8.7%) or oral anticoagulants (from 0.7% to 5.0%). After risk adjustment using multivariable analysis, there were statistically significant differences in the odds of prescribing between the years of the study – ACEI/ ARBs ($p<0.001$), β-blockers ($p<0.001$), statins ($p<0.001$), aspirin ($p<0.001$) and clopidogrel ($p<0.001$). Compared to prescribing in 1997, patients in 2005 were significantly more likely to be prescribed ACEI/ARBs (OR 5.25, 95% CI 3.40-8.11), β-blockers (OR 3.60, 95% CI 2.49-5.20), statins (OR 11.11, 95% CI 6.70-18.42), aspirin (OR 2.81, 95% CI 1.90-4.15) and oral anticoagulants (OR 5.91, 95% CI 1.15-30.37). However, there was no evidence of change over time for CCBs (OR 0.88, 95% CI 0.50-1.57) (Figure 9 and Table 4 appendix 6).

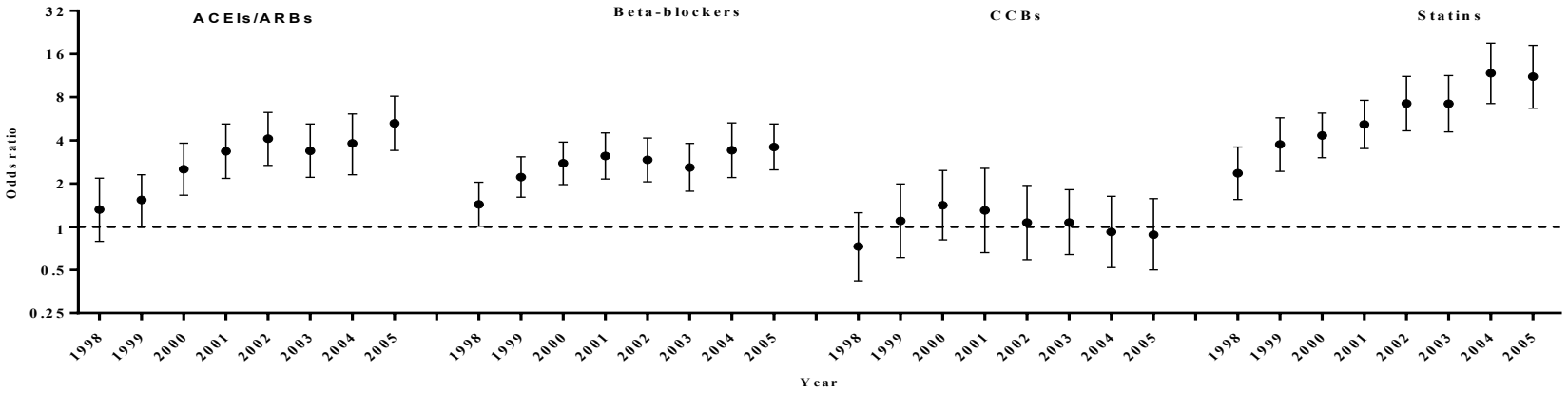
Figure 8 Trends over the time in prescribing of evidence based therapies trends (1997-2005) after a first myocardial infarction



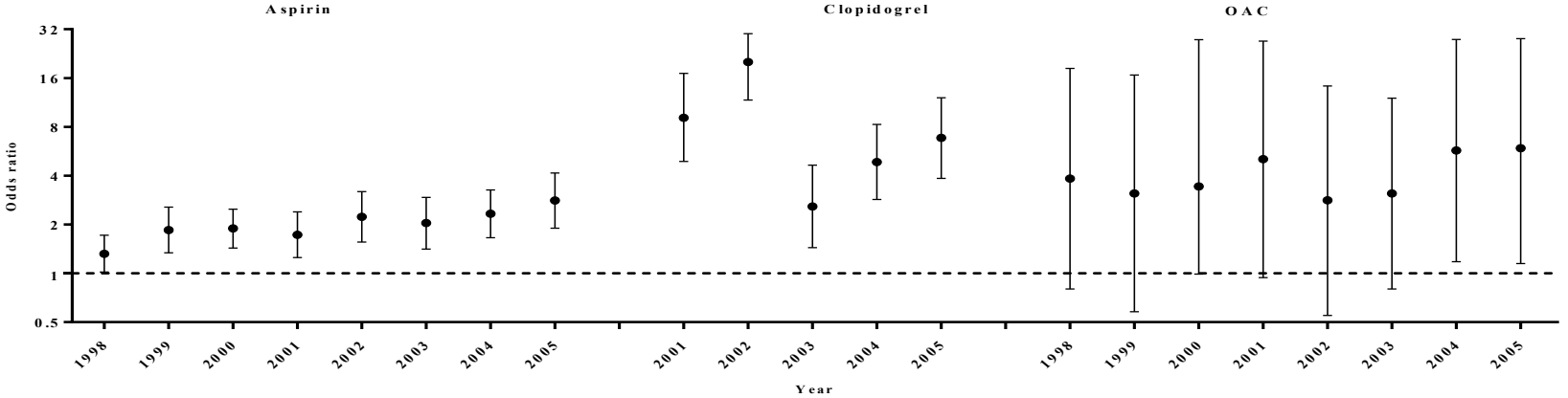
ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, OAC= Oral anticoagulant

Figure 9 Forest plot of odds ratio of trends over time (1997-2005) and prescribing evidence based therapies within 30 days after first myocardial infarction

A



B



Year 1997 is the reference. Adjusted for sex, age group, socioeconomic status, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, peripheral arterial disease, angina, clustered practices, and whether the drug was previously prescribed. **2000 is the reference for clopidogrel. Clopidogrel divided by 10 for years 2003-05
ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, OAC=Oral anticoagulant

5.1.1.5 Association between comorbidity and prescribing of evidence based therapies

Prescribing of EBTs was generally higher among patients with hypertension than those without hypertension (Figure 10 c). However, other concomitant diseases were associated with different patterns of prescribing particular drugs (Figures 10a-10j). Asthma/COPD was associated with a lower rate of β-blocker prescribing than no asthma/COPD, 38.2% vs. 16.6%, respectively, Table 25. Atrial fibrillation (AF) was associated with lower use of aspirin 32.5% than those without AF 43.9%. However, patients with AF received more prescriptions of oral anticoagulant 17.9% than those without AF 1.8%. Patients with renal failure were often prescribed β-blockers, those with HF or PAD were more often prescribed ACEI/ARBs.

As can be seen in Table 22, after adjustment using multivariable analysis, there were some statistically significant differences in the odds of prescribing a therapy in the presence of certain comorbidities. Patients with COPD/asthma were significantly less likely to receive β-blockers (OR 0.33; 95% CI 0.25-0.42), but more likely to receive CCBs (OR 2.17; 95% CI 1.65-2.86) than patients without COPD/asthma. Patients with AF were significantly less likely to receive aspirin (OR 0.61; 95%CI 0.50-0.75), or clopidogrel (OR 0.59; 95%CI 0.41-0.84), though they were more likely to be prescribed oral anticoagulants (OR 6.71; 95% CI 3.60-12.50) than patients without AF. Patients with hypertension were more likely to receive most EBTs than patients without hypertension. Patients with diabetes were less likely to receive statins (OR 0.71; 95% CI 0.59-0.85) than those without diabetes. Patients with HF were significantly more likely to be prescribed ACEI/ARBs (OR 1.94; 95% CI 1.57-2.40) than patients without HF. Patients with stroke were less likely to be prescribed most EBTs, however, they were more likely to receive oral anticoagulants (OR 1.86; 95% CI 0.97-3.57) than those without stroke. Patients with angina were more likely to be prescribed CCBs (OR 1.41; 95% CI 1.10-1.81) than those without angina.

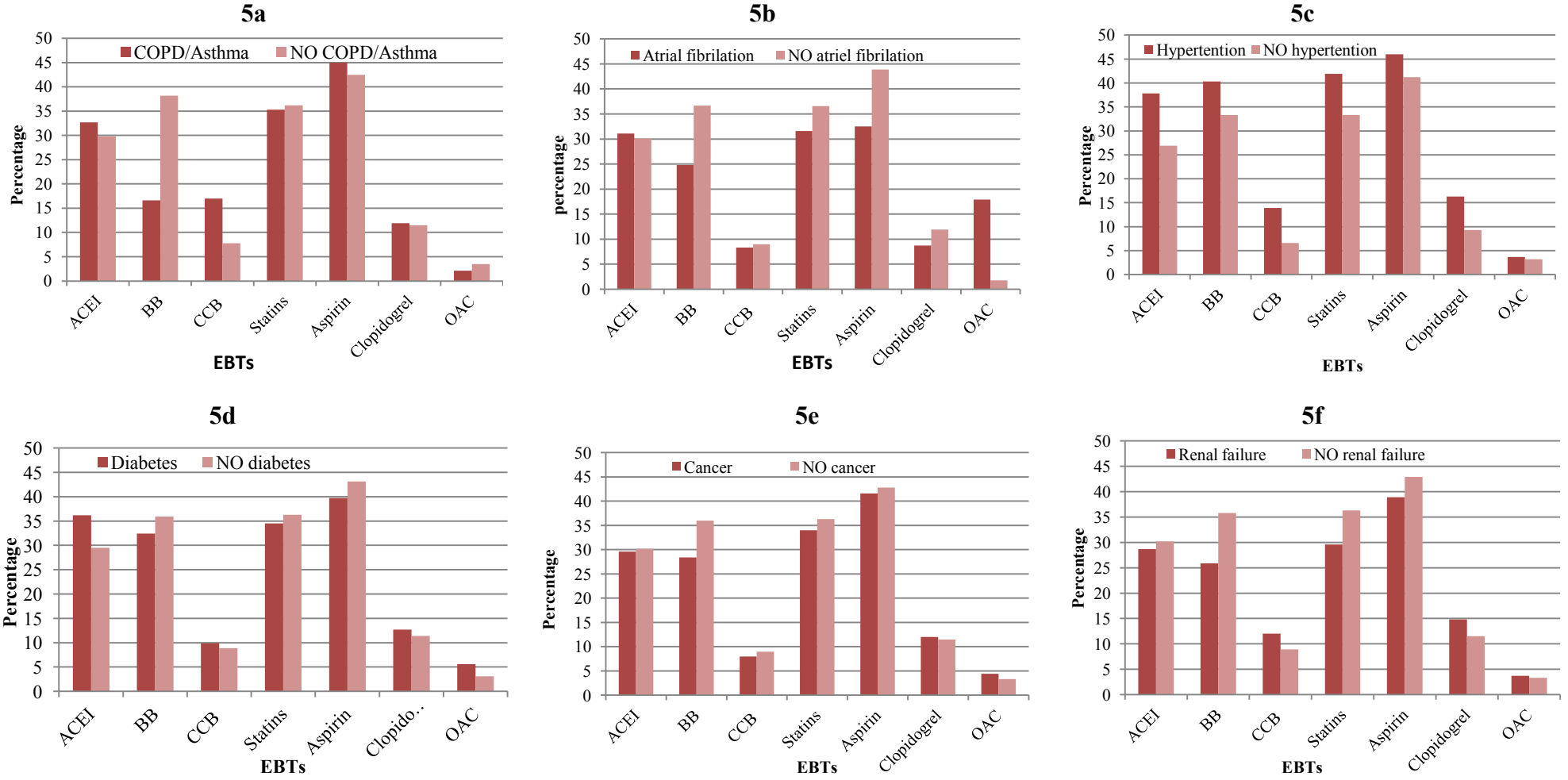
Table 22 Association between comorbidities and prescribing of evidence based therapies within 30 days after a first myocardial infarction

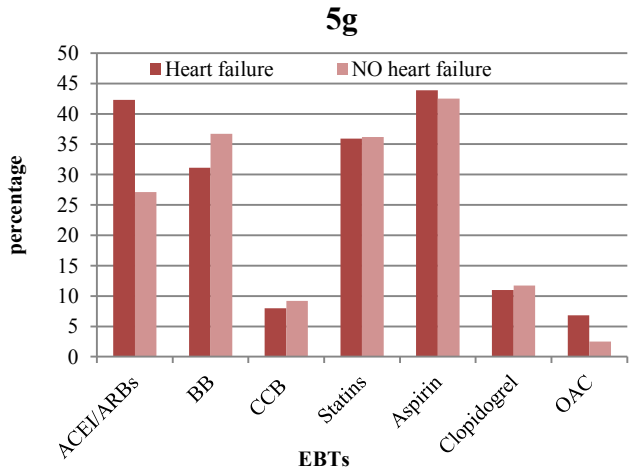
Adjusted OR, 95% CI, p value	ACEI/ABs	β-blockers	CCB	Statins	Aspirin	Clopidogrel	Oral-anticoagulant
COPD	0.99 (0.78-1.25), 0.90	0.33 (0.25-0.42), 0.01	2.17 (1.65-2.86), 0.01	0.87 (0.70-1.08), 0.21	1.07 (0.89-1.29), 0.45	0.80 (0.60-1.04), 0.16	0.37 (0.17-0.78), 0.01
AF	0.81 (0.63-1.02), 0.08	0.60 (0.46-0.78), 0.01	0.68 (0.48-0.96), 0.03	0.83 (0.65-1.07), 0.16	0.61 (0.50-0.75), 0.01	0.59 (0.41-0.84), 0.01	6.71 (3.60-12.50), 0.01
HYP	1.11 (0.95-1.29), 0.15	1.20(1.02-1.41), 0.02	1.29 (1.02-1.63), 0.03	1.23 (1.04-1.47), 0.02	1.19 (1.03-1.37), 0.01	1.40 (1.01-1.83), 0.02	0.66 (0.48-0.91), 0.01
Diabetes	0.96 (0.77-1.19), 0.73	0.79(0.65-0.98), 0.03	0.79 (0.53-1.18), 0.26	0.71 (0.59-0.85), 0.01	0.80 (0.67-0.96), 0.02	0.86 (0.65-1.16), 0.41	1.06 (0.61-1.86), 0.81
Cancer	0.85 (0.62-1.16), 0.33	0.79 (0.63-0.99), 0.04	0.78 (0.48-1.26), 0.32	0.96 (0.72-1.27), 0.80	0.97 (0.74-1.28), 0.87	0.88 (0.51-1.62), 0.73	0.89 (0.47-1.67), 0.72
Renal failure	0.53 (0.32-0.89), 0.02	0.64 (0.42-0.98), 0.04	1.06 (0.55-2.04), 0.84	0.69 (0.44-1.08), 0.12	0.85 (0.54-1.33), 0.48	1.14 (0.69-1.95), 0.60	0.28 (0.05-1.52), 0.14
HF	1.94 (1.57-2.40), 0.01	0.87 (0.70-1.09), 0.24	0.67 (0.51-0.90), 0.01	1.07 (0.88-1.30), 0.48	1.16 (0.96-1.40), 0.12	0.81 (0.66-1.04), 0.13	1.63 (0.90-2.95), 0.11
PAD	1.24 (0.92-1.68), o.15	0.81 (0.64-1.02), 0.08	0.94 (0.67-1.33), 0.76	1.07 (0.79-1.45), 0.63	0.89 (0.66-1.19), 0.46	1.06 (0.69-1.95), 0.70	1.16 (0.55-2.44), 0.70
Stroke	0.73 (0.59-0.92), 0.01	0.53 (0.42-0.67), 0.01	1.33 (0.88-2.00), 0.17	0.63 (0.50-0.80), 0.01	0.64 (0.50-0.83), 0.01	0.65 (0.40-1.07), 0.10	1.86 (0.97-3.57), 0.06
Angina	0.91 (0.76-1.07), 0.25	0.97 (0.79-1.19), 0.82	1.41 (1.10-1.81), 0.01	1.08 (0.87-1.33), 0.46	0.92 (0.77-1.11), 0.43	0.92 (0.66-1.35), 0.80	0.76 (0.47-1.23), 0.27

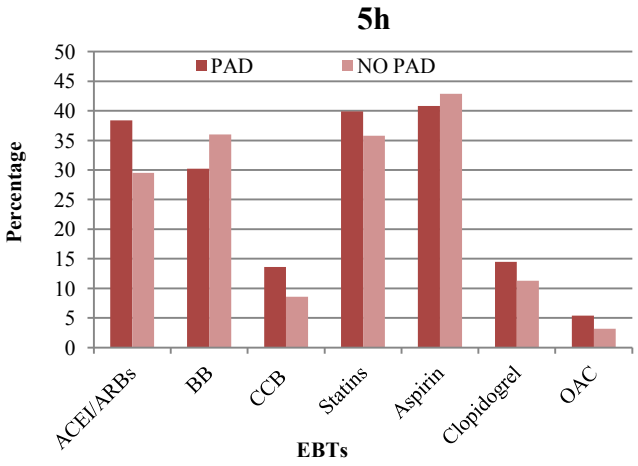
* Adjusted for sex, age group, socioeconomic status, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, peripheral arterial disease, angina, clustered practices, and whether the drug was previously prescribed. **2000 is the reference for clopidogrel,

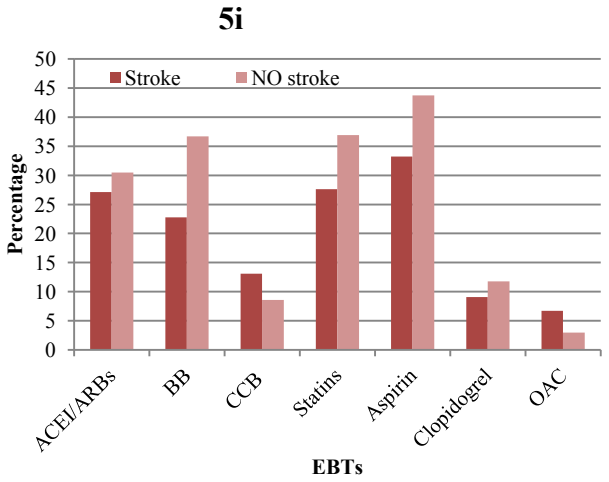
ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers.

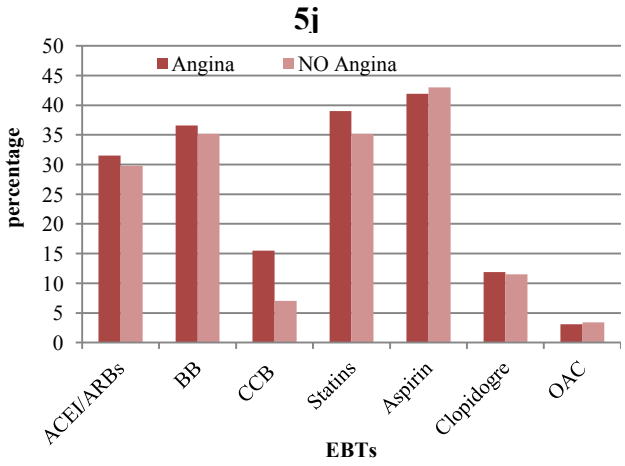
Figure 10 Plot of comorbidities and prescribing of evidence based therapies within 30 days after first MI











ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, BB=beta blockers, CCB= Calcium channel blockers, COPD=chronic obstructive pulmonary disease, OAC=oral anti-coagulants

5.1.1.6 Testing for interactions with year

Where statistically significant findings were found in sections 5.1.1.1–5.1.1.3 and 5.1.1.5, the interaction between that variable and year was tested (Table 23). It can be seen that the only statistically significant interaction was observed between age and year for ACEI/ARBs (p=0.03). To examine the nature of this interaction the adjusted ORs for age group are shown for each year in Table 24, and the unadjusted prescribing rates for ACEI/ARBs by age group and year are shown in Figure 11. It is clear that there is no overall trend and the interaction result will have been strongly influenced by 1999 where the association between age and prescribing of ACEI/ARBs is the opposite of that seen for all other years. The rationale for this was to assess whether any identified inequality was narrowing or widening over the study period.

Table 23 Interaction between year of diagnosis and selected variables and therapies. Variables and medications selected on the basis of significant multivariable associations.

Factors	Medication	P value
Age group		
	ACEI/ARBs	0.03
	β-blocker	0.65
	Statins	0.70
	Aspirin	0.63
	Clopidogrel	0.28
Sex		
	β-blocker	0.46
Socioeconomic deprivation		
	Oral anticoagulant	0.70

Table 24 Adjusted Odds ratio of the prescribing of ACEIs/ARBs and age stratified by year of diagnosis of myocardial infarction

	1997	1998	1999	2000	2001	2002	2003	2004	2005
<55	0.70 (0.15-3.14), 0.64	0.16 (0.02-1.36), 0.09	2.58 (0.94-7.09), 0.07	0.39 (0.13-1.09), 0.07	0.55 (0.23-1.29), 0.17	0.32 (0.13-0.75), 0.01	0.25 (0.09-0.68), 0.01	0.58 (0.23-1.41), 0.23	0.36 (0.15-0.89), 0.03
55-64	0.94 (031-2.87), 0.92	1.05 (0.35-3.20), 0,92	0.42 (0.13-1.32), 0.14	0.88 (0.33-2.47), 0.81	0.53 (0.19-1.47), 0.22	0.95 (0.34-2.61), 0.92	0.56 (0.21-1.52), 0.26	0.53 (0.19-1.48), 0.23	0.57 (0.21-1.59), 0.28
65-74	0.57 (20-1.61), 0,29	1.75 (0.61-4.96), 0.29	0.46 (0.15-1.36), 0.16	0.82 (0.32-2.12), 0.70	0.87 (0.34-2.22), 0.77	1.06 (0.41-2.73), 0.89	1.22 (0.47-3.14), 0.66	0.66 (0.25-1.74), 0.41	1.27 (0.48-3.38), 0.62
75-84	1.33 (0.40-4.41), 0.74	0.74 (0.22-2.48), 0.63	0.28 (0.08-0.98), 0.05	0.74 (0.23-2.30), 0.60	0.34 (0.12-1.04), 0.06	0.87 (0.28-2.67), 0.80	0.91 (0.30-2.79), 0.88	0.38 (0.12-1.21), 0.10	1.57 (0.49-4.97), 0.44
≥85	0.23 (0.02-3.11), 0.27	4.27 (0.32-56.1), 0.27	0.27 (0.04-1.64), 0.16	1.80 (0.29-11.1), 0.52	1.26 (0.23-7.05), 0.79	2.16 (0.38-12.5), 0.38	2.77 (0.46-16.7), 0.26	1.20 (0.21-6.89), 83	1.90 (0.33-10.8), 0.46

Figure 11 Years trends of prescribing ACEI/ARBs based on age

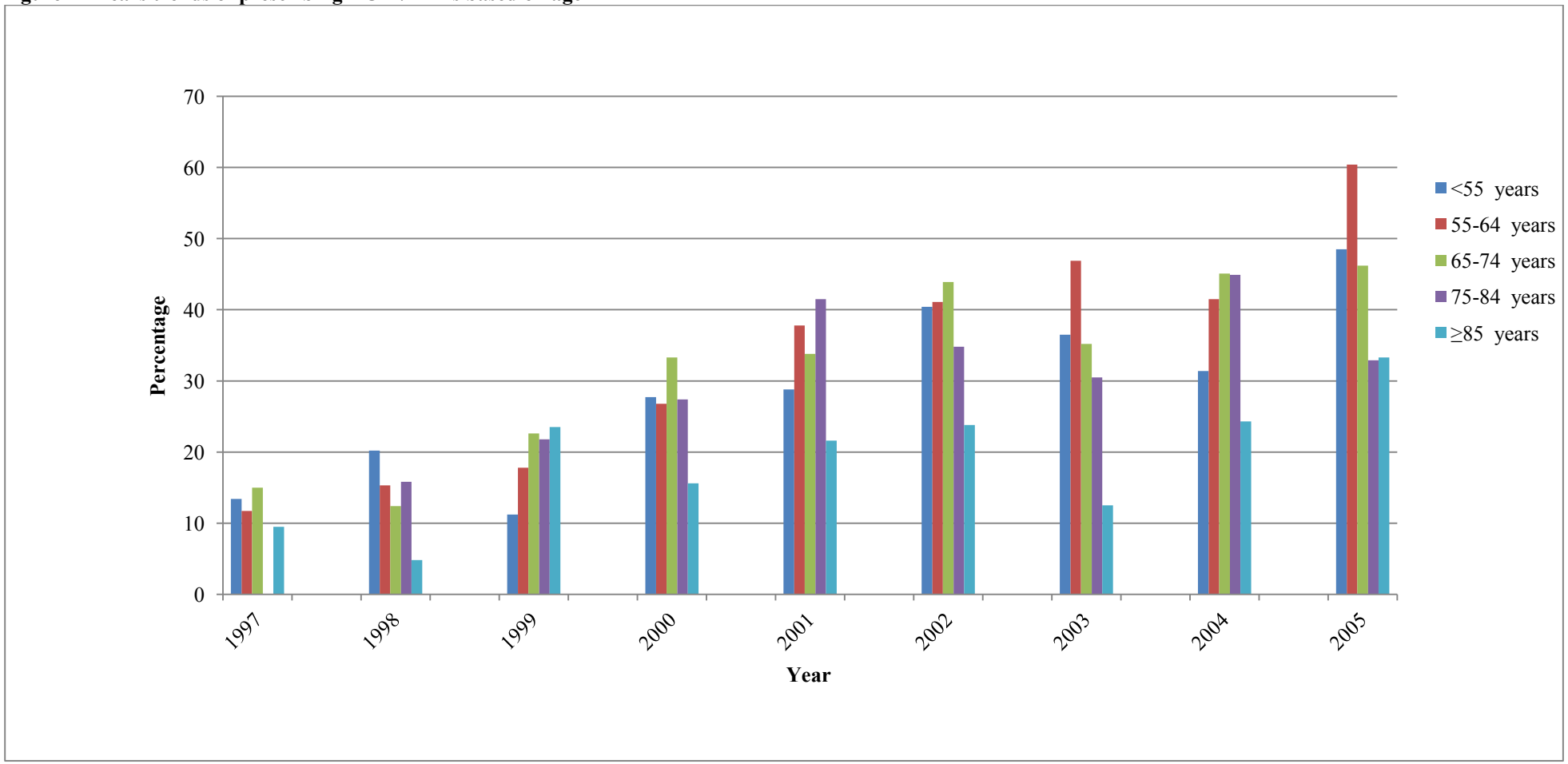


Table 25 Prescribing of evidence based therapies within 30 days after first MI for patients who survived the first 30 days after a first diagnosis (N=4305)

	ACEI/ARBs	β-blocker	CCB	Statins	Aspirin	Clopidogrel	Oral anticoagulant
N=4305	1299 (30.1%)	1530 (35.5%)	386 (9.0%)	1555 (36.1%)	1841 (42.8%)	498 (11.6%)	143 (3.3%)
Male (n=2628)	823 (31.3%)*	1004 (38.2%)	225 (8.6%)	1008 (38.4%)	1161 (44.2%)	325 (12.4%)	77 (2.9%)
Female (n=1677)	467 (28.0%)	526 (31.4%)	161 (9.6%)	547 (32.6%)	680 (40.5%)	173 (10.3%)	67 (4.0%)
Age (years)							
< 55 (n=977)	279 (28.6%)	397 (40.6%)	65 (6.7%)	401 (41.0%)	432 (44.2%)	124 (12.7%)	20 (2.0%)
55 – 64 (n=979)	330 (33.7%)	402 (41.1%)	82 (8.4%)	413 (42.2%)	448 (45.8%)	137 (14.0%)	28 (2.9%)
65 – 74 (n=1175)	375 (31.9%)	431 (36.7%)	116 (9.9%)	446 (38.0%)	522 (44.4%)	130 (11.1%)	45 (3.8%)
75 – 84 (n=877)	256 (29.2%)	243 (27.7%)	101 (11.5%)	253 (28.8%)	340 (38.8%)	84 (9.6%)	45 (5.1%)
85+ (n=297)	59 (19.9%)	57 (19.2%)	22 (7.4%)	42 (14.1%)	99 (33.3%)	23 (7.7%)	6 (2.0%)
Socioeconomic deprivation							
Q1 (n=309)	80 (25.9%)	109 (35.2 %)	26 (8.4%)	95 (30.7%)	124 (40.1%)	28 (9.1%)	11 (3.6%)
Q2 (n=233)	79 (33.9%)	83 (35.6%)	19 (8.1%)	93 (39.9%)	93 (39.9%)	27 (11.6%)	6 (2.6%)
Q3 (n=427)	122 (28.5%)	156 (36.5%)	36 (8.3%)	156 (36.5%)	182 (42.6%)	49 (11.5%)	14 (3.3%)
Q4 (n=406)	146 (35.9%)	156 (38.4%)	34 (8.4%)	151 (37.2%)	177 (43.6%)	53 (13.1%)	6 (1.5%)
Q5 (n=453)	140 (30.9%)	166 (36.6%)	31 (6.8%)	176 (38.8%)	198 (43.7%)	52 (11.5%)	23 (5.1%)
Q6 (n=650)	190 (29.2%)	234 (36.0%)	61 (9.3%)	225 (34.6%)	282 (43.4%)	73 (11.2%)	21 (3.2%)
Q7 (n=501)	140 (27.9%)	158 (31.5%)	46 (9.2%)	176 (35.1%)	203 (40.5%)	56 (11.2%)	22 (4.4%)
Q8 (n=459)	145 (31.6%)	161 (35.1%)	49 (10.7%)	165 (35.9%)	197 (42.9%)	59 (12.8%)	18 (3.9%)
Q9 (n=513)	156 (30.4%)	169 (38.2%)	47 (9.2%)	197 (38.4%)	234 (45.6%)	60 (11.7%)	14 (2.7%)
Q10 (n=354)	101 (28.5%)	111 (31.3%)	37 (10.4%)	121 (34.2%)	151 (42.4%)	41 (11.6%)	9 (2.5%)

Year		ACEI/ARBs	β-blocker	CCB	Statins	Aspirin	Clopidogrel	Oral anticoagulant
1997	**(n=422)**	52 (12.3%)	81 (19.2%)	28 (6.6%)	41 (9.7%)	122 (28.9%)	0 (0.0%)	3 (0.7%)
1998	**(n=474)**	72 (15.2%)	118 (24.9%)	28 (5.9%)	95 (20.0%)	165 (34.8%)	0 (0.0%)	13 (2.7%)
1999	**(n=461)**	86 (18.7%)	148 (32.1%)	37 (8.0%)	128 (27.8%)	194 (42.1%)	0 (0.0%)	15 (3.3%)
2000	**(n=460)**	129 (28.0%)	173 (37.6%)	47 (10.2%)	143 (31.1%)	199 (43.3%)	14 (3.0%)	12 (2.6%)
2001	**(n=516)**	175 (33.9%)	208 (40.3%)	58 (11.2%)	182 (35.3%)	210 (40.7%)	34 (6.6%)	22 (4.3%)
2002	**(n=532)**	208 (39.1%)	210 (39.5%)	55 (10.3%)	231 (43.4%)	251 (47.2%)	73 (13.7%)	18 (3.4%)
2003	**(n=545)**	194 (35.6%)	202 (37.1%)	54 (9.9%)	239 (43.9%)	245 (45.0%)	91 (16.7%)	17 (3.1%)
2004	**(n=471)**	186 (39.5%)	206 (43.7%)	42 (8.9%)	264 (56.1%)	229 (48.6%)	137 (29.1%)	23 (4.9%)
2005	**(n=424)**	197 (46.5%)	184 (43.4%)	37 (8.7%)	232 (54.7%)	226 (53.3%)	149 (35.1%)	21 (5.0%)
Comorbidities								
COPD/Asthma								
	Yes (529)	173 (32.7%)	88 (16.6%)	90 (17.0%)	187 (35.3%)	238 (45.0%)	63 (11.9%)	11 (2.1%)
	No (3776)	1126 (29.8%)	1442 (38.2%)	296 (7.8%)	1368 (36.2%)	1603 (42.5%)	435 (11.5%)	133 (3.5%)
Atrial fibrillation								
	Yes (424)	132 (31.1%)	105 (24.8%)	35 (8.3%)	134 (31.6%)	138 (32.5%)	37 (8.7%)	76 (17.9%)
	No (3881)	1167 (30.1%)	1425 (36.7%)	351 (9.0%)	1421 (36.6%)	1703 (43.9%)	461 (11.9%)	68 (1.8%)
Hypertension								
	Yes (1401)	530 (37.8%)	564 (40.3%)	195 (13.9%)	587 (41.9%)	644 (46.0%)	229 (16.3%)	52 (3.7%)
	No (2904)	769 (26.9%)	966 (33.3%)	191 (6.6%)	968 (33.3%)	1197 (41.2%)	269 (9.3%)	92 (3.2%)
Diabetes								
	Yes (426)	154 (36.2%)	138 (32.4%)	42 (9.9%)	147 (34.5%)	169 (39.7%)	54 (12.7%)	24 (5.6%)
	No (3879)	1145 (29.5%)	1392 (35.9%)	344 (8.9%)	1408 (36.3%)	1672 (43.1%)	444 (11.4%)	120 (3.1%)

		ACEI/ARBs	β-blocker	CCB	Statins	Aspirin	Clopidogrel	Oral anticoagulant
Cancer								
	Yes (250)	74 (29.6%)	71 (28.4%)	20 (8.0%)	85 (34.0%)	104 (41.6%)	30 (12.0%)	11 (4.4%)
	No (4055)	1225 (30.2%)	1459 (36.0%)	366 (9.0%)	1470 (36.3%)	1737 (42.8%)	468 (11.5%)	133 (3.3%)
Renal failure								
	Yes (108)	31 (28.7%)	28 (25.9%)	13 (12.0%)	32 (29.6%)	42 (38.9%)	16 (14.8%)	4 (3.7%)
	No (4197)	1268 (30.2%)	1502 (35.8%)	373 (8.9%)	1523 (36.3%)	1799 (42.9%)	482 (11.5%)	140 (3.3%)
Heart failure (HF)								
	Yes (863)	365 (42.3%)	268 (31.1%)	69 (8.0%)	310 (35.9%)	379 (43.9%)	95 (11.0%)	59 (6.8%)
	No (3442)	934 (27.1%)	1262 (36.7%)	317 (9.2%)	1245 (36.2%)	1462 (42.5%)	403 (11.7%)	85 (2.5%)
PAD								
	Yes (331)	127 (38.4%)	100 (30.2%)	45 (13.6%)	132 (39.9%)	135 (40.8%)	48 (14.5%)	18 (5.4%)
	No (3974)	1172 (29.5%)	1430 (36.0%)	341 (8.6%)	1423 (35.8%)	1706 (42.9%)	450 (11.3%)	126 (3.2%)
Stroke								
	Yes (373)	101 (27.1%)	85 (22.8%)	49 (13.1%)	103 (27.6%)	124 (33.2%)	34 (9.1%)	25 (6.7%)
	No (3932)	1198 (30.5%)	1445 (36.7%)	337 (8.6%)	1452 (36.9%)	1717 (43.7%)	464 (11.8%)	119 (3.0%)
Angina								
	Yes (1002)	315 (31.5%)	367 (36.6%)	155 (15.5%)	391 (39.0%)	420 (41.9%)	119 (11.9%)	31 (3.1%)
	No (3303)	984 (29.8%)	1163 (35.2%)	231 (7.0%)	1164 (35.2%)	1421 (43.0%)	379 (11.5%)	113 (3.4%)

* Proportions for each cell represent the number of those who prescribed an EBT e.g. ACEI/ARBs for each category e.g. men. For example, the proportion for men who are prescribed ACEI/ARBs within 30 days after 1st diagnosis is 823, the total men who survived 30 days after 1st diagnosis 2628 (prescribed and not prescribed ACEI/ARBs): 823/2628 x 100=31.3%. For the same drug and category, those not prescribed ACEI/ARBs 1805: 1805/2628 x 100=68.7%.

5.1.1.7 Slope index of inequalities (SII) and relative index of inequalities (RII)

In this study SII and RII are used to measure the socioeconomic relationship between the prescribing of EBTs within 30 days after hospital discharge of MI.

As can be seen in Tables 26 and 27, both the absolute and relative index of inequalities are small in magnitude across the classes of EBTs (values close to 0 and 1, respectively) and not statistically significant, indicating no inequality in the prescribing of EBTs in terms of socioeconomic deprivation. These findings are similar to the logistic regression models above.

Table 26 RII for myocardial infarction

	RII (95% CI)	P value
ACEI/ARBs	0.95 (0.71-1.26)	0.7
β-blockers	0.95 (0.73-1.23)	0.7
CCB	1.19 (0.85-1.66)	0.3
Statins	1.02 (0.80-1.29)	0.8
Aspirin	1.06 (0.79-1.41)	0.7
Clopidogrel	1.11 (0.78-1.57)	0.5
Oral anticoagulant	1.09 (0.59-2.00)	0.7

RII=Relative index of inequality

Table 27 SII for myocardial infarction

	SII (95% CI)	P value
ACEI/ARBs	-0.02 (-0.11-0.07)	0.6
β-blockers	-0.03 (-0.12-0.07)	0.5
CCB	-0.001 (-0.03-0.02)	0.9
Statins	-0.01 (-0.09-0.07)	0.8
Aspirin	0.02 (-0.1-0.14)	0.7
Clopidogrel	0.003 (-.02-0.03)	0.8
Oral anticoagulant	0.002 (-0.01-0.02)	0.8

SII=Slope index of inequality

5.1.1.8 Goodness of fit tests for MI

As can be seen in Table 28, the majority of ROC values ranged between 0.7 and 0.8 which shows acceptable discrimination, however, the ROC value for aspirin showed that the discrimination of the model was poorer for this medication. When the Hosmer-Lemeshow test was examined the model was well calibrated for each of the medications with the exception of CCBs. However, the calibration results were sensitive to the number of groups chosen. With 10 groups, evidence of poor fit was also seen for ACEI/ARBs, β-blockers and clopidogrel.

Table 28 ROC and Hosmer-Lemeshow

	ROC P value	Hosmer-Lemeshow group (5) P value	Hosmer-Lemeshow group (10) P value
ACEI/ARBs	0.71	0.14	0.01
β-blockers	0.69	0.13	0.01
CCB	0.78	0.01	0.03
Statins	0.72	0.14	0.41
Aspirin	0.61	0.48	0.11
Clopidogrel	0.84	0.23	0.01
Oral anticoagulant	0.84	0.37	0.70

5.1.2 Summary

5.1.2.1Incidene of myocardial infarction

The information services division (ISD) Scotland, a division of National Services Scotland that provides health information, health intelligence and statistical services, recently reported that the crude incidence rate per 100000 population for MI has declined over the years 2002-2012.[415] The rate reported for ISD Scotland for new hospitalised cases of MI in 2002/03 (266.8 per 100000), 2003/04 (252.7 per 10000), and 2004/05 (243.7 per 100000) and 2005/06 (299.1 per 100000) were similar to the results in my study (page 110).

5.1.2.3 Age differences in prescribing evidence based therapies after a first MI

I have shown that there was a clear association between age and the prescribing of EBTs after a first diagnosis of MI. In general, previous studies showed that the prescribing of EBTs declined as age increases with differences being particularly evident in those aged more than 85 years.[284-286,285,288]

Older patients were significantly less likely to receive prescriptions for ACEI/ARBs, β-blockers, statins, aspirin and clopidogrel, which has been reported previously.[282,283,287,289-291,294-296,312] A few other studies showed different trends in prescribing EBTs regarding age, particularly in prescribing ACEI/ARBs.[284-286,288] Significant differences in prescribing EBTs in the elderly aged ≥ 85 years may be explained by the lack of evidence of the efficacy of many of these therapies specifically in these age group.[416]

5.1.2.2 Sex differences in prescribing of evidence based therapies after a first MI

I found that prescribing of EBTs was higher in men than women but was only statistically significantly different for β-blockers. Similar to previous studies, the adjusted odds of prescribing ACEI/ARBs was higher among men compared to women.[284,287,288] Only one study has shown that men and women were equally likely to be prescribed ACEI/ARBs, however, the association was only adjusted for age.[305] The finding that men had statistically significantly higher odds of being prescribed β-blockers than women matches results from three other studies. [287, 284, 309] However, only

one study adjusted for a few covariates (demographics and year of MI) and examined the difference in patients aged ≥ 65 only. [290] Two studies reported that there was no difference in prescribing of β-blockers by sex after a MI.[283,310] Contrary to this study, one study found a higher odds of prescribing of CCB in women compared to men.[305] Only one study has demonstrated that the prescribing of statins was significantly lower among women compared to men,[282] one small study found that women were significantly more likely to receive prescriptions for statins than men (OR1.48.0; 95% CI 1.10-1.98).[306] Prescribing of aspirin was similar in men and women in keeping with prior studies.[282,284,305,306] No prior studies have examined differences in prescribing of clopidogrel and oral-anticoagulants.

5.1.2.4 Socioeconomic status differences in prescribing of evidence based therapies after a first MI

This study found no evidence for significant differences in prescribing by socioeconomic deprivation status. It seems plausible to attribute this finding to the fact that Scotland has a free health care system which includes medications for chronic disease. This is supported by a cross-sectional study in Scotland[223] which used similar data sets and found no significant difference in prescribing of secondary prevention therapies in patients with CHD. However, studies conducted in the USA and Canada, where they have different health care systems than Scotland, displayed the effect of socioeconomic status. [311,314]

5.1.2.5 Trends over time in prescribing of evidence based therapies after a first MI

Prescribing increased over the study period for all EBTs with the exception of CCBs. This is in agreement with previous studies that show that prescribing of secondary prevention post MI was associated with a reasonable improvement in the last couple of decades. The drug associated with the highest improvement was statins (OR 11.11; 95%CI 6.70-18.42). In this study prescribing was still considered suboptimal and needs to be encouraged. Compared to other studies the proportion of prescribing of ACEI/ARBs was almost similar to mine. The trends of prescribing β-blockers is lower in this study compared to some other previous studies, which potentially can be explained by increased prevalence of COPD or asthma.[319, 317, 316, 318,284, 322] However, compared to studies using multivariable analysis, only one study showed higher odds of prescribing β-blockers (OR 5.73; 95%CI 5.23-6.26) compared to this study.[312]

5.1.2.6 Comorbidities and their relation to prescribing of evidence based therapies after a first MI

In these analyses, several comorbidities influenced the prescribing of EBTs after a MI. One previous study showed[288] that the odds of prescribing ACEI/ARBs are higher among patients with than those without COPD/asthma, however this was not significant. Prescribing of ACEI/ARBs was statically significant in patients with diabetes,[287,328] HF,[287] than those without relevant disease. Though, in this study prescribing for ACEI/ARBs was only significantly higher in patients with than without HF. Lower prescribing of EBTs in concomitant disease can be attributed to the contraindications. For example, prescribing of β-blockers is similar to previous studies low in patients with COPD or asthma.[290,288] Furthermore, there was a high prevalence of older patients who are more likely to have more comorbidities. The severity of renal failure can influence the prescribing of EBTs for patients with renal disease. I found similar trends in the prescribing of EBTs in patients with renal failure to previous studies. Patients with renal failure received fewer prescriptions of β-blockers and statins.[308] Clinical trials have demonstrated that oral anticoagulants, e.g. warfarin are more effective to prevent vascular events in patients with AF which explains why oral anticoagulant use is higher than use of aspirin and clopidogrel in patients with AF.

Summary

Prescribing of EBTs within 30 days after a first MI has improved over time, however, it remains suboptimal. Prescribing of statins has increased greatly since 1997 and the influence of age, sex and comorbidities was evident. Differences in prescribing of EBTs by age were evident though differences by sex were only evident for β-blockers. Differences in prescribing EBTs due to socioeconomic status were not significant which may be attributable to the equity of access of the Scottish health system.

5.2 Angina

Baseline demographic characteristics

A total of 7309 individuals were identified as having a diagnosis of angina. In the study cohort, 6574 patients were diagnosed with angina in the primary care and 735 patients in the secondary care (Figure 12). Of these, 99 patients (38 from the primary care and 61 from the secondary care) did not survive 30 days after first diagnosis and were excluded from the analysis. In this study, 7210 (64.2%) patients who survived 30 days after first diagnosis were eligible to be included in the study. Of these, 6536 (90.7%) patients were identified in the primary care and 674 (9.3%) patients identified in the secondary care.

Table 29 summarises the characteristics of these patients and the subset of patients who survived 30 days after the first recorded diagnosis. It can be seen that approximately 55% of the angina patients were men and the largest proportion were aged between 65 and 74 years. Patients residing in areas among the most deprived quintile of socioeconomic deprivation had a higher percentage of patients than those residing in areas from the least deprived quintile, but the largest numbers were in the third and fourth deprivation groups. The most prevalent comorbidities were hypertension (32.2%), COPD/asthma (12.2%) and HF (11.8%). Table 30 shows the incidence of angina per 1000 population. The incidence rate was higher in men, 5.11 per 1000, than in women, 4.04 per 1000. The incidence of angina had a clear age gradient from 1.56 per 1000 in those aged less than 45 years compared to 17.61 per 1000 in those aged 75-84 years., There was then a decline for patients aged 85 years and more, 13.99 per 1000. The incidence rate of angina increased with increasing socioeconomic deprivation status from 2.93 per 1000 in the least deprived quintile to 5.67 per 1000 in the most deprived quintile. Over the year angina incidence declined to reach the lowest rate in 2005.

Figure 12 Flow chart showing the selection of patients with a first diagnosis of angina

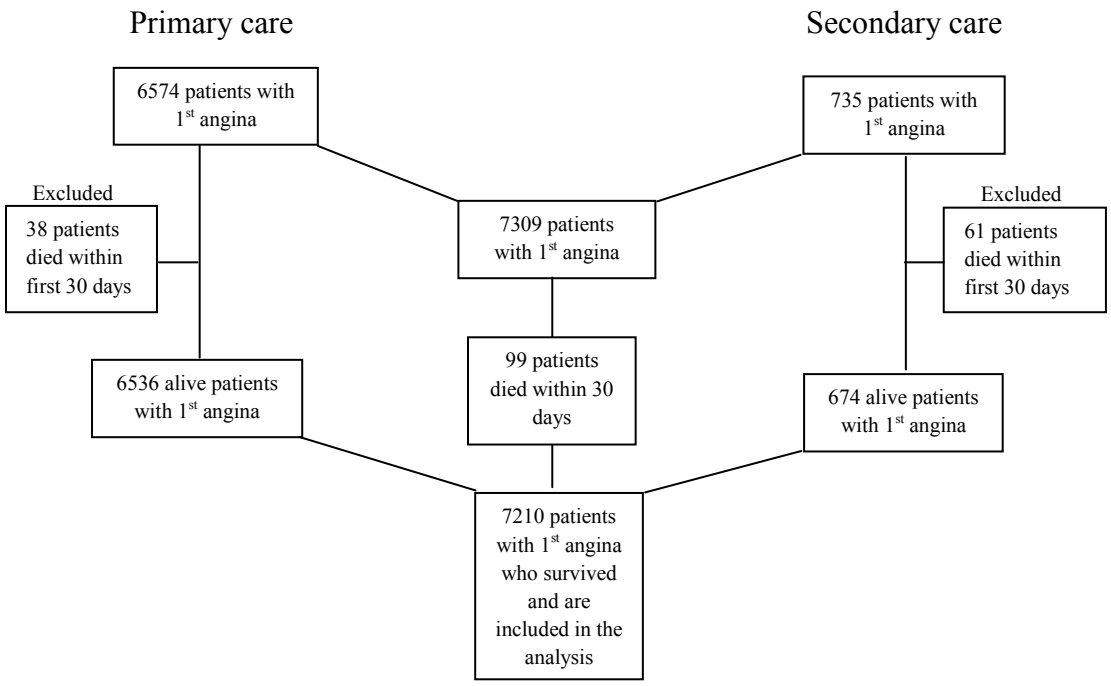


Table 29 Baseline demographic characteristics

	Survived 30 days (n=7210) §	Patients died within 30 days after 1st diagnosis (n=99)*	All patients (n=7309)
Male sex	3990 (55.3)	57 (57.6%)	4047 (55.4%)
SD/variance	0.5/0.2	0.5/0.2	0.5/0.2
Age (years):			
< 55	1479 (20.5%)	3 (3.0%)	1482 (20.3%)
55 – 64	1965 (27.3%)	11 (11.1)	1976 (27.0%)
65 – 74	2056 (28.5%)	17 (17.2%)	2073 (28.4%)
75 – 84	1381 (19.2%)	42 (42.4%)	1423 (19.5%)
85+	329 (4.6%)	26 (26.3%)	355 (4.9%)
Socioeconomic			
Q1 Least deprived	452 (6.2%)	5(5.1%)	452 (6.2%)
Q2	426 (5.9%)	8 (8.1%)	426 (5.9%)
Q3	770 (10.6%)	12 (12.1%)	770 (10.6%)
Q4	634 (8.7%)	15 (15.1%)	634 (8.7%)
Q5	753 (10.4%)	11 (11.1%)	753 (10.4%)
Q6	1106 (15.3%)	14 (14.1%)	1106 (15.3%)
Q7	838 (11.6%)	7 (7.1%)	838 (11.6%)
Q8	738 (10.2%)	10 (10.1%)	738 (10.2%)
Q9	877 (12.2%)	10 (10.1%)	877 (12.1%)
Q10 Most deprived	616 (8.5%)	7 (7.1%)	616 (8.5%)
Year			
1997	972 (13.5%)	9 (9.1%)	981 (13.4%)
1998	1081 (15.0%)	8 (8.1%)	1089 (14.9%)
1999	984 (13.6%)	15 (15.1%)	999 (13.7%)
2000	952 (13.2%)	17 (17.1%)	969 (13.3%)
2001	834 (11.6%)	14 (14.1%)	848 (11.6%)
2002	788 (10.9%)	10 (10.1%)	798 (10.9%)
2003	583 (8.1%)	7 (7.1%)	590 (8.1%)
2004	564 (7.8%)	11 (11.1%)	575 (7.9%)
2005	452 (6.3%)	8 (8.1%)	460 (6.3%)
Comorbidities			
COPD/Asthma	877 (12.2%)	20 (20.2%)	897 (12.2%)
Atrial fibrillation	497 (6.9%)	12 (12.2%)	509 (7.0%)
Hypertension	2365 (32.8%)	31 (31.3%)	2396 (32.2%)
Diabetes	411 (5.7%)	13 (13.1%)	424 (5.8%)
Cancer	414 (6.1%)	24 (24.2%)	465 (6.4%)
Renal failure	55 (0.8%)	12 (12.1%)	67 (0.9%)
Heart failure	824 (11.4%)	39 (39.3%)	863 (11.8%)
PAD	460 (6.4%)	17 (17.1%)	477 (6.5%)
Stroke	478 (6.6%)	20 (20.1%)	498 (6.8%)

* Only 34 (4.0%) patients died within 30 days and had a prescription, § No missing data
COPD=Chronic obstructive pulmonary disease, PAD=Peripheral arterial disease

Table 30 Rate per (1000) of incident angina

	Total population registered with GPs	Patients with angina	Rate
Sex			
Men	792651	4047	5.11
Women	807959	3262	4.04
Age			
<45	950345	1482	1.56
45-64	410998	1976	4.81
65-74	133058	2073	15.58
75-84	80828	1423	17.61
85+	25381	355	13.99
Socio-economic			
Q1	305557	895	2.93
Q2	358497	1426	3.98
Q3	401492	1887	4.70
Q4	305760	1589	5.20
Q5	266735	1512	5.67
Years			
1999	227690	999	4.39
2000	226503	969	4.28
2001	225806	848	3.76
2002	227146	798	3.51
2003	228766	590	2.58
2004	232554	575	2.47
2005	232343	460	1.98

Prescribing of evidence based therapies before and after first recorded diagnosis

Table 31 shows prescribing of EBTs before and after the first recorded diagnosis of angina. More than a third, 39.7% and 37.3%, of patients were prescribed aspirin and nitrates before a first diagnosis of angina, respectively. After a first diagnosis, prescribing of EBTs within 30 days declined slightly for most of EBTs, though for clopidogrel it increased from 3.5% to 4.9%, and for other anti-anginal treatment (nicorandil and ivabradine) from 2.3% to 3.7%. Prescribing of EBTs increased at least by double for all secondary prevention EBTs at any time point after first diagnosis.

Table 31 Evidence based therapies prescribing for patients with incident diagnosis of angina

Medicine	Prescribed drug before 1st diagnosis	Prescribed drug after 1st diagnosis at any time	Prescribed drug within 30 days after 1st diagnosis
ACEI/ARB	22.3%	58.7%	15.3%
β-blockers	33.2%	72.4%	30.5%
CCB	23.2%	54.1%	16.1%
Nitrates	37.3%	81.6%	36.0%
Statins	22.1%	83.8%	23.7%
Aspirin	39.7%	85.2%	34.1%
Clopidogrel	3.5%	22.8%	4.9%
Other anti-anginal drugs	2.3%	22.6%	3.7%

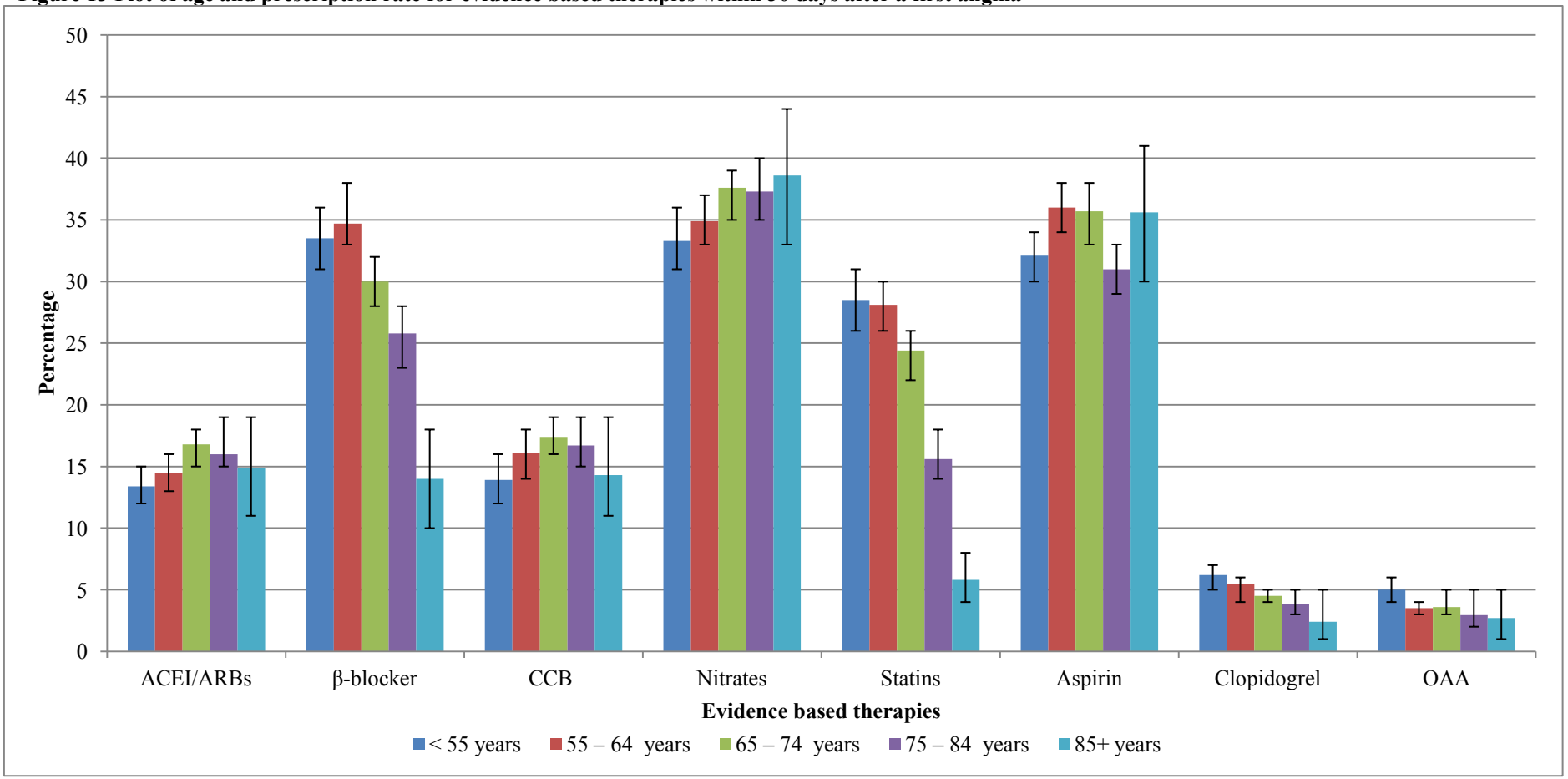
* This percentage is for patients alive 30 days after the 1st diagnosis, ACEI=Angiotensin converting enzyme inhibitor, ARBs=Angiotensin receptor blockers, CCB=calcium channel blockers.
Other anti-angina (Nicorandil and ivabradine)

5.2.1 Differences in prescribing of evidence based therapies for angina

5.2.1.1 Age differences in prescribing of evidence based therapies

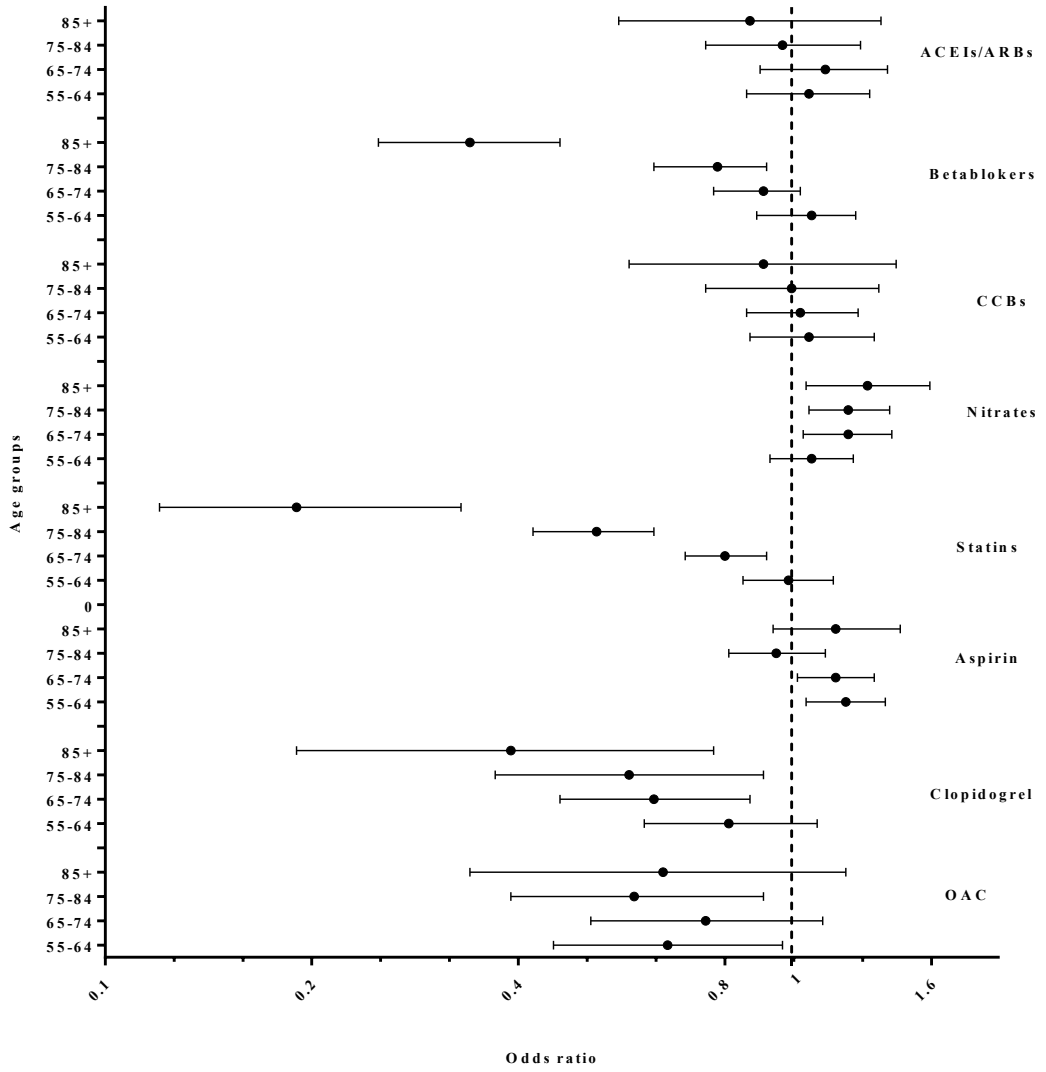
Generally, older patients received proportionally less prescription of EBTs than younger patients (Figure 13 and Table 36). Patients aged less than 55 years received more prescriptions of statins (28.5%), clopidogrel (6.2%) and other anti-anginal treatments (5.0%) than other age groups. Patients aged between 55 and 64 years received more prescriptions of β-blockers (34.7%) than all other age groups. Prescribing of ACEI/ARBs and CCBs was highest for age (from 65 to 74, from 16.8% and 17.4%, respectively). Patients aged ≥ 85 years had the highest percentage of nitrates prescribed (38.6%). After adjustment using multivariable analysis, there were statistically significant differences in the odds of prescribing between the age groups for β-blockers ($p<0.001$), nitrates ($p=0.03$), statins ($p<0.001$), aspirin ($p=0.01$), and clopidogrel ($p=0.02$), (Table 5 appendix 6). As can be seen in Figure 14, compared to youngest age group (> 55 years), the eldest patient group (≥ 85 years) were significantly less likely to be prescribed β-blockers (OR 0.34; 95% CI 0.25-0.46), statins (OR 0.19; 95% CI 0.12-0.33) and clopidogrel (OR 0.39; 95% CI 0.19-0.77). However, nitrates were more likely to be prescribed for patients ≥ 85 years than those aged < 55 years (OR 1.29; 95% CI 1.05-1.59). Aspirin was significantly more likely to be prescribed to age groups 55-64 years (OR 1.20; 95% CI 1.05-1.37) and 65-74 years (OR 1.16; 95% CI 1.02-1.32) as compared to those aged < 55 years. Significant differences were identified in age groups 65-74 and 75-84 years compared to <55 years for nitrates (OR 1.21; 95% CI 1.04-1.40 and OR 1.21; 95% CI 1.06-1.39, respectively). Prescribing of β-blockers (with exception for age group 55-64 years), statins and clopidogrel declined as age increased.

Figure 13 Plot of age and prescription rate for evidence based therapies within 30 days after a first angina



ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, OAA= Other antianginal.

Figure 14 Forest plot of odds ratio of age and prescribing evidence based therapies within 30 days after first diagnosis of angina



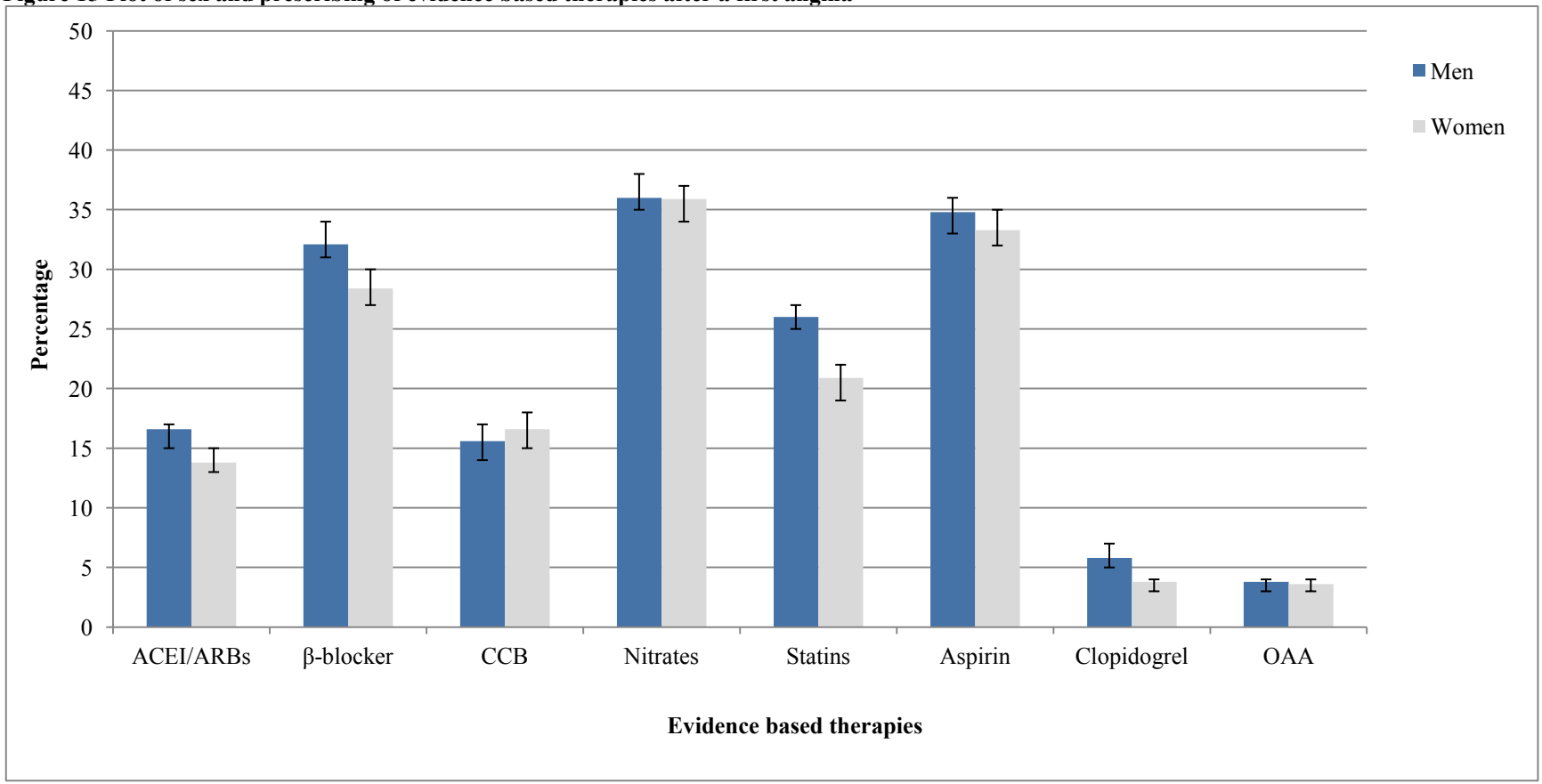
Patients aged <55 years are the reference category. Odds ratio adjusted for sex, socioeconomic status, year of diagnosis, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, peripheral arterial disease, clustered practices, and whether the drug was previously prescribed.

ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, OAA=Other antianginal

5.2.1.2 Sex differences in prescribing of evidence based therapies

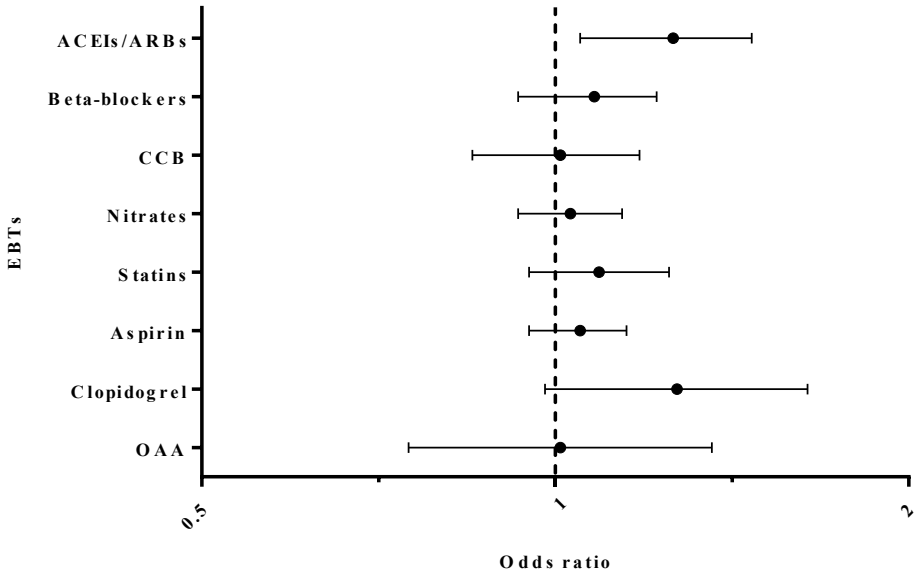
Prescribing of ACEI/ARBs, β-blockers, statins, aspirin and clopidogrel was higher in men compared with women, whereas women received more prescriptions for CCBs (Figure 15). There was no difference in prescribing of nitrates and other anti-anginal treatments between men and women. ACEI/ARBs were prescribed for 16.6% vs. 13.8% for women, β-blockers 32.1% for men vs. 28.4% for women, statins 26.0% for men vs. 20.9% for women (Table 36). After adjustment using multivariable analysis compared to women, men were significantly more likely to receive ACEI/ARBs (OR 1.26; 95% CI 1.05-1.47, p=0.005) than women. Furthermore, men had higher odds of being prescribed all other medications such as clopidogrel (OR 1.27; 95% CI 0.98-1.64, p=0.06), however the associations were not statistically significant (Figure 16 and Table 6 appendix 7).

Figure 15 Plot of sex and prescribing of evidence based therapies after a first angina



ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, OAA=Other antianginal

Figure 16 Forest plot of odds ratio of sex and prescribing evidence based therapies within 30 days after first diagnosis of angina



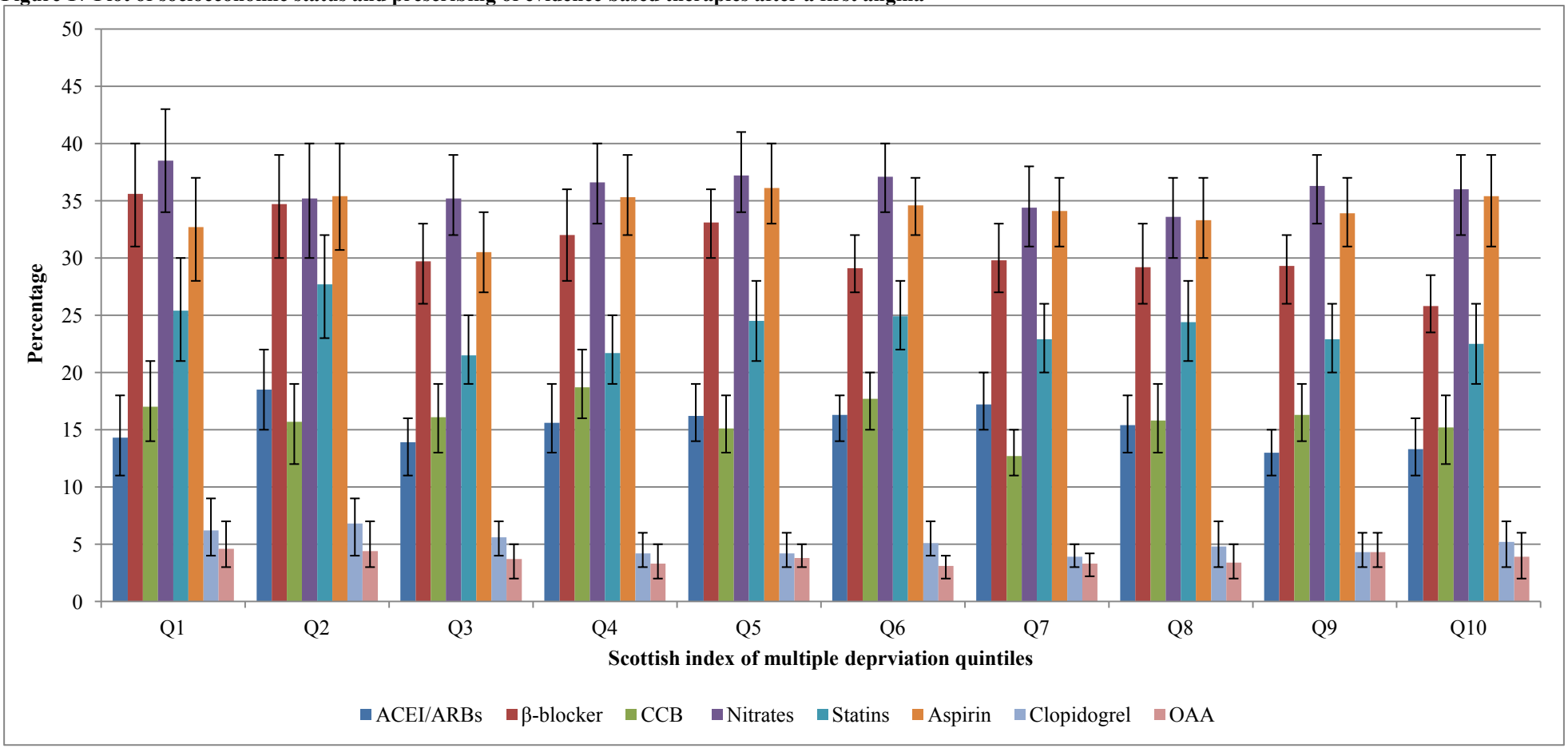
Women are the reference category. Odds ratio adjusted for age group, socioeconomic, year of diagnosis, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, stroke, peripheral arterial disease, clustered practices, and whether the drug was previously prescribed.

ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, OAA=Other antianginal

5.2.1.3 Socioeconomic differences in prescribing of evidence based therapies

For the most part, there were only minor differences in the prescribing of EBTs between socioeconomic deprivation groups (Figure 17). However, the proportion of β-blockers and statins prescribing is higher in quintile 1 than the other quintiles, particularly quintile 10. Table 36 shows the proportion differences in prescribing of EBTs between the deprivation quintiles. As can be seen, there are minor differences between the groups. The multivariable analyses (Figure 18) showed that after adjustment there was no evidence of differences in the odds of prescribing most of EBTs between the socioeconomic deprivation groups, however, β-blockers were significantly less likely to be prescribed for patients in quintile Q9 compared to the least deprived areas quintile Q1 (OR 0.76; 95% CI 0.57-0.99), (Table 7 appendix 6).

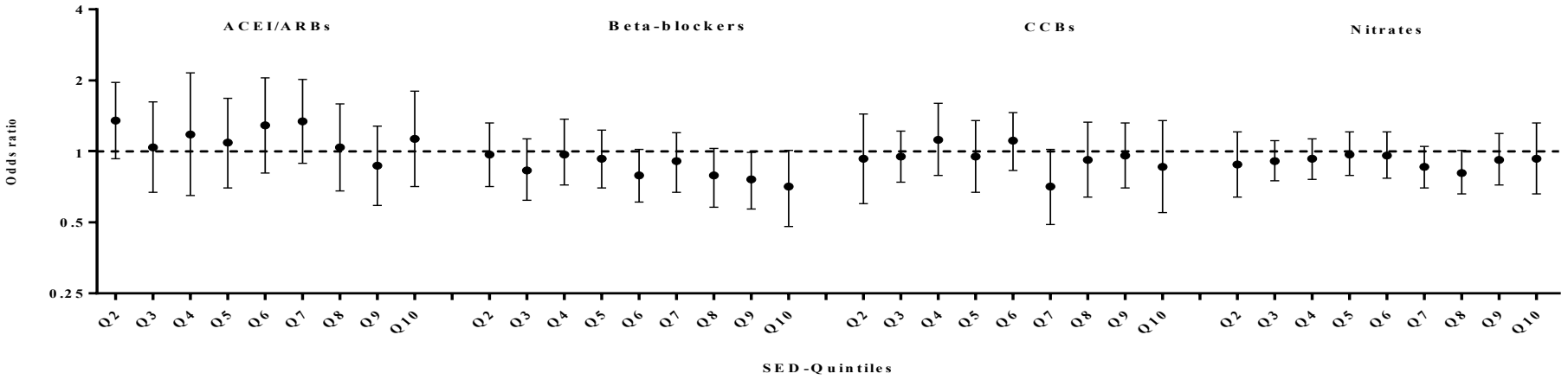
Figure 17 Plot of socioeconomic status and prescribing of evidence based therapies after a first angina



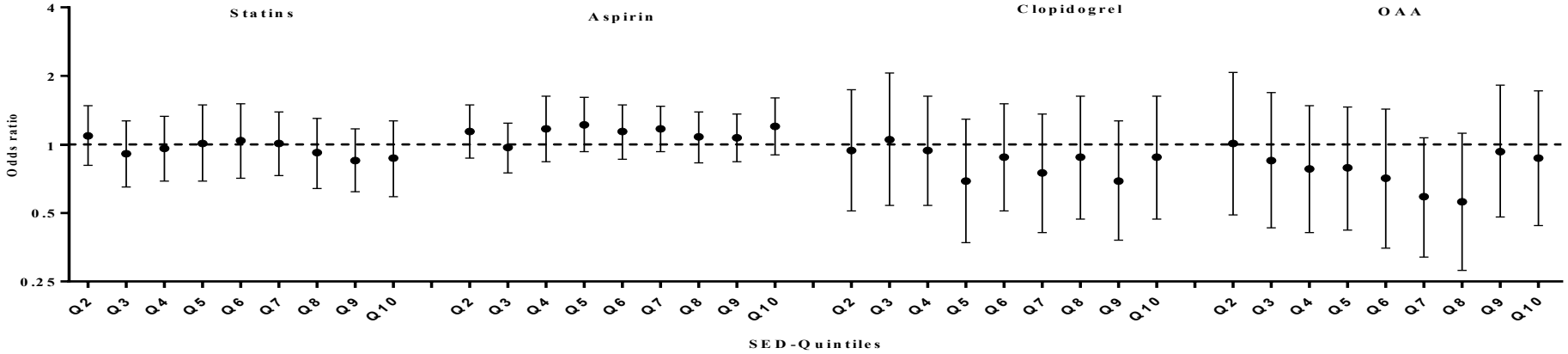
ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blocker

Figure 18 Forest plot of odds ratio of socioeconomic deprivation and prescribing evidence based therapies within 30 days after first diagnosis of angina

A



B



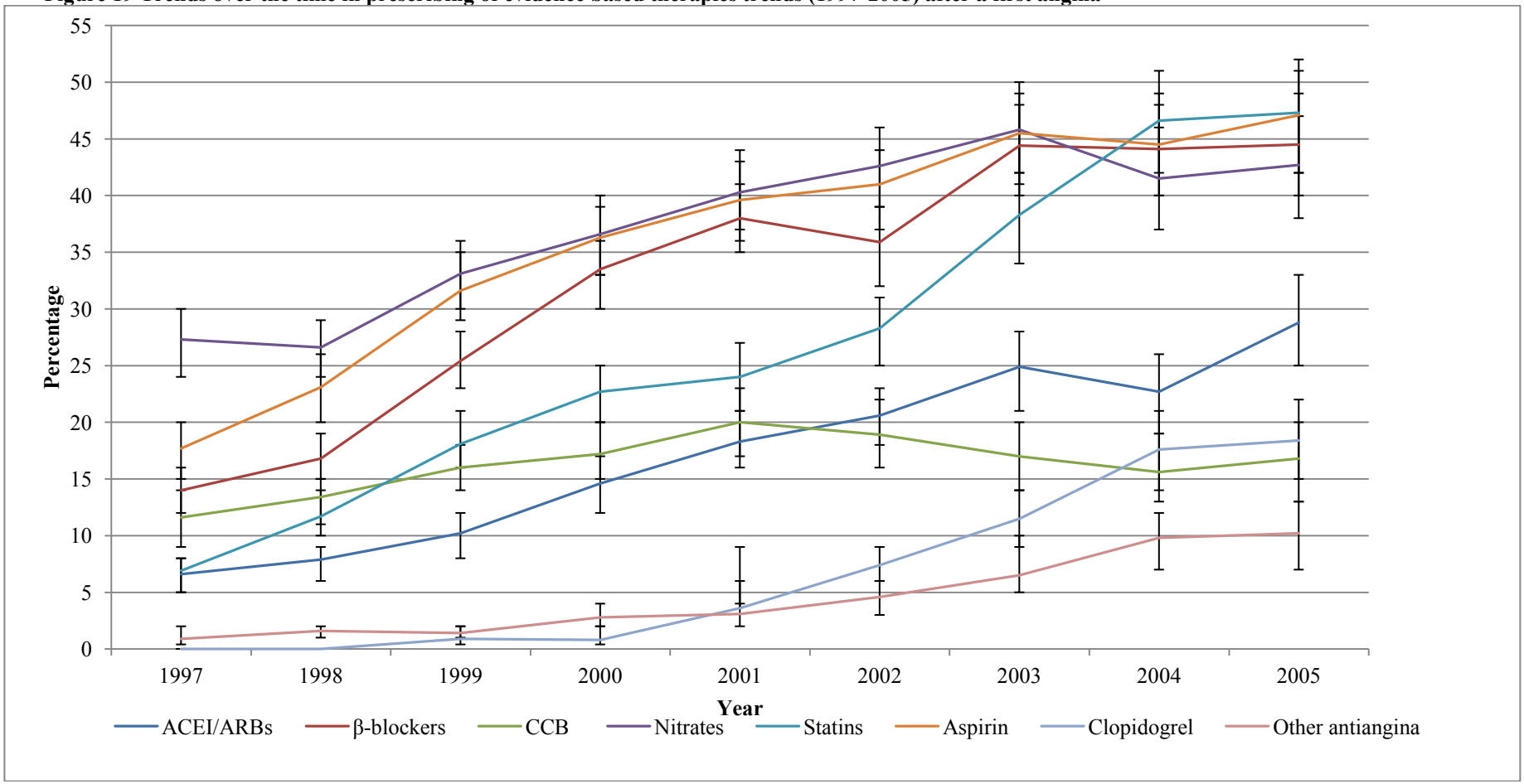
Quintile 1 (Q1) least deprived is a reference. Odds ratio adjusted for sex, age group, year of diagnosis, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, peripheral arterial disease, clustered practices, and whether the drug was previously prescribed.

SED=Socioeconomic deprivation ACEI=Angiotensin converting enzyme inhibitors, ARBs=Angiotensin receptor blockers, CCB=Calcium channel blockers, OAA=Other antianginal.

5.2.1.4 Trends of prescribing evidence based therapies from 1997 to 2005

Figure 19 shows the trend in prescribing of EBTs within 30 days after first diagnosis of angina over the study period. Prescribing of most EBTs increased steadily over the period. Prescribing of statins shows the greatest absolute increase from 1997 to 2005, followed by β-blockers. From 1997 to 2005, prescribing within 30 days after first diagnosis of angina increased for ACEI/ARBs (from 6.6% to 28.8%), β-blockers (from 14.0% to 44.5%), CCB (from 11.6% to 16.8%), nitrates (from 27.3% to 42.7%), statins (from 6.9% to 47.3%), aspirin (from 17.7% to 47.1%), clopidogrel (0.00% to 18.4%) and other anti-angina treatments (from 0.9% to 10.2%) Table 36. After adjustment using multivariable analysis (Figure 20), there were statistically significant differences in the odds of prescribing between the years of the study – with $p<0.001$ for all EBT classes. Compared to prescribing in 1997, patients in 2005 were significantly more likely to be prescribed ACEI/ARBs (OR 3.71; 95% CI 2.46-5.58), β-blockers (OR 4.75; 95% CI 3.26-6.73), nitrates (OR 1.77; 95% CI 1.32-2.38), statins (OR 8.11; 95% CI 5.89-11.15), aspirin (OR 2.99; 95% CI 2.24-4.00), and other anti-angina treatment (OR 7.69; 95% CI 3.03-19.5). Although the odds of prescribing CCBs in 2005 was not statistically different to 1997 (OR 1.31; 95% CI 0.95 to 1.79), the overall trend across all the study years was significant ($p < 0.001$) (Figure 20 and Table 8 appendix6).

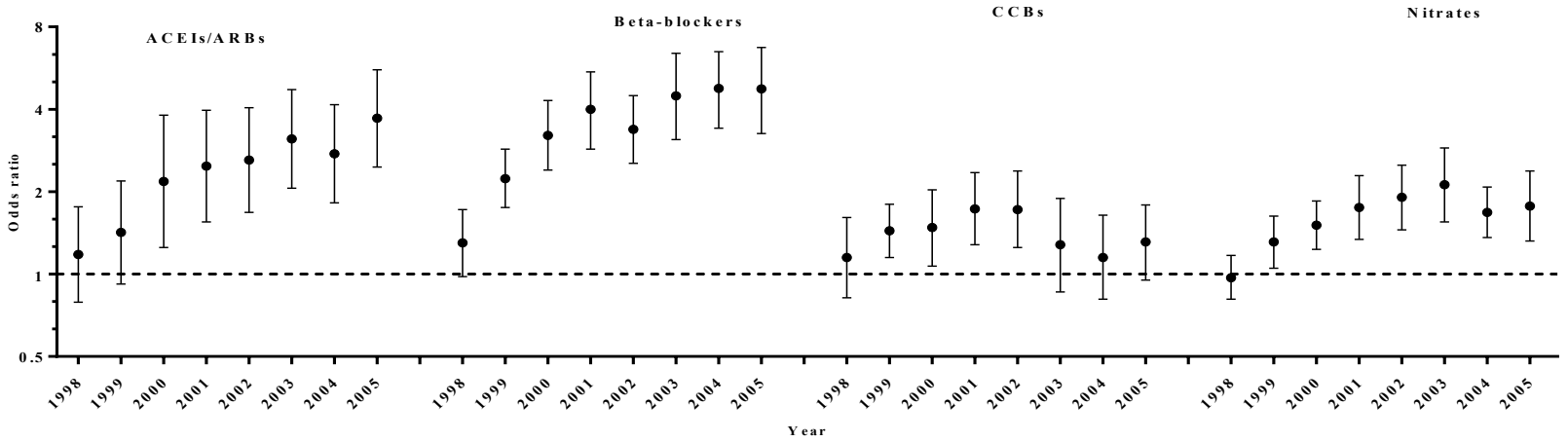
Figure 19 Trends over the time in prescribing of evidence based therapies trends (1997-2005) after a first angina



ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers

Figure 20 Forest plot of odds ratio of trends over time (1997-2005) and prescribing evidence based therapies within 30 days after first diagnosis of angina

A



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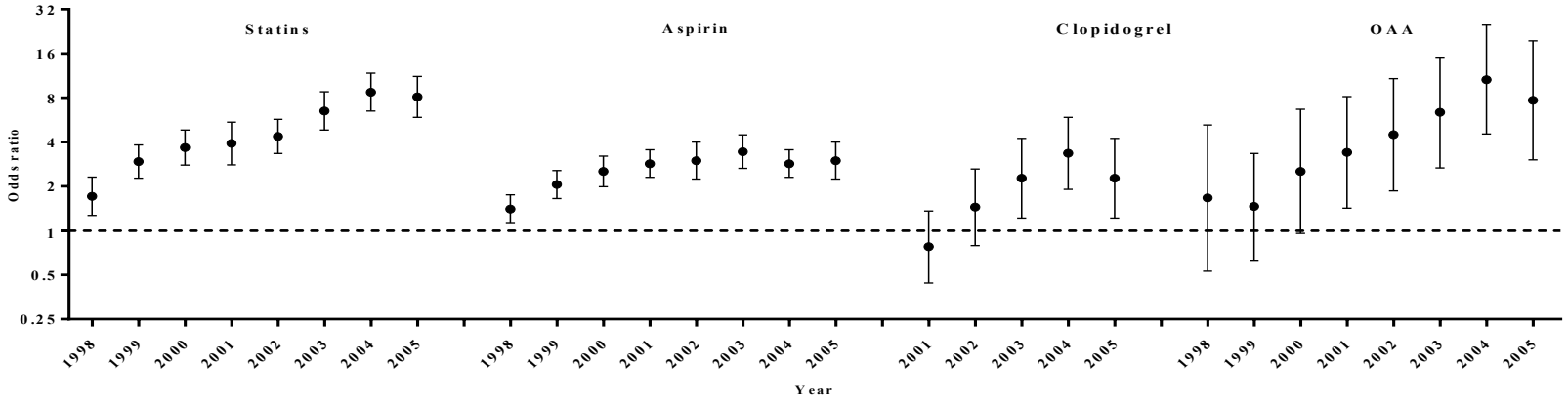


Year 1997 is the reference. Adjusted for sex, age group, socioeconomic status, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, peripheral arterial disease, clustered practices, and whether the drug was previously prescribed. **2000 is the reference for clopidogrel. Clopidogrel divided by 10 for years 2003-05
ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, OAA= Other antianginal.

5.2.1.5 Association between comorbidity and prescribing of evidence based therapies

Prescribing of EBTs was mostly higher in patients with COPD/asthma than those without COPD/asthma (Figure 21 a), and generally higher among patients with than without hypertension (Figure 21 c). Prescribing of EBTs was generally lower among patients with cancer than those without cancer (Figure 21 e).

From Table 36, it can be seen that 12.0% of patients with COPD/asthma received β-blockers compared to 33.0% of those without COPD/asthma, 21.5% with AF received ACEI compared with 14.9% without AF. Patients with HF was associated with higher use of ACEI/ARBs (34.6%) compared with 12.9% in those without HF. Prescribing of β-blockers was lower among those with PAD (21.7%) compared to 31.1% in those without PAD, 23.8% with stroke received β-blockers compared with 30.9% in those without stroke.

After adjustment using multivariable analysis (Table 32), patients with asthma/COPD were much less likely to receive β-blockers (OR 0.29; 95% CI 0.23-0.37), though they were more likely to receive CCB (OR 1.57; 95% CI 1.21-2.03) than those without COPD. Patients with AF were less likely to be prescribed nitrates (OR 0.78; 95% CI 0.61-1.01) and aspirin (OR 0.63; 95% CI 0.49-0.81) than those without AF. Patients with diabetes were less likely to be prescribed β-blockers (OR 0.73; 95% CI 0.56-0.91), statins (OR 0.72; 95% CI 0.58-91) than those without diabetes. Patients with cancer were less likely to receive a CCB (OR 0.62; 95% CI 0.45-0.87), and other anti-angina treatments (OR 0.40; 95% CI 0.16-0.95) than those without cancer. Prescribing of ACEI/ARBs was significantly lower (OR 0.34; 95% CI 0.19-0.63) among patients with renal failure than those without renal failure. Patients with HF were significantly less likely to be prescribed β-blockers (OR 0.78; 95% CI 0.63-0.93) and CCB (OR 0.71; 95% CI 0.56-0.91) but significantly more likely to be prescribed ACEI/ARBs (OR 1.75; 95% CI 1.43-2.14). Patients with PAD were significantly less commonly prescribed ACEI/ARBs (OR 0.67; 95% CI 0.51-0.89), β-blockers (OR 0.60; 95% CI 0.47-0.77) than patients without PAD. Patients with stroke were less likely to receive β-blockers (OR 0.71; 95% CI 0.58-0.82) and aspirin (OR 0.76; 95% CI 0.63-0.91) than patients without stroke.

Table 32 Association between comorbidities and prescribing of evidence based therapies within 30 days after a first angina

Adjusted OR, 95% CI, P value	ACEI/ARBs	Beta blocker	CCB	Nitrates	Statins	Aspirin	Clopidogrel	Other anti-angina
COPD	0.91 (0.69-1.21), 0.56	0.29 (0.23-0.37), 0.01	1.57 (1.21-2.03), 0.01	1.13 (0.99-1.30), 0.06	0.87 (0.73-1.04), 0.14	0.93 (0.75-1.16), 0.75	1.02 (0.70-1.49), 0.90	1.22 (0.80-1.88), 0.34
AF	0.97 (0.70-1.33), 0.85	0.89 (0.72-1.13), 0.36	0.90 (0.68-1.19), 0.47	0.78 (0.61-1.01), 0.06	0.88 (0.68-1.15), 0.37	0.63 (0.49-0.81), 0.01	0.87 (0.57-1.33), 0.54	1.05 (0.64-1.73), 0.90
HYP	1.19 (1.04-1.36), 0.01	1.06 (0.91-1.21), 0.34	1.11 (0.94-1.31), 0.21	1.10 (0.99-1.22), 0.05	1.01 (0.88-1.14), 0.82	1.11 (0.99-1.24), 0.05	0.91 (0.69-1.19), 0.50	1.16 (0.90-1.49), 0.23
Diabetes	0.96 (0.68-1.35), 0.95	0.73 (0.56-0.91), 0.02	0.99 (0.78-1.25), 0.91	1.05 (0.83-1.31), 0.60	0.72 (0.58-0.91), 0.01	0.78 (0.63-0.95), 0.02	0.90 (0.50-1.60), 0.72	1.46 (0.80-2.65), 0.22
Cancer	0.67 (0.48-0.94), 0.03	0.92 (0.75-1.13), 0.45	0.62 (0.45-0.87), 0.01	0.90 (0.72-1.12), 0.40	0.84 (0.64-1.11), 0.24	0.84 (0.69-1.04), 0.13	0.69 (0.38-1.25), 0.22	0.40 (0.16-0.95), 0.04
Renal failure	0.34 (0.19-0.63), 0.01	0.78 (0.42-1.39), 0.45	0.93 (0.38-2.27), 0.86	0.88 (0.49-1.57), 0.74	0.73 (0.36-1.46), 0.42	1.10 (0.69-1.75), 0.61	2.17 (0.90-5.23), 0.07	2.35 (0.81-6.77), 011
HF	1.75 (1.43-2.14), 0.01	0.78 (0.63-0.93), 0.02	0.71 (0.56-0.91), 0.01	0.93 (0.82-1.05), 0.31	0.86 (0.71-1.04), 0.16	0.92 (0.78-1.07), 0.33	0.71 (0.52-0.96), 0.03	0.99 (0.61-1.60), 0.94
PAD	0.67 (0.51-0.89), 0.01	0.60 (0.47-0.77), 0.01	1.09 (0.83-1.43), 0.51	0.80 (0.64-1.01), 0.07	0.80 (0.64-0.99), 0.05	0.82 (0.63-1.09), 0.20	0.96 (0.64-1.45), 0.90	0.95 (0.50-1.83), 0.90
Stroke	0.74 (0.53-1.03), 0.08	0.71 (0.58-0.82), 0.01	1.01 (0.77-1.31), 0.10	0.87 (0.72-1.04), 0.20	0.87 (0.69-1.09), 0.28	0.76 (0.63-0.91), 0.01	1.25 (0.86-1.83), 0.22	0.87 (0.45-1.68), 0.70

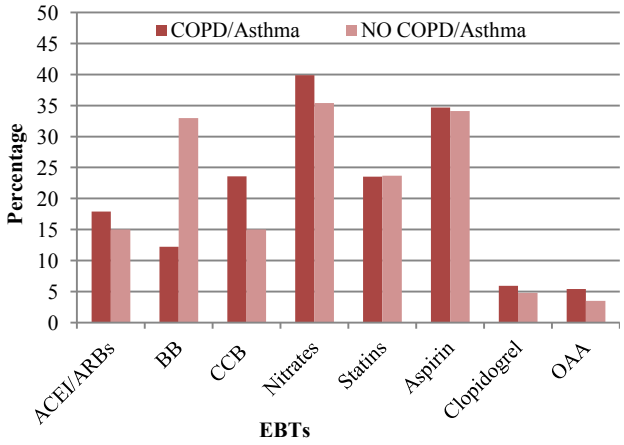
* Adjusted for sex, age group, socioeconomic status, year of diagnosis, chronic obstructive pulmonary disease (COPD), asthma, atrial fibrillation (AF), hypertension (HTN), diabetes, cancer, renal failure, heart failure (HF), and stroke, peripheral arterial disease (PAD), angina, and whether the drug was previously prescribed.

ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers

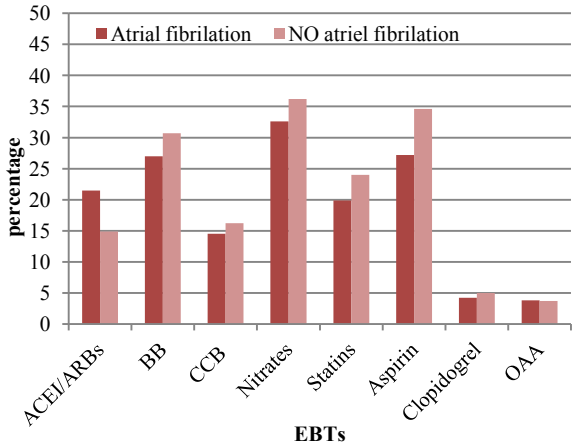
NB: comparator for all comorbidities is No disease

Figure 21 Plot of comorbidities and prescribing of evidence based therapies

21 a



21 b



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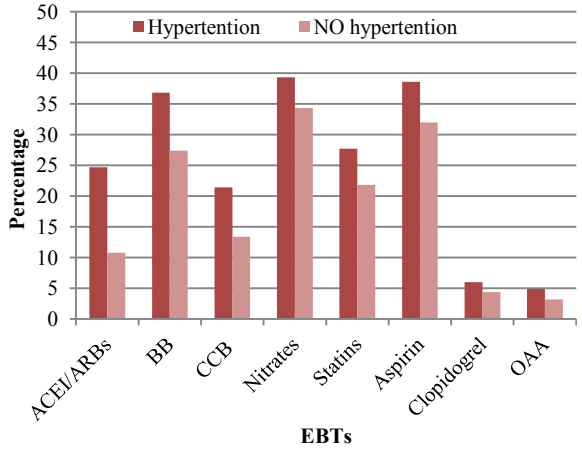

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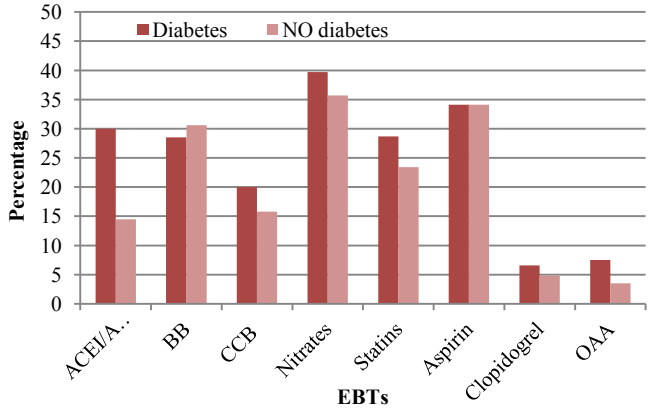

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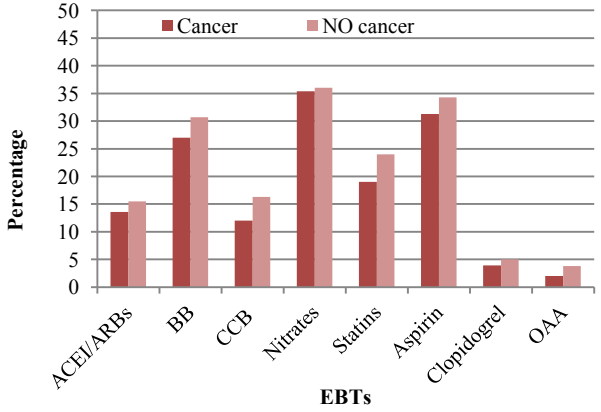

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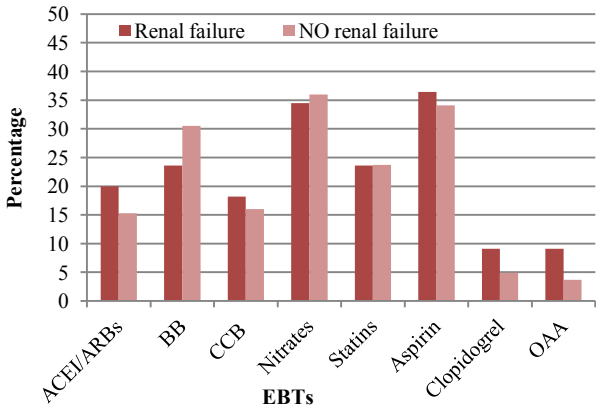
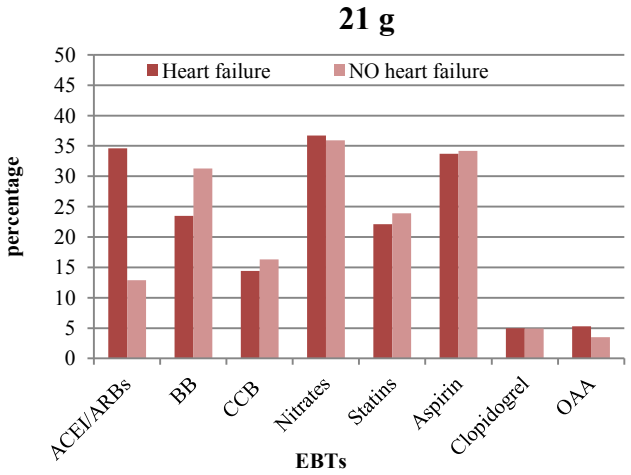
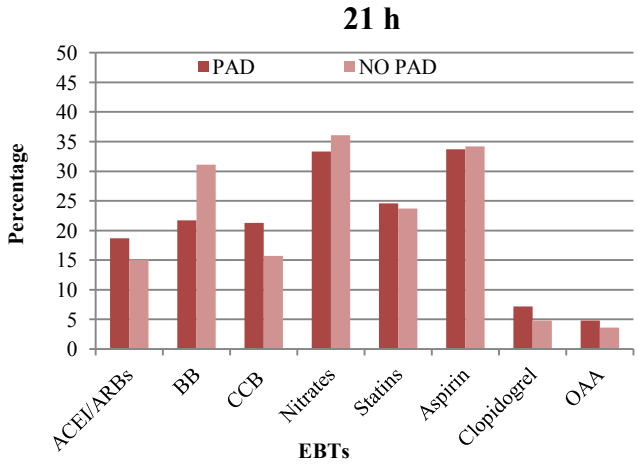
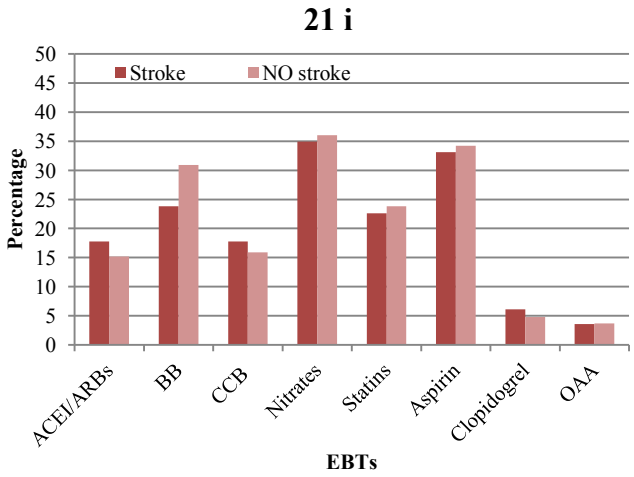








ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, BB=beta blockers, CCB= Calcium channel blockers, COPD=chronic obstructive pulmonary disease, OAA=other anti-angial.

5.2.1.6 Interactions by year of diagnosis

Where statistically significant findings were found in sections 5.2.1.1–5.2.1.3, the interaction between that variable and year was tested (Table 33). It can be seen that the only statistically significant interaction was observed between sex and year for ACEI/ARBs (p=0.04). To examine the nature of this interaction the adjusted ORs for age group and sex are shown for each year in Table 34 and Table 35, and the unadjusted prescribing rates for ACEI/ARBs by sex and year are shown in Figure 22. It is clear that there is no overall trend and the interaction result will have been influenced by 1999 and 2004 where the association between sex and prescribing of ACEI/ARBs is the opposite of that seen for all.

Table 33 Interaction between year of diagnosis and selected variables and therapies. Variables and medications selected on the basis of significant multivariable associations.

Factors	Medication	P for interaction
Age group		
	Beta blocker	<0.001
	Nitrates	0.18
	Statins	0.19
	Aspirin	0.30
	Clopidogrel	0.98
Sex		
	ACEI/ARBs	0.03

Table 34 Adjusted Odds ratio of the prescribing of β-blockers and age stratified by year of diagnosis of angina

	1998	1999	2000	2001	2002	2003	2004	2005
<55	0.16 (0.02-1.27), 0.08	0.08 (0.02-0.35), 0.02	0.41 (0.17-0.96), 0.04	0.61 (0.29-0.31), 0.21	0.49 (0.22-1.08), 0.08	0.47 (0.13-1.66), 0.24	0.52 (0.17-1.57), 0.25	0.18 (0.06-0.57), 0.01
55-64	0.78 (0.39-1.59), 0.51	1.67 (0.87-3.19), 0.87	1.55 (0.79-3.02), 0.19	1.12 (0.57-2.20), 0.73	1.34 (0.67-2.69), 0.40	0.50 (0.24-1.04), 0.07	1.02 (0.48-2.14), 0.95	1.69 (0.77-3.69), 0.19
65-74	1.06 (0.51-2.20), 0.87	1.53 (0.78-3.01), 0.78	1.29 (0.65-2.56), 0.45	0.99 (0.50-1.97), 0.98	1.23 (0.60-2.51), 0.56	0.49 (0.23-1.05), 0.07	0.80 (0.37-1.72), 0.58	1.24 (0.57-2.67), 0.58
75-84	0.81 (0.35-1.85), 0.61	1.25 (0.58-2.70), 0.58	1.09 (0.51-2.36), 0.81	0.82 (0.38-1.78), 0.62	1.23 (0.55-2.74), 0.60	0.83 (0.36-1.90), 0.66	0.65 (0.27-1.53), 0.32	0.91 (0.38-2.18), 0.84

Table 35 Adjusted Odds ratio of the prescribing of ACEIs/ARBs and sex stratified by year of diagnosis of angina

	1997	1998	1999	2000	2001	2002	2003	2004	2005
Male vs. female	1.03 (0.59-1.77), 0.91	1.35 (0.82-2.22), 0.23	0.70 (0.45-1.08), 0.11	1.03 (0.67-1.58), 0.87	1.44 (0.94-2.22), 0.09	1.90 (1.23-2.92), 0.01	1.95 (1.20-3.16), 0.01	0.93 (0.56-1.54), 0.80	1.33 (0.79-2.24), 0.28

Figure 22 Years trends of prescribing ACEI/ARBs based on sex

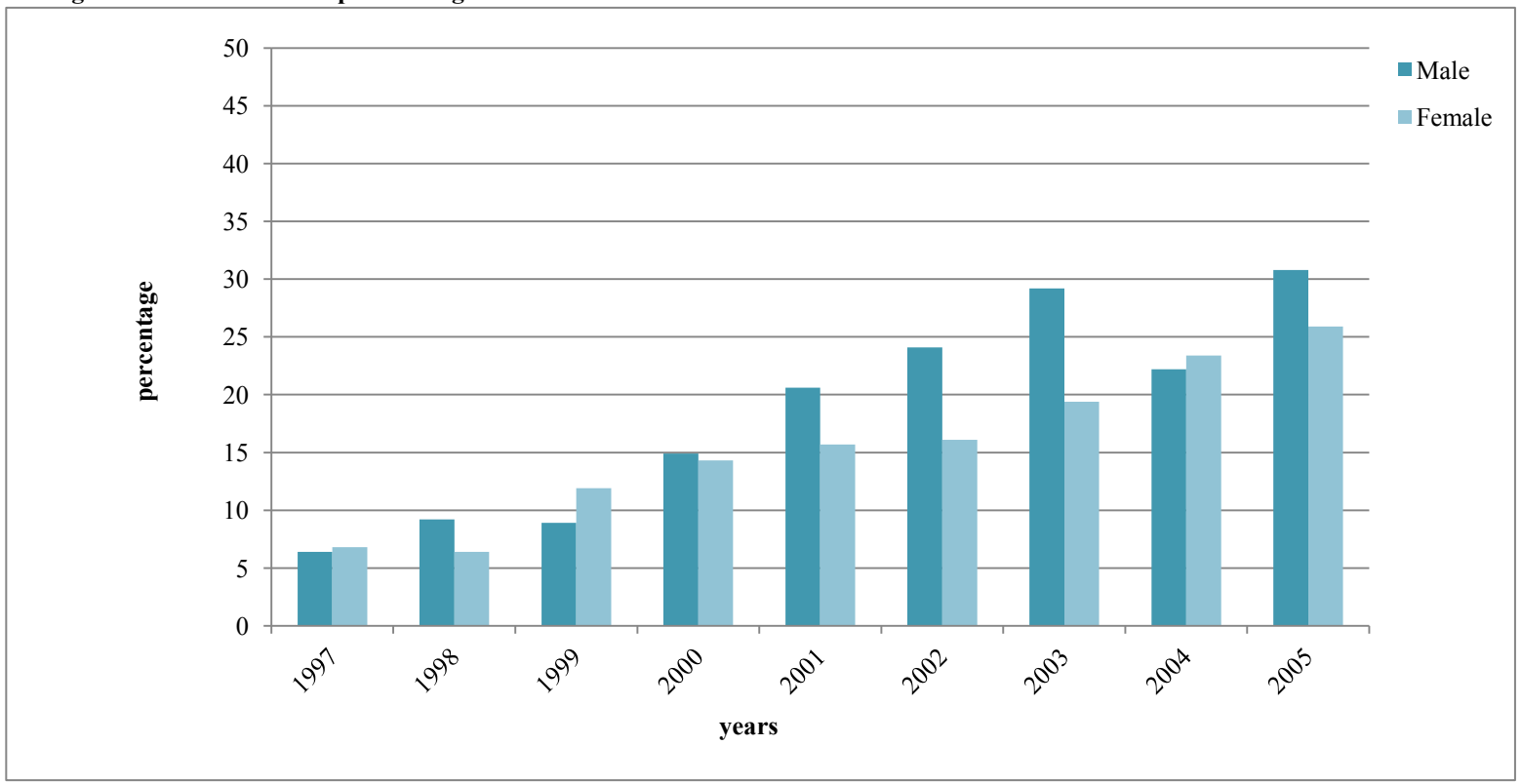


Table 36 Prescribing of evidence based therapies within 30 days after angina for patients who survived the first 30 days after a first diagnosis (N=7210)

	ACEI/ARB	β-blocker	CCB	Nitrates	Statins	Aspirin	Clopidogrel	Other anti-anginal
N=7210	1106(15.3%)	2196 (30.5%)	1158 (16.1%)	2593 (36.0%)	1710 (23.7%)	2461 (34.1%)	354 (4.9%)	268 (3.7%)
Male (n=3990)	661 (16.6%)*	1281(32.1%)	622 (15.6%)	1437(36.0%)	1036 (26.0%)	1390 (34.8%)	231 (5.8%)	153 (3.8%)
Female (3220)	445 (13.8%)	915 (28.4%)	536 (16.6%)	1156 (35.9%)	674 (20.9%)	1071 (33.3%)	123 (3.8%)	115 (3.6%)
Age (years)								
< 55 (n=1479)	198 (13.4%)	496 (33.5%)	206 (13.9%)	493 (33.3%)	421 (28.5%)	475 (32.1%)	92 (6.2%)	74 (5.0%)
55 – 64 (n=1965)	285 (14.5%)	681 (34.7%)	316 (16.1%)	685 (34.9%)	553 (28.1%)	707 (36.0%)	109 (5.5%)	69 (3.5%)
65 – 74 (n=2065)	346 (16.8%)	617 (30.0%)	358 (17.4%)	773 (37.6%)	502 (24.4%)	734 (35.7%)	93 (4.5%)	75 (3.6%)
75 – 84 (n=1381)	228 (16%)	356 (25.8%)	231 (16.7%)	515 (37.3%)	215 (15.6%)	428 (31.0%)	52 (3.8%)	41 (3.0%)
85+ (n=329)	49 (14.9%)	46 (14.0%)	47 (14.3%)	127 (38.6%)	19 (5.8%)	117 (35.6%)	8 (2.4%)	9 (2.7%)
Deprivation								
Q1 (n=452)	65 (14.3%)	161 (35.6%)	77 (17.0%)	174 (38.5%)	115 (25.4%)	148 (32.7%)	28 (6.2%)	21 (4.6%)
Q2 (n=426)	79 (18.5%)	148 (34.7%)	67 (15.7%)	150 (35.2%)	118 (27.7%)	151 (35.4%)	29 (6.8%)	19 (4.4%)
Q3 (n=770)	107 (13.9%)	229 (29.7%)	124 (16.1%)	271 (35.2%)	166 (21.5%)	235 (30.5%)	43 (5.6%)	29 (3.7%)
Q4 (n=634)	99 (15.6%)	203 (32.0%)	119 (18.7%)	232 (36.6%)	138 (21.7%)	224 (35.3%)	27 (4.2%)	21 (3.3%)
Q5 (n=753)	122 (16.2%)	249 (33.1%)	114 (15.1%)	280 (37.2%)	185 (24.5%)	272 (36.1%)	32 (4.2%)	29 (3.8%)
Q6 (n=1106)	180 (16.3%)	324 (29.1%)	196 (17.7%)	410 (37.1%)	276 (24.9%)	383 (34.6%)	56 (5.1%)	34 (3.1%)
Q7 (n=838)	144 (17.2%)	250 (29.8%)	107 (12.7%)	288 (34.4%)	192 (22.9%)	286 (34.1%)	33 (3.9%)	28 (3.3%)
Q8 (n=738)	114 (15.4%)	216 (29.2%)	117 (15.8%)	248 (33.6%)	180 (24.4%)	246 (33.3%)	36 (4.8%)	25 (3.4%)
Q9 (n=877)	114 (13%)	257 (29.3%)	143 (16.3%)	318 (36.3%)	201 (22.9%)	298 (33.9%)	38 (4.3%)	38 (4.3%)
Q10 (n=616)	82 (13.3%)	159 (25.8%)	94 (15.2%)	222 (36.0%)	139 (22.5%)	218 (35.4%)	32 (5.2%)	24 (3.9%)

Year		ACEI/ARB	β-blocker	CCB	Nitrates	Statins	Aspirin	Clopidogrel	Other anti-anginal
1997 (n=972)		64 (6.6%)	136 (14.0%)	113(11.6%)	265 (27.3%)	67 (6.9%)	172 (17.7%)	0 (0.0%)	9 (0.9%)
1998 (n=1081)		85 (7.9%)	182 (16.8%)	145 (13.4%)	288 (26.6%)	126 (11.7%)	250 (23.1%)	0 (0.0%)	17 (1.6%)
1999 (n=984)		100 (10.2%)	250 (25.4%)	157 (16.0%)	326 (33.1%)	178 (18.1%)	311 (31.6%)	9 (0.9%)	14 (1.4%)
2000 (n=952)		139 (14.6%)	319 (33.5%)	164 (17.2%)	348 (36.6%)	216 (22.7%)	346 (36.3%)	8 (0.8%)	27 (2.8%)
2001 (n=834)		153 (18.3%)	317 (38.0%)	167 (20.0%)	336 (40.3%)	200 (24.0%)	330 (39.6%)	30 (3.6%)	26 (3.1%)
2002 (n=788)		162 (20.6%)	283 (35.9%)	149 (18.9%)	336 (42.6%)	223 (28.3%)	323 (41.0%)	58 (7.4%)	36 (4.6%)
2003 (n=583)		145 (24.9%)	259 (44.4%)	99 (17.0%)	267 (45.8%)	223 (38.3%)	265 (45.5%)	67 (11.5%)	38 (6.5%)
2004 (n=564)		128 (22.7%)	249 (44.1%)	88 (15.6%)	234 (41.5%)	263 (46.6%)	251 (44.5%)	99 (17.6%)	55 (9.8%)
2005 (n=452)		130 (28.8%)	201 (44.5%)	76 (16.8%)	193 (42.7%)	214 (47.3%)	213 (47.1%)	83 (18.4%)	46 (10.2%)
Comorbidities									
COPD/Asthma									
	Yes (877)	157 (17.9%)	106 (12.2%)	207 (23.6%)	350 (39.9%)	206 (23.5%)	304 (34.7%)	52 (5.9%)	47 (5.4%)
	No (6333)	949 (15.0%)	2090 (33.0%)	951 (15.0%)	2243 (35.4%)	1504(23.7%)	2157 (34.1%)	302 (4.8%)	221 (3.5%)
Atrial fibrillation									
	Yes (497)	107 (21.5%)	134 (27.0%)	72 (14.5%)	62 (32.6%)	99 (19.9%)	135 (27.2%)	21 (4.2%)	19 (3.8%)
	No (6713)	999 (14.9%)	2062 (30.7%)	1086(16.2%)	2431 (36.2%)	1611 (24.0%)	2326 (34.6%)	333 (5.0%)	249(3.7%)
Hypertension									
	Yes(2365)	584 (24.7%)	870 (36.8%)	507 (21.4%)	930 (39.3%)	654 (27.7%)	912 (38.6%)	142 (6.0%)	115 (4.9%)
	No (4845)	522 (10.8%)	1326 (27.4%)	651 (13.4%)	1663 (34.3%)	1056 (21.8%)	1549(32.0%)	212 (4.4%)	153 (3.2%)

		ACEI/ARB	β-blocker	CCB	Nitrates	Statins	Aspirin	Clopidogrel	Other anti-anginal
Diabetes									
	Yes (411)	12 (30.0%)	117 (28.5%)	82 (20.0%)	163 (39.7%)	118 (28.7%)	140(34.1%)	27 (6.6%)	31 (7.5%)
	No (6799)	983(14.5%)	2079 (30.6%)	1076 (15.8%)	2430 (35.7%)	1592 (23.4%)	2321 (34.1%)	327 (4.8%)	237 (3.5%)
Cancer									
	Yes (414)	60 (13.6%)	119 (27.0%)	53 (12.0%)	156 (35.4%)	84 (19.0%)	138 (31.3%)	17 (3.9%)	9 (2.0%)
	No (6796)	1046 (15.5%)	2077 (30.7%)	1105 (16.3%)	2437 (36.0%)	1626 (24.0%)	2323 (34.3%)	337 (5.0%)	259 (3.8%)
Renal failure									
	Yes (55)	11 (20.0%)	13 (23.6%)	10 (18.2%)	19 (34.5%)	13 (23.6%)	20 (36.4%)	5 (9.1%)	5 (9.1%)
	No (7155)	1095(15.3%)	2183 (30.5%)	1148 (16.0%)	2574 (36.0%)	1697 (23.7%)	2441 (34.1%)	349 (4.9%)	263 (3.7%)
Heart failure									
	Yes (824)	285 (34.6%)	194 (23.5%)	119 (14.4 %)	302 (36.7%)	182 (22.1%)	278 (33.7%)	41 (5.0%)	44 (5.3%)
	No (6386)	821 (12.9%)	2002 (31.3%)	1039 (16.3%)	2291 (35.9%)	1528 (23.9%)	2183 (34.2%)	313(4.9%)	224 (3.5%)
PAD									
	Yes (460)	86 (18.7%)	100 (21.7%)	98 (21.3%)	153 (33.3%)	113 (24.6%)	155 (33.7%)	33 (7.2%)	22 (4.8%)
	No (6750)	1020 (15.1%)	2096 (31.1%)	1060 (15.7%)	2440 (36.1%)	1597 (23.7%)	2306 (34.2%)	321 (4.8%)	246 (3.6%)
Stroke									
	Yes (478)	85 (17.8%)	114 (23.8%)	85 (17.8%)	167 (34.9%)	108 (22.6%)	158 (33.1%)	29 (6.1%)	17 (3.6%)
	No (6732)	1021 (15.2%)	2082 (30.9%)	1073 (15.9%)	2426 (36.0%)	1602 (23.8%)	2303 (34.2%)	325 (4.8%)	251 (3.7%)

* Proportions for each cell represent the number of those who are prescribed an EBT e.g. ACEI/ARBs for each category e.g. men. For example, the proportion for men who are prescribed ACEI/ARBs within 30 days after 1st diagnosis is 661, the total male survived 30 days after 1st diagnosis 3990 (prescribed and not prescribed ACEI/ARBs): 661/3990 x 100=16.6%. For the same drug and category, those not prescribed ACEI/ARBs 3329: 3329/3990 x 100=83.4%.

ACEI= Angiotensin converting enzyme inhibitor, ARBs=Angiotensin receptor blockers, CCB= calcium channel blockers, COPD= Chronic obstructive pulmonary disease, PAD=Peripheral arterial disease.

5.2.1.7 Slope index of inequalities (SII) and relative index of inequalities (RII)

In this study SII and RII were used to measure the socioeconomic relationship between the prescribing of EBTs within 30 days after hospital diagnosis angina.

As can be seen in Tables 37 and 38, inequality in prescribing β-blockers through the socioeconomic deprivation quintiles is evident after first diagnosis of angina. This can be seen clearly as the p value for RII and SII were statistically significant at 0.02 and 0.001, respectively. However, for the other EBTs both the absolute and relative index of inequalities are small in magnitude across the classes (values close to 0 and 1, respectively) and not statistically significant, indicating not much evidence of inequality in the prescribing of EBTs in terms of socioeconomic deprivation.

Table 37 Relative index of inequality (RII)

	RII (95% CI)	P value
ACEI/ARBs	0.95 (0.82-1.11)	0.6
β-blockers	0.85 (0.75-0.96)	0.02
CCB	0.89 (0.71-1.21)	0.3
Nitrates	0.96 (0.81-1.13)	0.6
Statins	0.89 (0.76-1.06)	0.2
Aspirin	1.04 (0.92-1.16)	0.5
Clopidogrel	0.8 (0.58-1.11)	0.2
Other anti-angina	0.85 (0.56-1.28)	0.45

Table 38 Slope index of inequality (SII)

	SII (95% CI)	P value
ACEI/ARBs	0.001 (-0.02-0.02)	0.9
β-blockers	-0.07 (-0.11- -0.04)	0.001
CCB	-0.02 (-0.05-0.01)	0.2
Nitrates	-0.01 (-0.07-0.05)	0.6
Statins	-0.01 (-0.04-0.01)	0.3
Aspirin	0.01 (-0.03-0.05)	0.7
Clopidogrel	-0.006 (-0.04-0.001)	0.1
Other anti-angina	-0.004 (-0.01-0.01)	0.4

5.2.1.8 Goodness of fit tests for angina

As can be seen in Table 39, the majority of ROC values ranged between 0.7 and 0.8 which demonstrates acceptable discrimination. As was seen for MI, the ROC value was low for aspirin and, in addition, for nitrates. The Hosmer-Lemeshow test suggested that the calibration of the model was not good for all medications with the exception of CCB, clopidogrel and other anti-angina medications. Sensitivity analyses using 10 groups for the test confirmed that the models were not well calibrated for most EBMs.

Table 39 ROC and Hosmer-Lemeshow

	ROC P value	Hosmer-Lemeshow group (5) P value	Hosmer-Lemeshow group (10) P value
ACEI/ARBs	0.85	<0.001	<0.001
β-blockers	0.75	<0.001	<0.001
CCB	0.76	0.20	0.23
Nitrates	0.61	<0.001	<0.001
Statins	0.80	<0.001	<0.001
Aspirin	0.66	<0.001	<0.001
Clopidogrel	0.88	0.60	0.56
Other anti-angina	0.83	0.31	0.20

5.2.2 Summary

5.2.2.1 Incidence of angina

The Murphy *et al.* study[329] is the only study that estimates angina incidence rate in Scotland. This study used the primary care data base for 55 GPs (2001/02) across Scotland. Generally it reported that the incidence of angina was higher in men than in women and increased with increasing age (for < 45 years 0.1/1000 vs. ≥ 75 years 5.2/1000) and socioeconomic deprivation (least deprived 0.8/1000 vs. most deprived 2.2/1000), which was similar to this study. Compared with this study, the Murphy study showed lower incidence rate of angina in the matched year 2001/2002 (1.6 per 1000 vs. 3.7 per 1000), however, the present study included all patients diagnosed in primary and secondary care.

5.2.2.2 Age differences in prescribing of evidence based therapies after a first angina

I have shown that age had a clear influence on the prescribing of EBTs after a first diagnosis of MI. This study showed that older patients received significantly fewer prescriptions for β-blockers, statins and clopidogrel. In addition, age was associated with lower odds of being prescribed ACEI/ARBs and CCB. This is supported by prior studies that reported the similar finding that older patients received significantly fewer prescriptions of β-blockers, statins or lipid lowering drugs (LLD).[238,293] However, Bennett *et al.*[238] showed a conflicting result for prescribing ACEI/ARBs to this study, however this study adjusted for sex and health region. Unadjusted studies also similarly demonstrated that older patients were less commonly prescribed β-blockers, statins or LLD.[329,330] Older patients may come with different comorbidities, deterioration in organ function, e.g. renal function. These can be age related factors that may influence prescribing of EBTs. Furthermore, the lower use of EBTs may be due to physicians' perception that these medications are less effective and less cost effective among older patients.

5.2.2.3 Sex differences in prescribing of evidence based therapies after a first angina

I found that the prescribing of EBTs was higher in men compared to women but was only statistically significantly different for ACEI/ARBs. This finding is similar to a prior study which reported that men were significantly more likely to be prescribed

ACEI/ARBs than women.[238] Furthermore, Murphy *et al.*'s study,[329] using the Scottish primary care database (CMR), reported that women were significantly less likely to receive ACEI/ARBs compared to men. In this study, difference of prescribing β-blockers was statistically insignificant for men and this finding was reported in two prior studies.[238,334] Murphy *et al.*'s study, showed that women, compared to men, were significantly less likely to be prescribed β-blockers (OR 0.86, 95% CI 0.78-0.93), CCB (OR 0.85, 95% CI 0.78-0.93), and statins (OR 0.83, 95% CI 0.76-0.91). Similar to MI, discrepancy of prescribing EBTs after angina according to sex is evident. This can be due to age as women are approximately 10 years older than men in angina incidence. It is known that angina is commonly diagnosed in GP, so practitioners may believe that women diagnosed with angina less commonly have other serious cardiovascular disease. Generally women have less access to health services.

5.2.2.4 Socioeconomic status association in prescribing of evidence based therapies after a first angina

In this study I found no evidence for significant differences in prescribing by socioeconomic deprivation status. It seems plausible to attribute this finding to the fact that Scotland has a free health care system that includes medications for chronic disease. Simpson *et al.*[223] used similar data sets and found no significant difference in prescribing secondary prevention in patients with CHD. A cross-sectional study[293] conducted in Britain used the occupation definition to examine the difference in prescribing LLD. It included only 286 men diagnosed with angina. Compared to non-manual workers, those who do manual work received less LLD (39.0% vs. 44.0%). After adjustment for covariate, manual workers had lower odds of being prescribed LLD (OR 0.75; 95% CI 0.42 to 1.32). However, in the Murphy *et al.* study, most deprived patients were significantly more likely to be prescribed ACEI/ARBs, β-blockers, and CCB.

5.2.2.5 Trends over time in prescribing of evidence based therapies after a first angina

Prescribing has increased over the study period for all EBTs. Only one study[335] has been found that examined the trends of prescribing EBTs after angina diagnosis over 5 years. It used unadjusted analysis to determine the change in the trends over 5 years for 885 patients diagnosed with angina. It also showed an increase in the percentage rate of prescribing ACEI/ARB, β-blocker, aspirin, however, this was contradicted in nitrates

(from 81.0% in 1990 to 72.2% in 1995). Furthermore, it showed increase for dihydropyridine CCB (from 12.1% to 26.5%), but not for non-dihydropyridine (from 56.9% to 40.1%). In this study, prescribing for ACEI/ARBs, aspirin, β-blockers and nitrates is associated with better improvement than the previous one.

5.2.2.6 Comorbidities association in prescribing evidence based therapies after first angina

In this analysis, several of concomitant diseases have been included in the analysis to identify their influence in prescribing EBTs after angina. Only one previous study examined the influence of comorbidities in prescribing EBTs after angina. It showed that, from unadjusted analysis, the prescribing of antiplatelet (exception for patients with diabetes), β-blockers and LLD were significantly lower in patients with COPD/asthma, HF and diabetes than those without relevant disease. Prescribing of antiplatelet was significantly higher among patients with than without diabetes (unadjusted OR 1.13; 95%CI 1.01-1.26).[330]

Summary

Prescribing EBTs within 30 days after first angina improved over the time period; however, it remains low. Prescribing of statins was associated with a great increase since 1997 and the influence of age, sex and comorbidities existed. Differences in prescribing of EBTs were only significant in ACEI/ARBs for sex; however, age differences were significant for all EBTs. Differences in prescribing EBTs due to socioeconomic status were not significant, which may be attributable to the equity of access of the Scottish health system.

5.3 Isolated PAD

Baseline demographic characteristics

A total of 3532 individuals were identified as having a diagnosis of PAD. In the study cohort, 2581 patients identified with first PAD in the primary care and 951 patients in the secondary care (Figure 23). Of these, 147 patients (20 from the primary care and 127 from the secondary care) did not survive 30 days after hospital discharge and excluded. In this study, 3,385 (95.8%) patients survived 30 days after first diagnosis were eligible to be included in the study. Of these, 2561 (75.6%) patients had first diagnosis in the primary care and 824 (24.3%) patients had first diagnosis in the secondary care. Table 40, summarises the characteristics of these patients and the subset of patients who survived 30 days after the first recorded diagnosis. It can be seen that men had a slightly higher proportion of incident PAD (53.5%) than women. The largest proportion was aged between 65 and 74 years. Patients residing in the most deprived area (quintile 5) had a higher percentage of patients in the dataset compared to those residing in areas from the least deprived area (quintile 1), but the largest numbers are in the third and fourth deprived quintile groups. The most prevalent comorbidities were hypertension (31.2%), COPD/asthma (12%) and stroke (9.7%).

Table 41 shows the incidence of PAD per 1000 population. The incidence rate was higher in men, 2.37 per 1000, than in women, 2.05 per 1000. The incidence of PAD increased with age from 0.58 per 1000 in those aged less than 45 years compared to 10.36 per 1000 in those in aged 85 years and over. The incidence rate of PAD increased with increasing socioeconomic deprivation status from 1.30 per 1000 in the least deprived quintile to 2.92 per 1000 in the most deprived quintile. The rate of PAD incidence has declined gradually from 2.05 per 1000 in 1999 to 1.18 per 1000 in 2005.

Figure 23 Flow chart to show the selection of patients with a first diagnosis of PAD

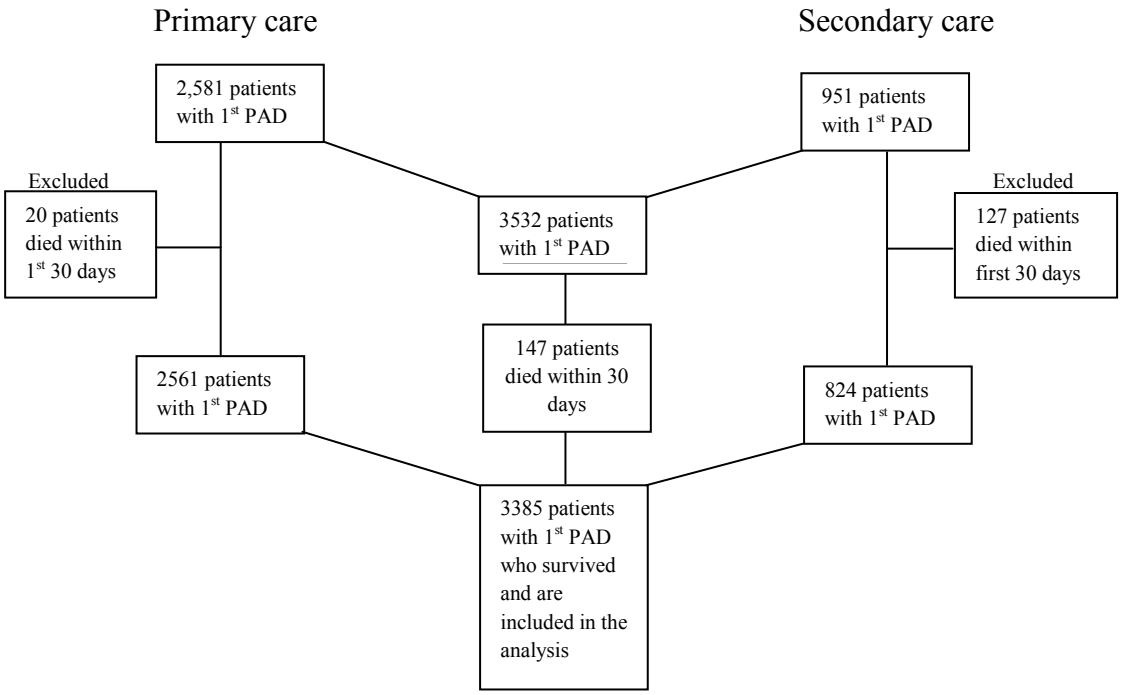


Table 40 Baseline demographic characteristics

	Within 30 days (n=3385)[§]	Patients died within 30 days after 1st diagnosis (n=147)*	All patients (n=3582)
Male sex	1812 (53.5%)	63 (42.8%)	1875 (53.1%)
SD/variance	1.15/1.33	0.95/0.91	1.17/1.37
Age (years):			
< 55	551 (16.3%)	2 (1.4%)	553 (15.7%)
55 – 64	780 (23.0%)	9 (6.1%)	789 (22.3%)
65 – 74	1024 (30.3%)	28 (19.1%)	1052 (29.8%)
75 – 84	819 (24.2%)	56 (38.1%)	875 (24.8%)
85+	211 (6.2%)	52 (35.3%)	263 (7.4%)
Socioeconomic deprivation			
Q1 least deprived	210 (6.2 %)	6 (4.1%)	216 (6.1%)
Q2	172 (5.1%)	8 (5.4%)	180 (5.1%)
Q3	372 (10.9%)	17 (11.6%)	389 (11.0%)
Q4	249 (8.7%)	21 (14.3%)	315 (8.9%)
Q5	335 (9.9%)	11 (7.5%)	346 (9.8%)
Q6	490 (14.5%)	21 (14.3%)	511 (14.4%)
Q7	421 (12.4%)	17 (11.6%)	438 (12.4%)
Q8	345 (10.2%)	14 (9.5%)	359 (10.1%)
Q9	460 (13.6%)	21 (14.3%)	481 (13.6%)
Q1 most deprived 0	286 (8.5%)	11 (7.5%)	297 (8.41%)
Year			
1997	370 (10.9%)	8 (5.4%)	378 (10.7%)
1998	403 (11.9%)	13 (8.8%)	416 (11.8%)
1999	453 (13.4%)	14 (9.5%)	467 (13.2%)
2000	432 (12.8%)	15 (10.2%)	447 (12.7%)
2001	400 (11.0%)	23 (15.6%)	423 (12.0%)
2002	386 (11.4%)	24 (16.3%)	410 (11.6%)
2003	357 (10.5%)	21 (14.3%)	378 (10.7%)
2004	324 (9.6%)	51 (10.2%)	339 (9.6%)
2005	260 (7.7%)	14 (9.5%)	274 (7.8%)
Comorbidities			
COPD/Asthma	398 (11.8%)	27 (18.4%)	425 (12%)
Atrial fibrillation	156 (4.6%)	28 (19.1%)	184 (5.2%)
Hypertension	1055 (31.2%)	46 (31.3%)	1101 (31.2%)
Diabetes	267 (7.9%)	16 (10.8%)	283 (8.0%)
Cancer	267 (7.9%)	32 (21.7%)	299 (8.5%)
Renal failure	57 (1.7%)	19 (12.9%)	76 (2.2%)
Heart failure	165 (4.9%)	30 (20.4%)	195 (5.5%)
Stroke	306 (9.0%)	38 (25.8%)	344 (9.7%)

*Only 10 (6.8%) patients died within 30 days and had a prescription, **§ No missing data**

COPD=Chronic obstructive pulmonary disease

Table 41 Rate per (1000) of incident isolated PAD

	Total population registered with GPs	Patients with PAD	Rate
Sex			
Men	792651	1875	2.37
Women	807959	1657	2.05
Age			
<45	950345	553	0.58
45-64	410998	789	1.92
65-74	133058	1052	7.91
75-84	80828	875	10.83
85+	25381	263	10.36
Socio-economic			
Q1	305557	397	1.30
Q2	358497	701	1.96
Q3	401492	857	2.13
Q4	305760	799	2.61
Q5	266735	778	2.92
Years			
1999	227690	467	2.05
2000	226503	447	1.97
2001	225806	423	1.87
2002	227146	410	1.81
2003	228766	378	1.65
2004	232554	339	1.46
2005	232343	274	1.18

GPs=General practitioners

Prescribing of EBTs before and after first recorded diagnosis

Table 42 shows prescribing of EBTs before and after the first recorded diagnosis of PAD. More than a quintile (23.0%) of patients were prescribed aspirin before first diagnosis of PAD and almost a quintile (18.7%) were prescribed β-blockers. After a first diagnosis, prescribing within 30 days was at a lower percentage than before the first diagnosis for all classes apart from aspirin and oral anti-coagulants. However, prescribing at any time after first diagnosis of PAD increased for all classes.

Table 42 Evidence based therapies prescribing for patients with incident diagnosis of PAD

Medicine	Prescribed drug before 1st diagnosis	Prescribed drug after 1st diagnosis at any time	Prescribed drug within 30 days after 1st diagnosis*
ACEI/ARB	16.5%	43.0%	8.9%
β-blockers	18.7%	29.0%	5.8%
CCB	16.4%	36.7%	9.5%
PVD	2.8%	11.0%	4.1%
Statins	10.8%	59.8%	10.9%
Aspirin	23.0%	63.7%	19.2%
Clopidogrel	1.1%	11.9%	1.2%
Oral anti-coagulant	3.8%	8.8%	2.2%

* This percentage is for patients alive 30 days after the 1st diagnosis, ACEI=Angiotensin converting enzyme inhibitor, ARBs=Angiotensin receptor blockers, CCB=Calcium channel blockers. PVD=peripheral vasodilator

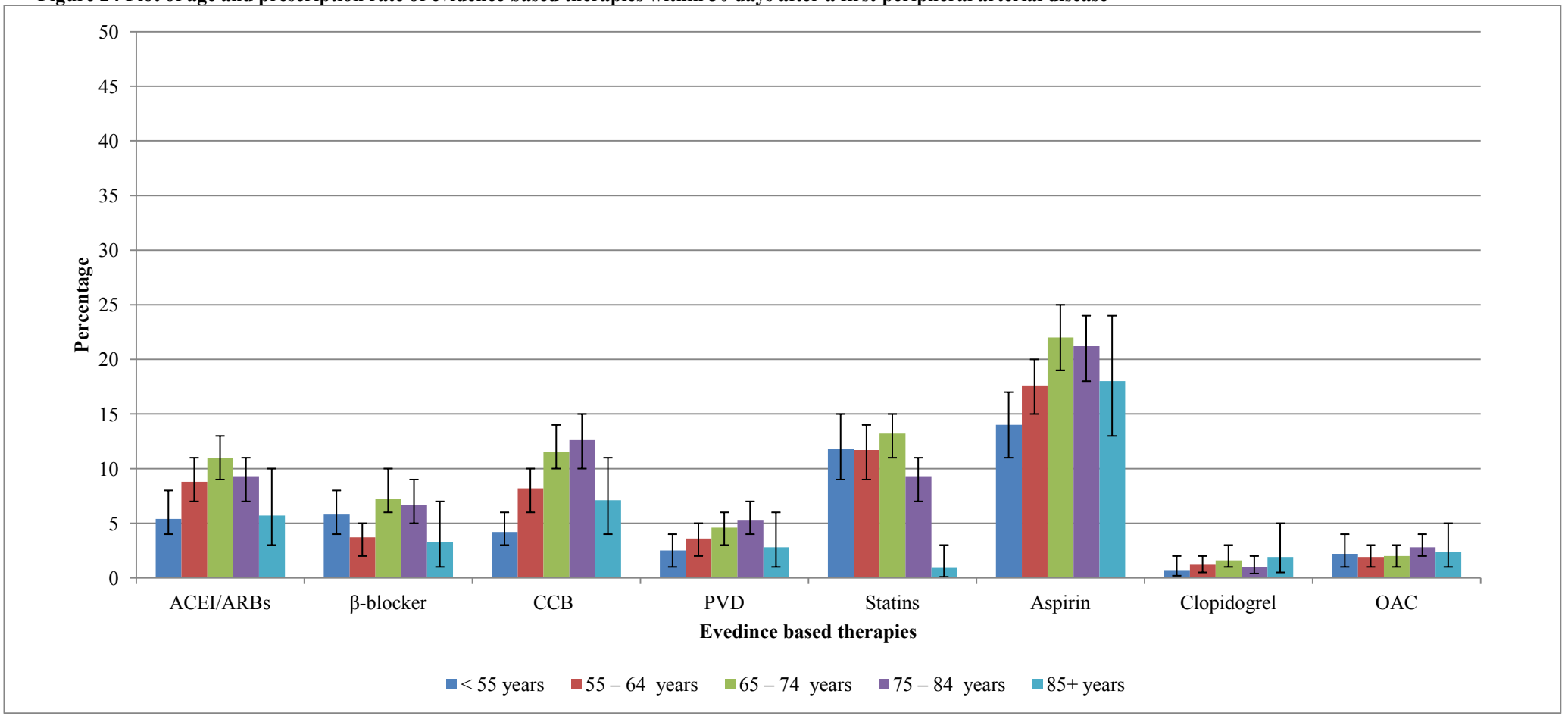
5.3.1 Differences in prescribing of evidence based therapies for PAD

5.3.1.1 Age differences in prescribing of evidence based therapies

Figure 24 shows that patients in age groups 65-74 and 75-84 years received proportionally more prescriptions of ACEI/ARBs, β-blockers, CCBs, peripheral vasodilator (PVD) and aspirin. Prescribing of statins was highest among age group 65-74 years and lowest among those aged 85 years and over. However, older patients received more prescriptions of clopidogrel than others. The percentage of prescribing for patients in age group 65-74 years was 11.0% and 7.2% for ACEI/ARBs and β-

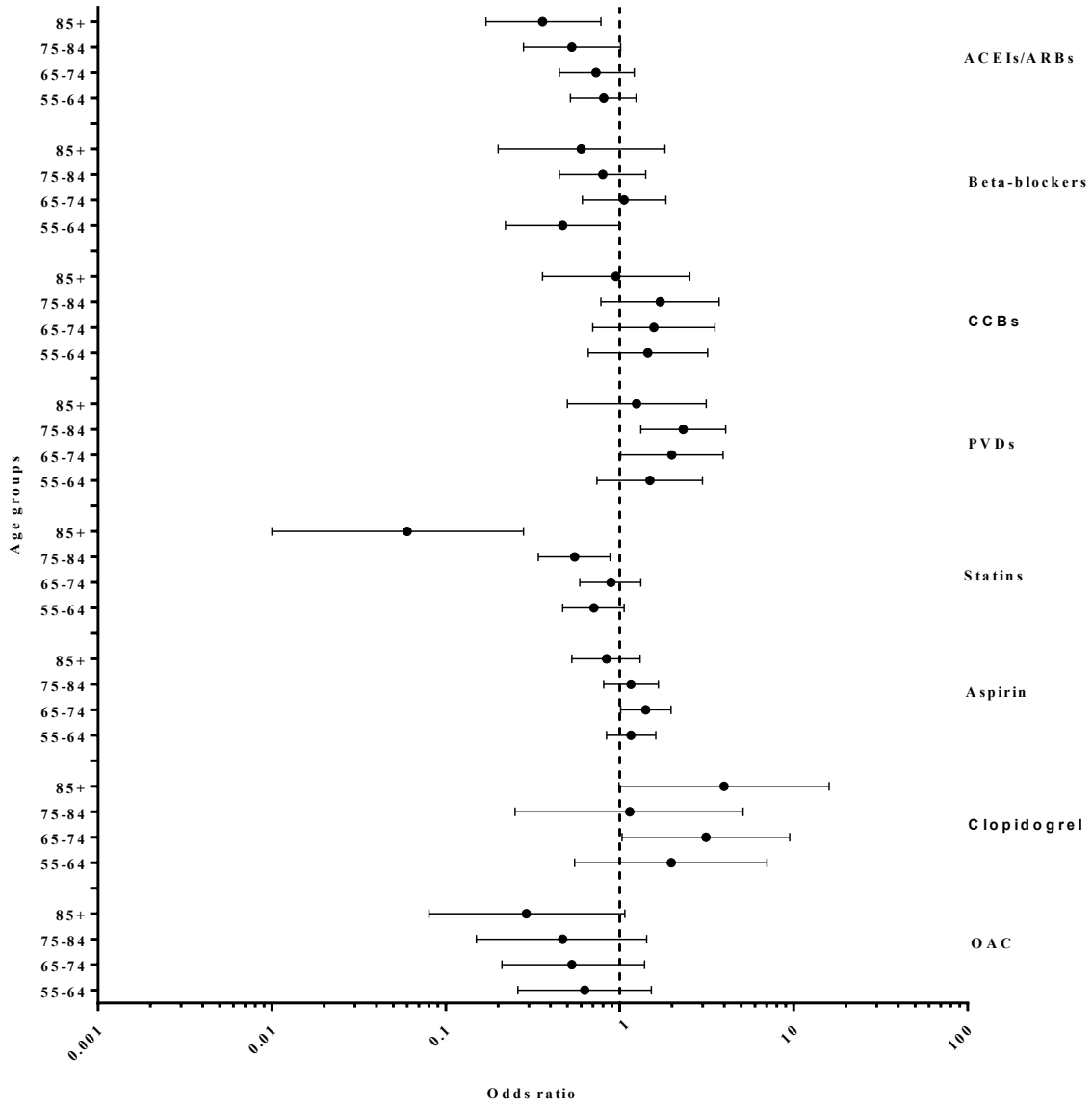
blockers, respectively (Table 45). Proportions of prescribing CCB (12.6%), PVD (5.3%), and oral anticoagulants (2.8%) were higher for patients in age group 75-84 years. After adjustment using multivariable analysis there were statistically significant differences in the odds of prescribing between the age groups for β-blockers (overall p value = 0.02), statins (0.001), aspirin (0.05). Compared to those younger than 55 years, elderly patients (≥ 85 years) were significantly less likely to receive ACEI/ARBs (OR 0.36; 95%CI 0.17-0.78), and statins (OR 0.06; 95%CI 0.01-0.28). The clearest age gradient in the adjusted results was seen for ACEI/ARBs, with odds of prescribing falling as age increases (Figure 25 and Table 9 appendix 6).

Figure 24 Plot of age and prescription rate of evidence based therapies within 30 days after a first peripheral arterial disease



ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, PVD=peripheral vasodilator, OAC=Oral anticoagulant

Figure 25 Forest plot of odds ratio of age and prescribing evidence based therapies within 30 days after first diagnosis of peripheral arterial disease.



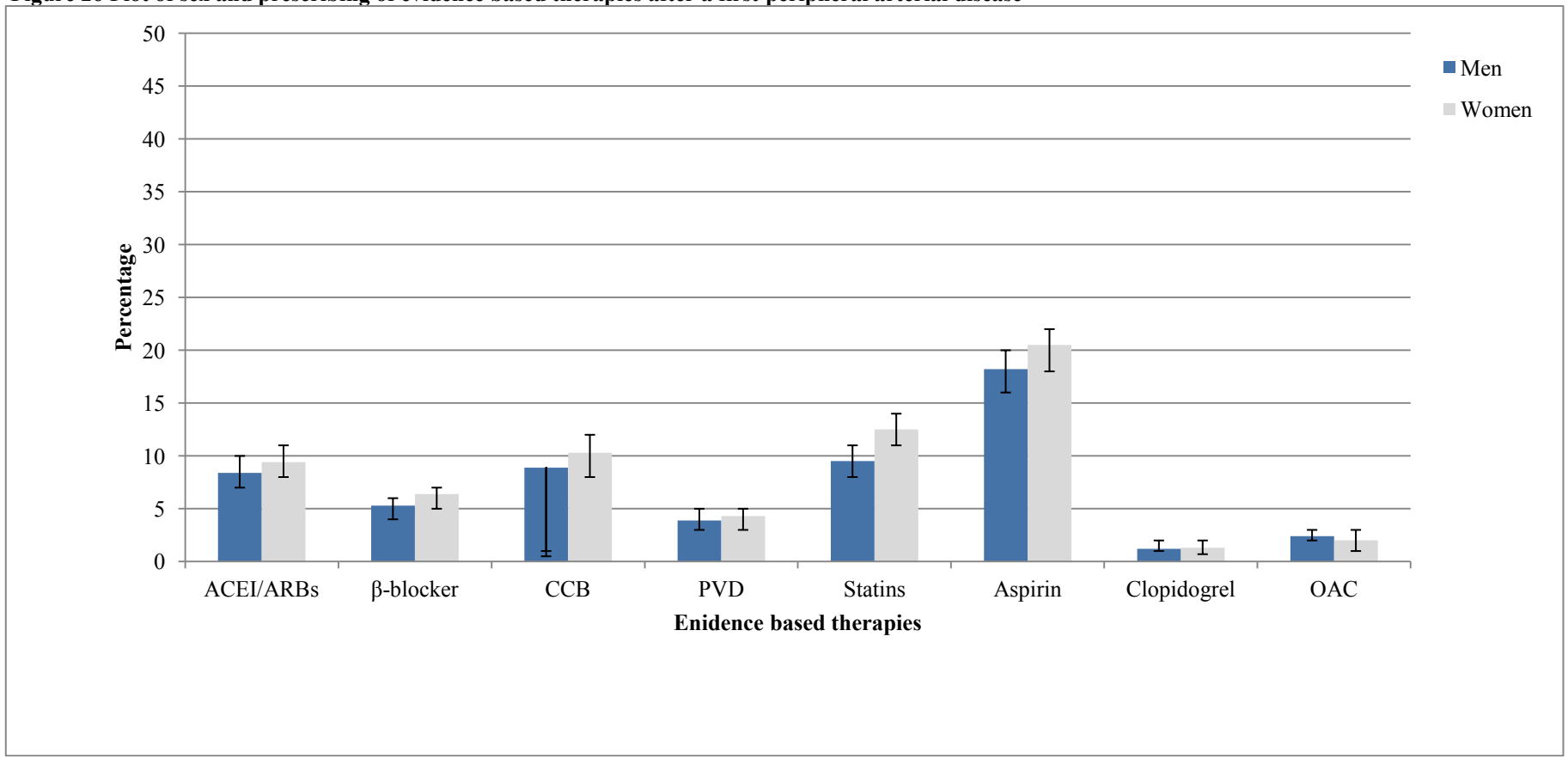
Patients aged <55 years are the reference category. Odds ratio adjusted for sex, socioeconomic status, year of diagnosis, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, clustered practices, and whether the drug was previously prescribed.

ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, OAC= Oral anticoagulants.

5.3.1.2 Sex differences in prescribing of evidence based therapies

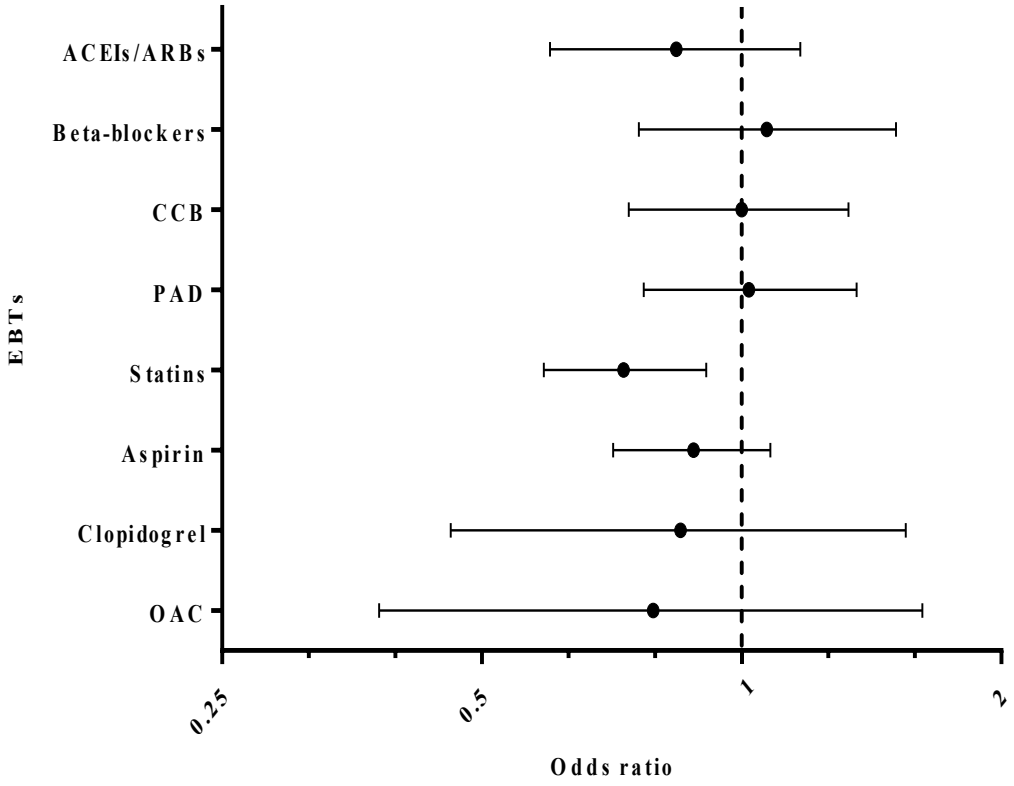
Prescribing of EBTs was higher in women compared with men apart for oral anticoagulants. However, the difference in the percentages of prescribing EBTs was modest for most classes (Figure 26). CCBs were prescribed for 8.9% of men vs. 10.3% of women, statins 9.5% of men vs. 12.5% of women (Table 45). After adjustment using multivariable analysis, compared to women (Figure 27), men were significantly less likely to receive statins (OR 0.73; 95% CI 0.59-0.91, p=0.004) than women, which is the largest observed difference between men and women. Furthermore, men had lower, but not statistically significant, odds of being prescribed all other medications, apart from β-blockers, CCBs and PVD (Table 10 appendix 6).

Figure 26 Plot of sex and prescribing of evidence based therapies after a first peripheral arterial disease



ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, PVD= peripheral vasodilator, OAC=Oral anticoagulants.

Figure 27 Forest plot of odds ratio of sex and prescribing evidence based therapies within 30 days after first diagnosis of peripheral arterial disease



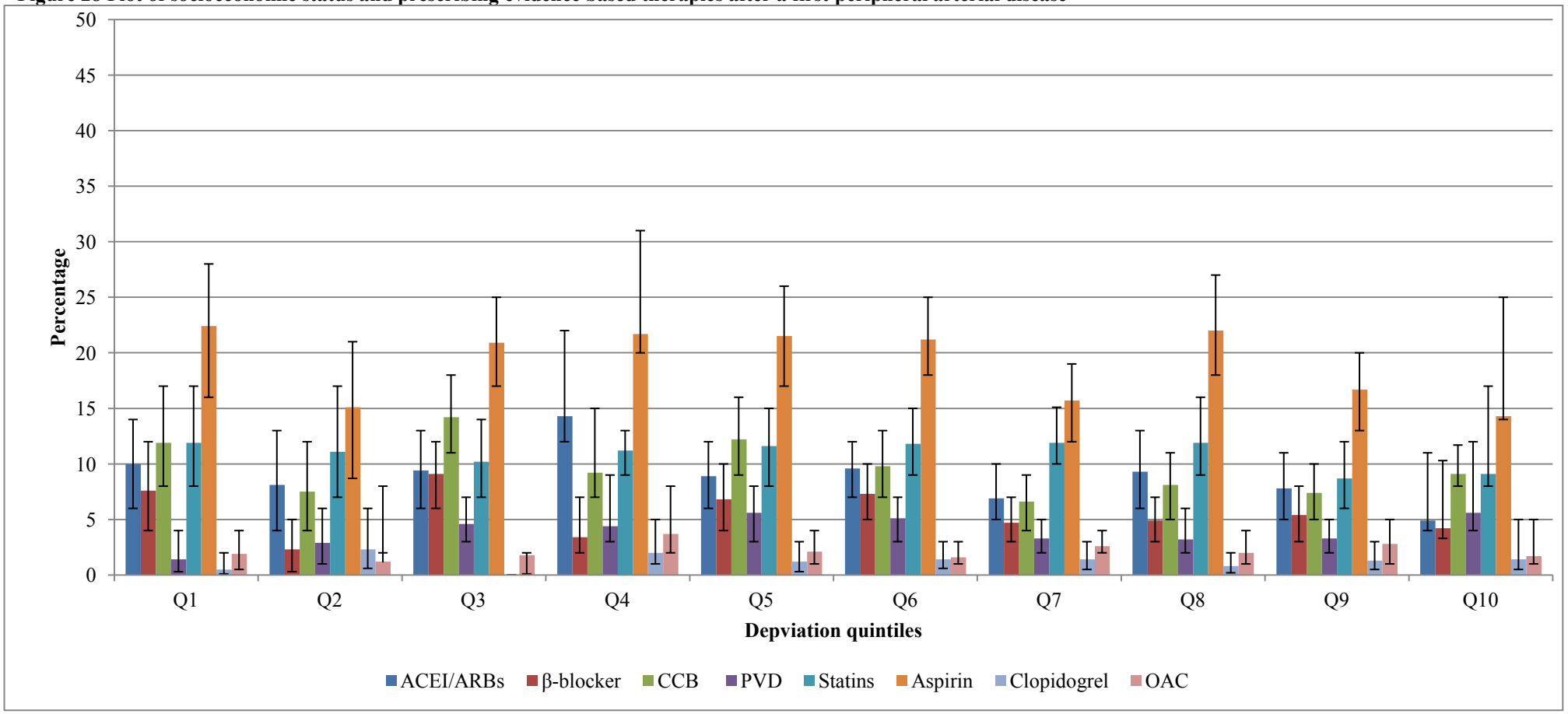
Women are the reference category. Odds ratio adjusted for age group, socioeconomic, year of diagnosis, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, stroke, clustered practices, and whether the drug was previously prescribed.

ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, OAC= Oral anticoagulants.

5.3.1.3 Socioeconomic differences in prescribing of evidence based therapies

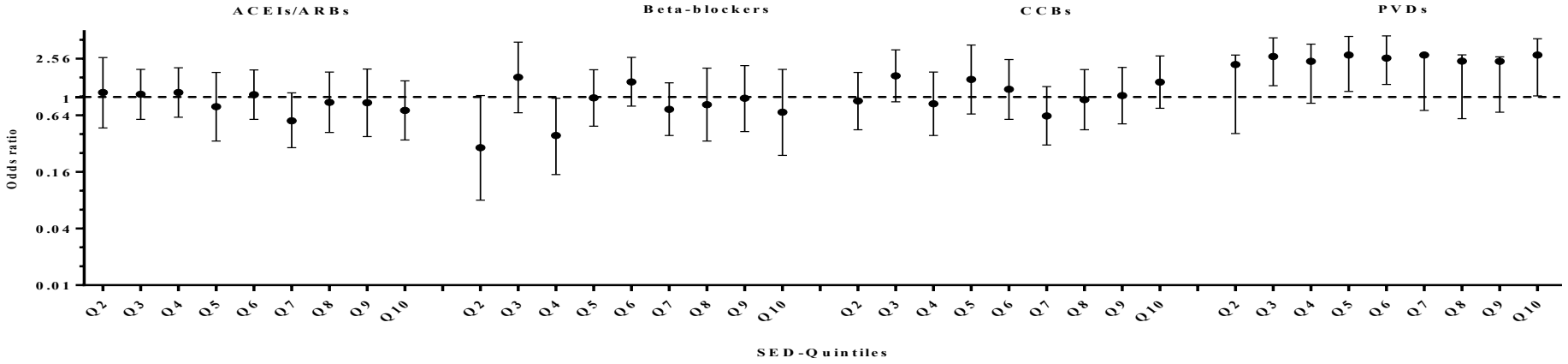
Figure 28 shows the differences in prescribing EBTs according to socioeconomic status. Variations in prescribing EBTs between the deprivation quintiles were similar across the classes of EBTs. As can be seen in Table 45, those living in the most deprived areas (Q10) received less prescriptions than those living in the least deprived areas (Q1) for ACEI/ARBs (4.9% vs. 9.1%), β-blockers (4.2% vs. 7.6%), CCBs (9.1% vs. 11.9%), statins (9.1% vs. 11.9%) and aspirin (14.3% vs. 22.4%). In contrast, they received more prescription of PVD (5.6% vs. 1.4%), clopidogrel PVD (1.4% vs. 0.5%) than those living in quintile Q10. The multivariable analyses showed that, compared to those patients living in the least deprived areas (Q1), patients residing in more deprived areas were more likely to be prescribed PVD, apart from Q2, Q5 and Q6 (Figure 29). However, they were significantly less likely to be prescribed aspirin (OR 0.55, 95% CL0.37-0.83). There was no evidence of differences in the odds between the socioeconomic deprivation groups for the other classes of EBT (Figure 29 and Table 11, appendix 6).

Figure 28 Plot of socioeconomic status and prescribing evidence based therapies after a first peripheral arterial disease

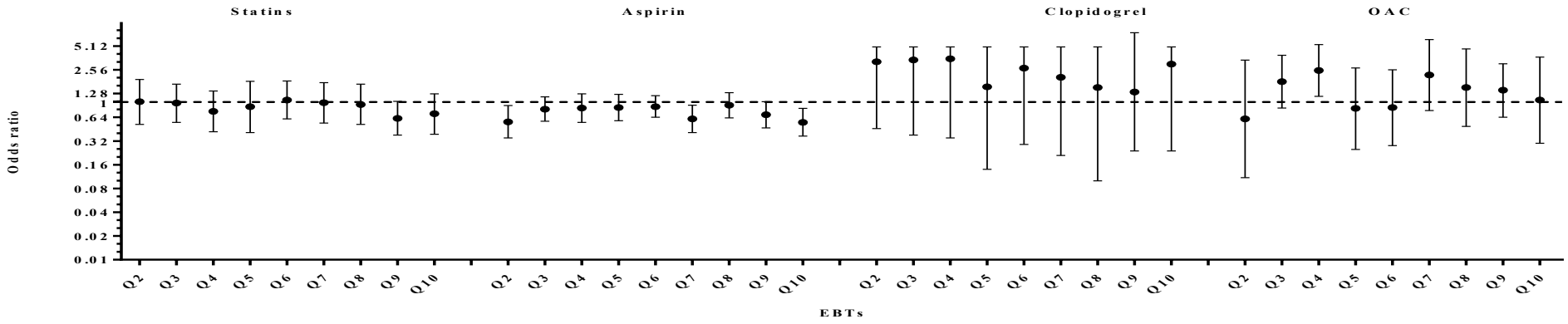


ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, PVD=peripheral vasodilator, OAC=Oral anticoagulant

Figure 29 Forest plot of odds ratio of socioeconomic deprivation and prescribing evidence based therapies within 30 days after first diagnosis of peripheral arterial disease



B

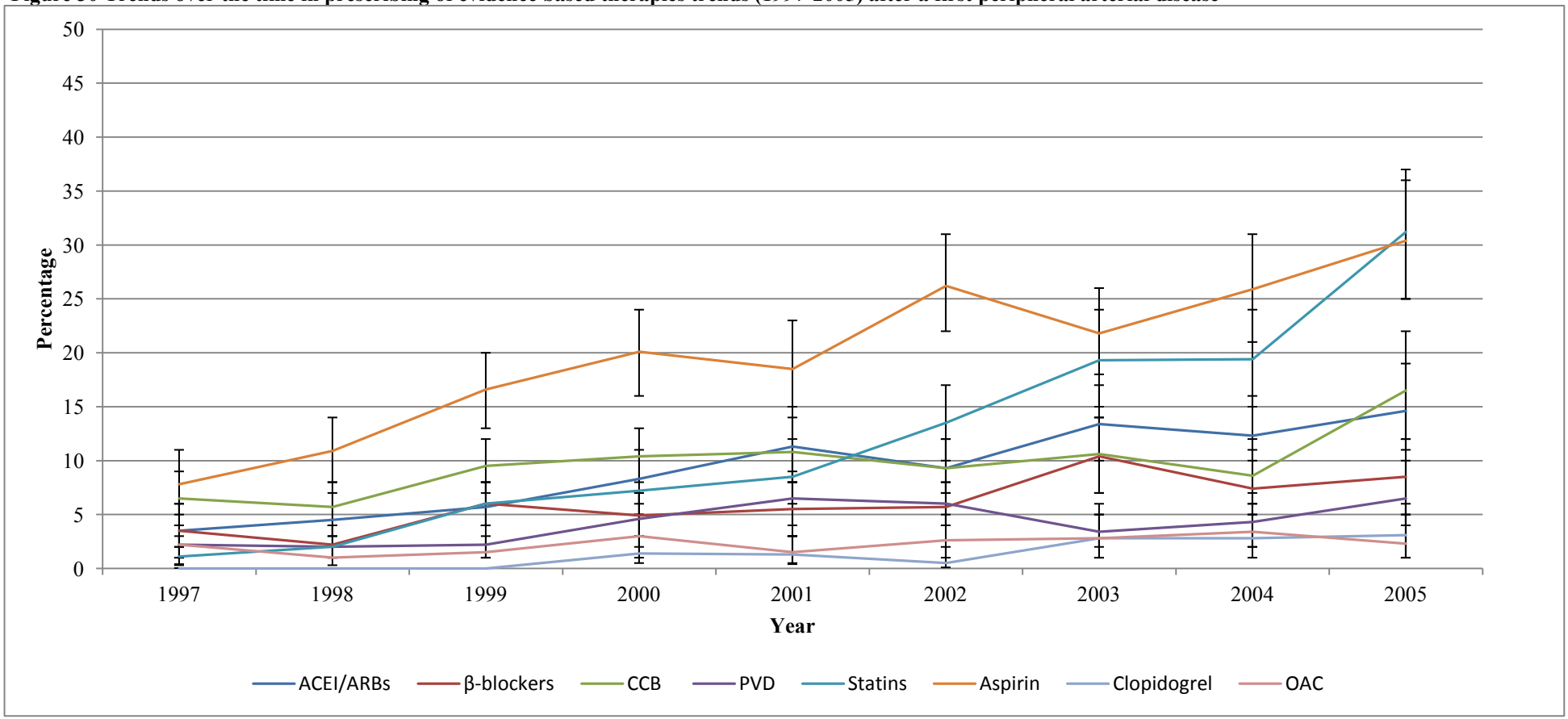


Quintile 1 (Q1) least deprived is a reference. Odds ratio adjusted for sex, age group, year of diagnosis, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, clustered practices, and whether the drug was previously prescribed. Upper 95% CI for PAD has configured in the plot "see appendix. SED=Socioeconomic deprivation ACEI=Angiotensin converting enzyme inhibitors, ARBs=Angiotensin receptor blockers, CCB=Calcium channel blockers, OAC= oral anticoagulant.

5.3.1.4 Trends of prescribing evidence based therapies from 1997 to 2005

Figure 30 shows trends of prescribing EBTs within 30 days after first diagnosis of PAD over the 9 years of the study. Prescribing of EBTs has increased slightly from 1997 to 2005 for most classes. However, marked increases in the prescribing of aspirin and statins were observed over the study period. As can be seen in Table 45, from 1997 to 2005, prescribing of EBTs within 30 days after a first PAD increased for ACEI/ARBs from 4.5% to 14.6%, for CCB from 6.5% to 16.5%. As already stated, the highest increase among prescribing EBTs was for statins from 1.1% to 31.2% and aspirin from 7.8% to 30.4%. After adjustment using multivariable analysis (Figure 31), there were statistically significant differences in the odds of prescribing between the years of the study for PVD (overall $p<0.001$), statins ($p<0.001$), aspirin ($p<0.001$) and clopidogrel (0.02). Compared to prescribing in 1997, patients in 2005 were significantly more likely to be prescribed PVD (OR 4.71; 95% CI 1.98 to 11.21), statins (OR 20.22; 95% CI 8.7-46.9), and aspirin (OR 4.06; 95% CI 2.62-6.29). The clearest gradient over time in the adjusted results was seen for statins, with odds of prescribing increasing steadily over the study period (Figure 31 and Table 12 appendix 6).

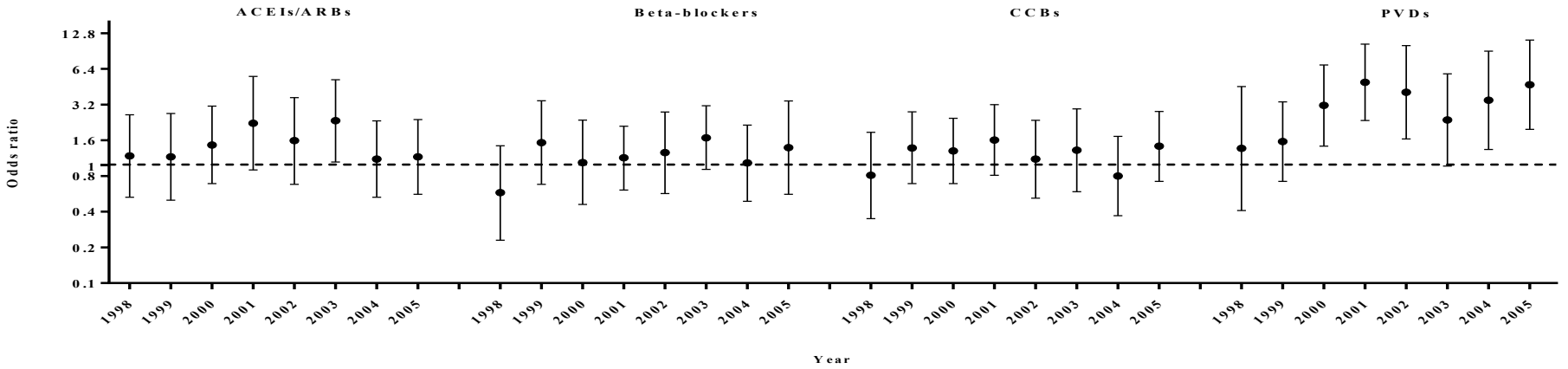
Figure 30 Trends over the time in prescribing of evidence based therapies trends (1997-2005) after a first peripheral arterial disease



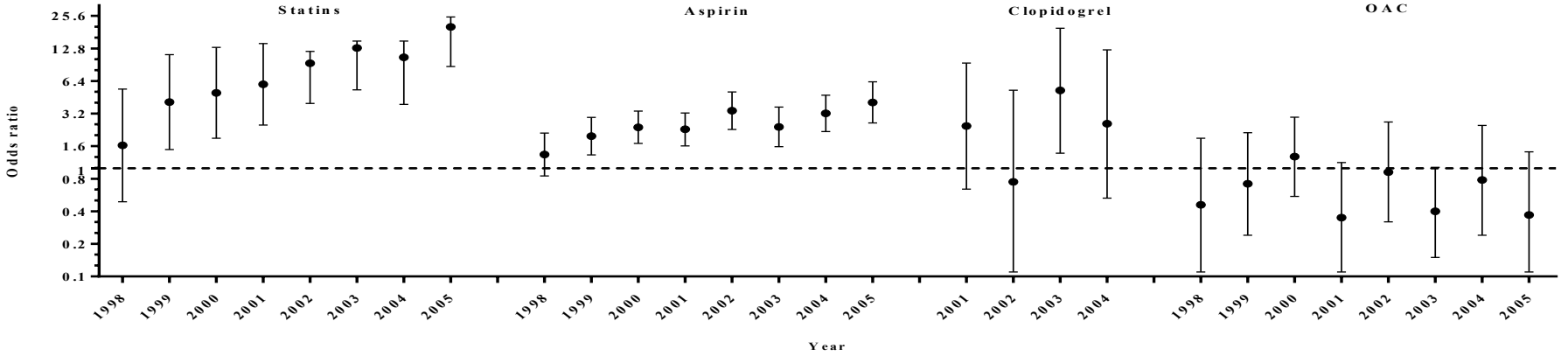
ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, PVD=peripheral vasodilator, OAC=Oral anticoagulant

Figure 31 Forest plot of odds ratio of trends over time (1997-2005) and prescribing evidence based therapies within 30 days after first diagnosis of peripheral arterial disease

A



B



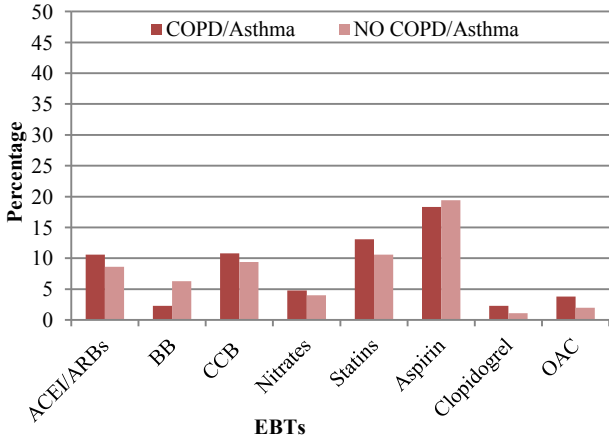
Year 1997 is the reference. Adjusted for sex, age group, socioeconomic status, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, peripheral arterial disease, clustered practices, and whether the drug was previously prescribed. **2000 is the reference for clopidogrel. Upper 95% CI for years 2002-05 has configured for statins see table in appendix.
ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, OAC= oral anticoagulant.

5.3.1.5 Association between comorbidity and prescribing of evidence based therapies

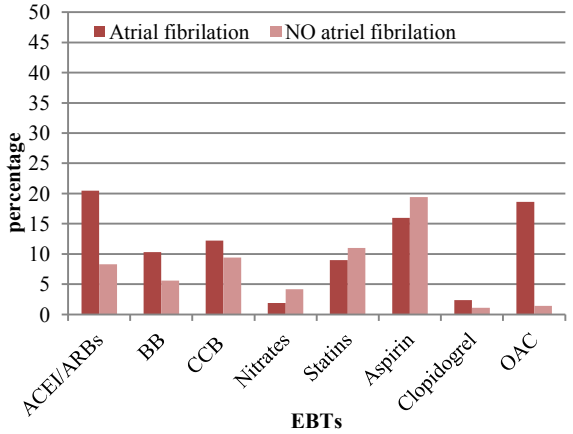
Prescribing of EBTs was generally higher among patients with hypertension than those without hypertension (Figure 32c), almost as in patients with diabetes (Figure 32d) and patients with stroke (Figure 32h). As can be seen in Table 45, patients with COPD/asthma associated with higher proportion of prescriptions for statins (13.1%) than those without COPD/asthma. Patients with AF had higher percentage for ACEI/ARBs (20.1% vs. 8.3%). Patients with hypertension had higher percentage for ACEI/ARBs (21.8%) than patients without hypertension (3.0%). Patients with diabetes had higher percentage for ACEI/ARBs (24.0%) than those without diabetes (7.6%). Patients with stroke had higher percentage for aspirin (29.7% vs. 18.2%). After adjustment using multivariable analysis, patients with AF were more likely to be prescribed oral anticoagulants (OR 3.39; 95% CI 1.63-7.04), though they were significantly less likely to have received aspirin (OR 0.46; 95% CI 0.27-0.79) (Table 43). Patients with hypertension were less likely to be prescribed PVD (OR 0.66; 95% CI 0.36-1.21). Patients with diabetes were less likely to receive CCB (OR 0.54; 95% CI 0.34-0.83) than those without diabetes. Patients with renal failure were significantly less likely to be prescribed ACEI/ARBs (OR 0.32; 95% CI 0.12-0.85) than those without renal failure.

Figure 32 Plot of comorbidities and prescribing of evidence based therapies

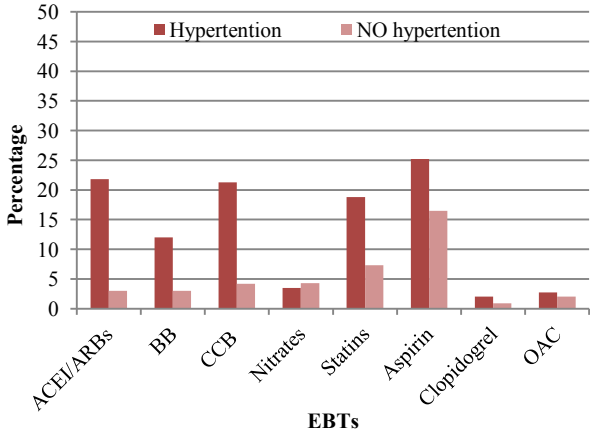
32a



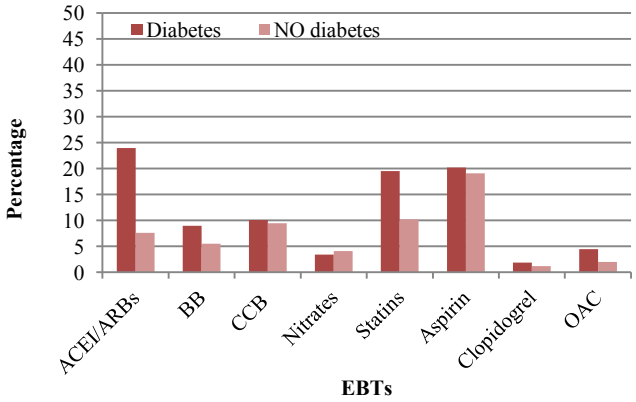
32b



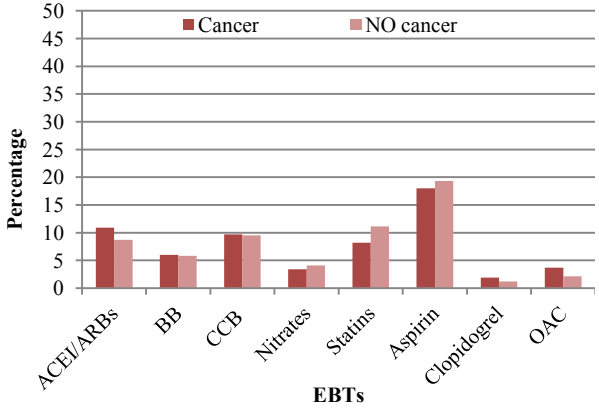
32c



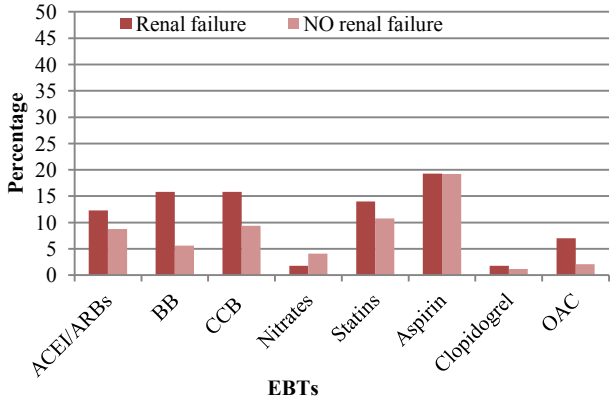
32d



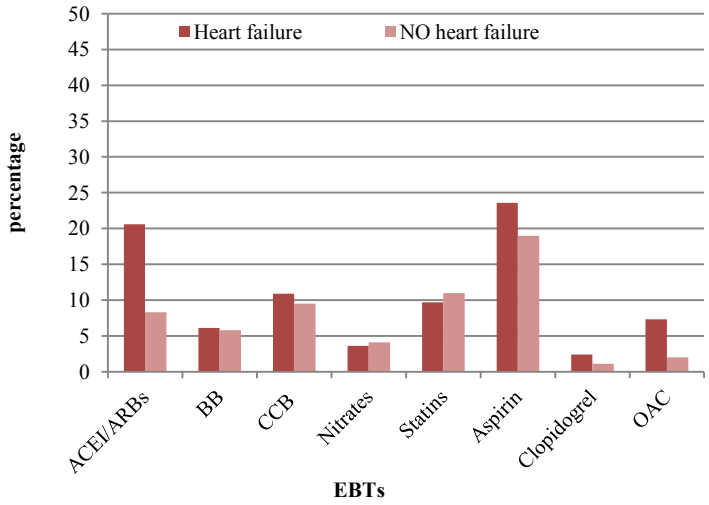
32e



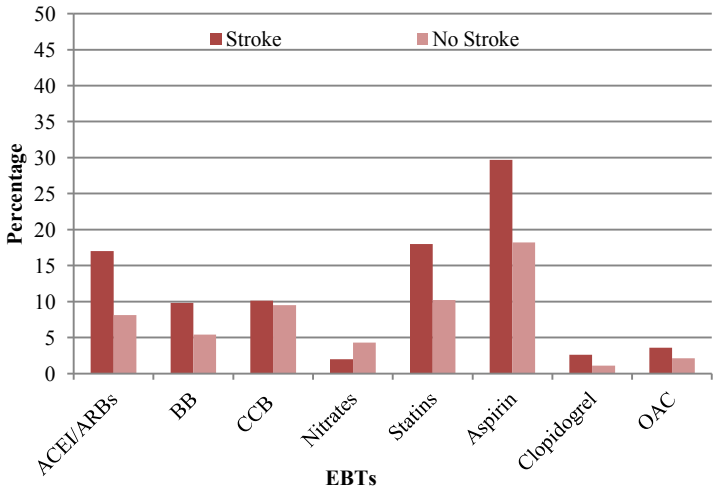
32f



32g



32h



ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, BB= beta blocker PVD= Peripheral vasodilator, OAC=Oral anti-coagulant

Table 43 Association between comorbidities and prescribing evidence based therapies within 30 days after a first peripheral arterial disease

Adjusted OR, 95% CI	ACEI/ARBs	β-blocker	CCB	PVD	Statins	Aspirin	Clopidogrel	Oral anticoagulant
COPD	1.12 (0.73-1.69), 0.60	0.60 (0.28-1.27), 0.18	1.21 (0.76-1.91), 0.41	1.01 (0.62-1.63), 0.96	1.18 (0.85-1.64), 0.30	0.87 (0.70-1.09), 0.25	1.57 (0.74-3.32), 0.23	1.80 (0.93-3.48), 0.08
AF	1.83 (0.95-3.51), 0.07	1.20 (0.57-2.51), 0.62	0.72 (0.44-1.15), 0.17	0.37 (0.11-1.29), 0.15	0.75 (0.37-1.51), 0.43	0.46 (0.27-0.79), 0.01	1.06 (0.39-2.87), 0.90	3.39 (1.63-7.04), 0.01
HTN	1.92 (1.28-2.88), 0.01	1.01 (0.62-1.63), 0.96	2.32 (1.63-3.29), 0.01	0.66 (0.36-1.21), 0.25	1.65 (1.32-2.06), 0.01	1.11 (0.91-1.36), 0.30	1.35 (0.68-2.68), 0.38	0.90 (0.43-1.89), 0.80
Diabetes	1.08 (0.64-1.81), 0.76	1.09 (0.66-1.81), 0.72	0.54 (0.34-0.83), 0.01	0.84 (0.34-2.08), 0.76	0.75 (0.52-1.09), 0.13	0.68 (0.48-0.97), 0.03	0.61 (0.19-1.96), 0.40	1.51 (0.61-3.68), 0.40
Cancer	1.21 (0.75-1.95), 0.43	1.12 (0.61-2.04), 0.70	0.82 (0.51-1.34), 0.44	0.77 (0.42-1.43), 0.50	0.67 (0.42-1.06), 0.10	0.82 (0.59-1.13), 0.24	1.67 (0.77-3.62), 0.19	1.68 (0.90-3.15), 0.10
Renal failure	0.32 (0.12-0.85), 0.02	1.75 (0.76-4.01), 0.18	0.94 (0.36-2.44), 0.90	0.53 (0.09-2.92), 0.50	0.79 (0.33-1.92), 0.61	0.90 (0.47-1.73), 0.76	1.14 (0.38-3.46), 0.80	1.09 (0.21-5.56), 0.91
HF	1.04 (0.56-1.94), 0.88	0.98 (0.41-2.35), 0.97	0.92 (0.45-1.85), 0.81	1.08 (0.47-2.49), 0.83	0.93 (0.48-1.81), 0.84	1.27 (0.92-1.77), 0.14	1.21 (0.33-4.42), 0.76	0.91 (0.36-2.30), 0.84
Stroke	1.47 (0.90-2.39), 0.12	1.14 (0.65-2.01), 0.63	0.74 (0.48-1.14), 0.18	0.45 (0.16-1.24), 0.17	1.18 (0.74-1.86), 0.47	1.15 (0.87-1.53), 0.30	1.81 (0.56-5.81), 0.31	0.76 (0.40-1.44), 0.41

* Adjusted for sex, age group, socioeconomic, year, chronic obstructive pulmonary disease (COPD), asthma, atrial fibrillation (AF), hypertension (HTN), diabetes, cancer, renal failure, heart failure (HF), and stroke, whether the drug was previously prescribed.

ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers

NB: comparator for all comorbidities is No disease.

5.3.1.6 Interactions by year of diagnosis

Where statistically significant findings were found in sections 5.3.1.1 – 5.3.1.3, the interaction between that factor and year was tested (Table 44). It can be seen that there was no significant interactions between sex, age groups, socioeconomic deprivation and year. This indicates that there was little evidence to support the hypothesis that the effects of sex, age and socioeconomic deprivation were modified by study year.

Table 44 Interaction between year of diagnosis and selected variables and therapies. Variables and medications selected on the basis of significant multivariable associations.

Factors	Medication	P for interaction
Age group		
	β-blocker	0.80
	Statins	0.24
	Aspirin	0.95
Sex		
	Statins	0.62
Socioeconomic deprivation		
	Peripheral vasodilator	0.99

Table 45 Prescribing evidence based therapies within 30 days after PAD for patients who survived the first 30 days after a first diagnosis (N=3385)

	ACEI/ARBs	β-blockers	CCB	PVD	Stains	Aspirin	Clopidogrel	Oral anti coagulant
N=3385	300 (8.9%)	197 (5.8%)	323 (9.5%)	138 (4.1%)	369 (10.9%)	651 (19.2%)	41(1.2%)	75 (2.2%)
Male (n=1812)	152 (8.4%)	96 (5.3%)	16 (8.9%)	70 (3.9%)	172 (9.5%)	329 (18.2%)	21(1.2%)	43 (2.4%)
Female (n=1573)	148(9.4%)	101 (6.4%)	162 (10.3%)	68 (4.3%)	197 (12.5%)	322 (20.5%)	20 (1.3%)	32 (2.0%)
Age (years)								
< 55 (n=551)	30 (5.4%)	32 (5.8%)	23 (4.2%)	14 (2.5%)	65 (11.8%)	77 (14.0%)	4 (0.7%)	12 (2.2%)
55 – 64 (n=780)	69 (8.8%)	29 (3.7%)	64 (8.2%)	28 (3.6%)	91 (11.7%)	137 (17.6%)	9 (1.2%)	15 (1.9%)
65 – 74 (n=1024)	113 (11.0%)	74 (7.2%)	118 (11.5%)	47 (4.6%)	135 (13.2%)	225 (22.0%)	16 (1.6%)	20 (2.0%)
75 – 84 (n=819)	76 (9.3%)	55 (6.7%)	103 (12.6%)	43 (5.3%)	76 (9.3%)	174 (21.2%)	8 (1.0%)	23 (2.8%)
85+ (n=211)	12 (5.7%)	7 (3.3%)	15 (7.1%)	6 (2.8%)	2 (0.9%)	38 (18.0%)	4 (1.9%)	5 (2.4%)
Deprivation								
Q1 (n=210)	21 (10.0%)	16 (7.6%)	25 (11.9%)	3 (1.4%)	25 (11.9%)	47 (22.4%)	1 (0.5%)	4 (1.9%)
Q2 (n=172)	14 (8.1%)	4 (2.3%)	13 (7.5%)	5 (2.9%)	19 (11.1%)	26 (15.1%)	4 (2.3%)	7 (1.2%)
Q3 (n=372)	35 (9.4%)	34 (9.1%)	53 (14.2%)	17 (4.6%)	38 (10.2%)	78 (20.9%)	0 (0.0%)	2 (1.8%)
Q4 (n=249)	42 (14.3%)	10 (3.4%)	27 (9.2%)	13 (4.4%)	33 (11.2%)	64 (21.7%)	6 (2.0%)	11 (3.7%)
Q5 (n=335)	30 (8.9%)	23 (6.8%)	41 (12.2%)	19 (5.6%)	39 (11.6%)	72 (21.5%)	4 (1.2%)	7 (2.1%)
Q6 (n=490)	47 (9.6%)	36 (7.3%)	48 (9.8%)	25 (5.1%)	58 (11.8%)	104 (21.2%)	7 (1.4%)	8 (1.6%)
Q7 (n=421)	29 (6.9%)	20 (4.7%)	28 (6.6%)	14 (3.3%)	50 (11.9%)	66 (15.7%)	6 (1.4%)	11 (2.6%)
Q8 (n=345)	32 (9.3%)	17 (4.9%)	28 (8.1%)	11 (3.2%)	41 (11.9%)	76 (22.0%)	3 (0.8%)	7 (2.0%)
Q9 (n=460)	36 (7.8%)	25 (5.4%)	34 (7.4%)	15 (3.3%)	40 (8.7%)	77 (16.7%)	6 (1.3%)	13 (2.8%)
Q10 (n=210)	14 (4.9%)	12 (4.2%)	26 (9.1%)	16 (5.6%)	26 (9.1%)	41 (14.3%)	4 (1.4%)	5 (1.7%)

		ACEI/ARBs	β-blockers	CCB	PVD	Stains	Aspirin	Clopidogrel	Oral anti coagulant
Year									
1997 (n=370)		13(3.5%)	13(3.5%)	24 (6.5%)	8 (2.2%)	4 (1.1%)	29 (7.8%)	0 (0.0%)	8 (2.2%)
1998 (n=403)		18(4.5%)	9 (2.2%)	23 (5.7%)	8 (2.0%)	8 (2.0%)	44 (10.9%)	0 (0.0%)	4 (1.0%)
1999 (n=453)		26 (5.7%)	27 (6.0%)	43(9.5%)	10 (2.2%)	27 (6.0%)	75 (16.6%)	0(0.0%)	7 (1.5%)
2000 (n=432)		36 (8.3%)	21(4.9%)	45 (10.4%)	20 (4.6%)	31(7.2%)	87 (20.1%)	6 (1.4%)	13 (3.0%)
2001 (n=400)		45 (11.3%)	22 (5.5%)	43 (10.8%)	26 (6.5%)	34 (8.5%)	74 (18.5%)	5 (1.3%)	6 (1.5%)
2002 (n=386)		36 (9.3%)	22(5.7%)	36 (9.3%)	23 (6.0%)	52 (13.5%)	101 (26.2%)	2 (0.5%)	10 (2.6%)
2003 (n=357)		48 (13.4%)	37 (10.4%)	38 (10.6%)	12 (3.4%)	69 (19.3%)	78 (21.8%)	10 (2.8%)	10 (2.8%)
2004 (n=324)		40 (12.3%)	24 (7.4%)	28 (8.6%)	14 (4.3%)	63 (19.4%)	84 (25.9%)	9 (2.8%)	11(3.4%)
2005 (n=260)		38 (14.6%)	22 (8.5%)	43 (16.5%)	17 (6.5%)	81 (31.2%)	79 (30.4%)	8 (3.1%)	6 (2.3%)
Comorbidities									
COPD/Asthma									
	Yes (398)	42 (10.6%)	9 (2.3%)	43(10.8%)	19 (4.8%)	52 (13.1%)	73 (18.3%)	9 (2.3%)	15 (3.8%)
	No (2978)	258 (8.7%)	188 (6.3%)	280 (9.4%)	119 (4.0%)	317 (10.6%)	578 (19.4%)	32 (1.1%)	60(2.0%)
Atrial fibrillation									
	Yes (156)	32 (20.5%)	16 (10.3%)	19 (12.2%)	3 (1.9%)	14 (9.0%)	25 (16.0%)	4 (2.4%)	29 (18.6%)
	No (3229)	268 (8.3%)	181 (5.6%)	304 (9.4%)	135 (4.2%)	355 (11.0%)	626 (19.4%)	37 (1.1%)	46 (1.4%)
Hypertension									
	Yes (1055)	230 (21.8%)	127 (12.0%)	225 (21.3%)	37 (3.5%)	198 (18.8%)	266 (25.2%)	21 (2.0%)	28 (2.7%)
	No (2330)	70 (3.0%)	70 (3.0%)	98 (4.2%)	101 (4.3%)	171 (7.3%)	385 (16.5%)	20 (0.9%)	47 (2.0%)
Diabetes									
	Yes (267)	64 (24.0%)	24 (9.0%)	27 (10.1%)	9 (3.4%)	52 (19.5%)	54 (20.2%)	5 (1.9%)	12 (4.5%)
	No (3118)	236 (7.6%)	173 (5.5%)	296 (9.5%)	129 (4.1%)	317 (10.2%)	597 (19.1%)	36 (1.2%)	63 (2.0%)

		ACEI/ARBs	β-blockers	CCB	PVD	Stains	Aspirin	Clopidogrel	Oral anti coagulant
Cancer									
	Yes (267)	29 (10.9%)	16 (6.0%)	26 (9.7%)	9 (3.4%)	22 (8.2%)	48 (18.0%)	5 (1.9%)	10 (3.7%)
	No (3118)	271 (8.7%)	181 (5.8%)	297 (9.5%)	129 (4.1%)	347 (11.1%)	603 (19.3%)	36 (1.2%)	65 (2.1%)
Renal failure									
	Yes (57)	7 (12.3%)	9 (15.8%)	9 (15.8%)	1 (1.8%)	8 (14.0%)	11 (19.3%)	1 (1.8%)	4 (7.0%)
	No (3328)	293 (8.8%)	188 (5.6%)	314 (9.4%)	137 (4.1%)	361 (10.8%)	640 (19.2%)	40 (1.2%)	71 (2.1%)
Heart failure (HF)									
	Yes (165)	34 (20.6%)	10 (6.1%)	18 (10.9%)	6 (3.6%)	16 (9.7%)	39 (23.6%)	4 (2.4%)	12 (7.3%)
	No (3220)	266 (8.3%)	187 (5.8%)	305 (9.5%)	132 (4.1%)	353 (11.0%)	612 (19.0%)	37 (1.1%)	63 (2.0%)
Stroke									
	Yes (306)	52 (17.0%)	30 (9.8%)	31 (10.1%)	6 (2.0%)	55 (18.0%)	91 (29.7%)	8 (2.6%)	11 (3.6%)
	No (3079)	248 (8.1%)	167 (5.4%)	292 (9.5%)	132 (4.3%)	314 (10.2%)	250 (18.2%)	33 (1.1%)	64 (2.1%)

* Proportions for each cell represent the number of those who are prescribed an EBT e.g. ACEI/ARBs for each category e.g. men. For example, the proportion for men who are prescribed ACEI/ARBs within 30 days after 1st diagnosis is 152, the total men survived 30 days after 1st diagnosis 1812 (prescribed and not prescribed ACEI/ARBs): 152/1812 x 100=8.4%. For the same drug and category, those not prescribed ACEI/ARBs 1660: 1660/1812 x 100=91.6%.

5.3.1.7 Slope index of inequalities (SII) and relative index of inequalities (RII)

In this study the SII and RII were used to measure the socioeconomic relationship between the prescribing of EBTs within 30 days after hospital diagnosis of PAD.

As can be seen in Table 46, the relative index of inequalities are small in magnitude across the classes of EBTs (values close to 0 and 1, respectively) and not statistically significant, which indicates not much evidence of inequality in the prescribing of EBTs in terms of socioeconomic deprivation. However, the absolute index of inequalities (Table 47) shows significant p value for CCB and aspirin, which indicate association between prescribing these drugs and socioeconomic deprivation.

Table 46 Relative risk of inequality (RII) for PAD

	RII (95% CI)	P value
ACEI/ARBs	0.77 (0.54-1.11)	0.2
β-blockers	0.91 (0.61-1.51)	0.8
CCB	0.96 (0.71-1.31)	0.8
PAV	1.10 (0.43-2.80)	0.8
Statins	0.87 (0.69-1.10)	0.3
Aspirin	0.80 (0.62-1.04)	0.1
Clopidogrel	1.09 (0.42-2.91)	0.9
Oral anticoagulant	1.15 (-0.62-2.13)	0.6

Table 47 Slope index of inequality (SII) for PAD

	SII (95% CI)	P value
ACEI/ARBs	-0.03 (-0.07-0.003)	0.07
β-blockers	-0.02 (-0.04-0.01)	0.2
CCB	-0.03 (-0.04- -0.01)	0.006
PVD	0.002 (-0.03-0.04)	0.9
Statins	-0.02 (-0.04- 0.0004)	0.06
Aspirin	-0.05 (-0.09- -0.01)	0.01

5.3.1.8 Goodness of fit tests for PAD

The model discrimination for EBTs used for PAD was generally good (see Table 48). Similarly, the calibration of the model as assessed by the Hosmer-Lemeshow test was also good and better than MI or angina. However, the calibration results were sensitive to the number of groups chosen. With 10 groups, evidence of poor fit was seen for more EBM classes (CCB, statins and aspirin).

Table 48 ROC and Hosmer-Lemeshow

	ROC P value	Hosmer-Lemeshow group (5) P value	Hosmer-Lemeshow group (10) P value
ACEI/ARBs	0.92	0.03	0.13
β-blockers	0.93	0.53	0.77
CCB	0.87	0.06	0.02
PVD	0.73	0.75	0.80
Statins	0.86	0.21	0.01
Aspirin	0.72	0.07	0.03
Clopidogrel	0.86	0.32	0.09
Oral anticoagulant	0.87	0.21	0.22

5.4 PAD with CHD

Baseline demographic characteristics

A total of 1351 individuals were identified as having a diagnosis of PAD with CHD (PAD/CHD). In the study cohort, 481 patients identified as having first diagnosed in the primary care and 510 patients in the secondary care (Figure 33). Of these, 83 patients (4 from the primary care and 79 from the secondary care) did not survive 30 days after hospital discharge and were excluded. In this study, 1268 (93.8%) patients who survived 30 days after first diagnosis were eligible to be included in the study. Of these, 837 (66.0%) patients were identified in the primary care and 431 (34.0%) patients identified in the secondary care. Table 49 summarises the characteristics of these patients and the subset of patients who survived 30 days after the first recorded diagnosis, n = 1268 (93.8%). Approximately 60% of the PAD/CHD patients were men and the largest proportion were aged between 65 and 74 years. Patients residing in areas among the most deprived quintile (quintile 10) made a higher percentage of the dataset than those residing in areas from the least deprived area (quintile 1), but the largest numbers were in the third and fourth deprived quintile groups. The most prevalent comorbidities were hypertension (42.0%) and HF (26.6%).

Table 50 shows the incidence of PAD/CHD per 1000 population. The incidence rate was higher in men, 1.06 per 1000, than in women, 0.63 per 1000. The incidence of PAD/CHD increased with age from 0.13 per 1000 in those aged less than 45 years compared to 3.59 per 1000 in those aged 85 years and over. However, the highest rate was among those aged between 75 and 84 years, 6.07 per 1000. In general, the incidence rate of PAD/CHD increased as socioeconomic deprivation status increased from 0.5 per 1000 in the least deprived quintile to 1.13 per 1000 in the most deprived quintile. The most recent study year, 2005, reported a lower incidence rate of PAD/CHD, 0.52 per 1000, than the first study year, 1999, 0.73 per 1000, though incidence rate reached its peak in 1999/2000, 0.80 per 1000.

Figure 33 Flow chart demonstrates patients with a first diagnosis of PAD/CHD

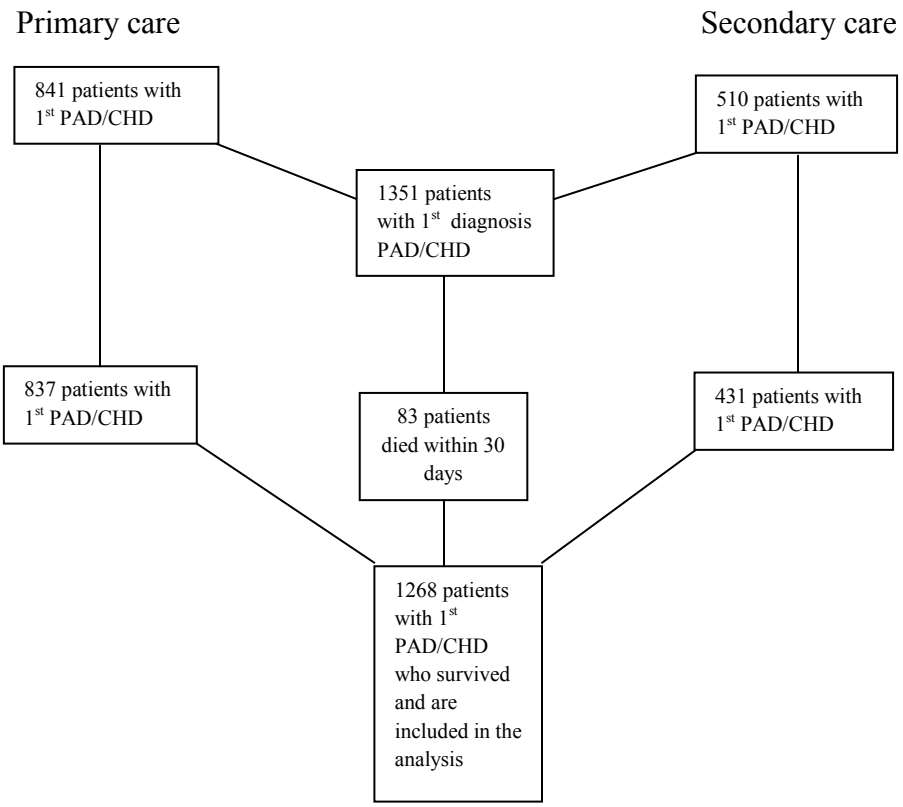


Table 49 Baseline demographic characteristics

	Within 30 days (n=1268)	Patients died within 30 days after 1st diagnosis (n=83)	All patients (n=1351)
Male sex	796 (62.8%)	45 (54.2%)	841 (62.3%)
SD/Variance	1.05/1.12	0.87/0.76	1.07/1.14
Age (years):			
< 55	119 (9.4%)	1 (1.2%)	120 (8.9%)
55 – 64	298 (23.0%)	4 (4.8%)	302 (22.4%)
65 – 74	418 (33.0%)	19 (23.0%)	437 (32.3%)
75 – 84	362 (28.5%)	39 (47.0%)	491 (29.7%)
85+	71 (5.6%)	20 (24.1%)	91 (6.7%)
Deprivation			
Q1 Least deprived	71 (5.6%)	6 (7.2%)	77 (5.7%)
Q2	69 (5.4%)	5 (6.0%)	74 (5.4%)
Q3	116 (9.1%)	7 (8.4%)	123 (9.1%)
Q4	112 (8.8%)	5 (6.0%)	117 (8.6%)
Q5	130 (10.2%)	9 (10.8%)	139 (10.2%)
Q6	194 (15.3%)	13 (15.6%)	207 (15.3%)
Q7	142 (11.2%)	10 (12.0%)	152 (11.2%)
Q8	149 (11.7%)	7 (8.4%)	156 (11.5%)
Q9	158 (12.4%)	13 (15.6%)	171 (12.6%)
Q 10 Most deprived	127 (10.0%)	8 (9.6%)	135 (9.9%)
Year			
1997	111 (8.8%)	5 (6.02%)	116 (8.6%)
1998	135 (10.6%)	5 (6.02%)	140 (10.4%)
1999	161 (12.7%)	5 (6.02%)	166 (12.3%)
2000	170 (13.4%)	12 (14.4%)	182 (13.5%)
2001	138 (10.9%)	9 (10.8%)	147 (10.9%)
2002	152 (12.0%)	12 (14.4%)	164 (12.1%)
2003	157 (12.4%)	12 (14.4%)	169 (12.5%)
2004	136 (10.7%)	11 (13.2%)	147 (10.9%)
2005	108 (8.5%)	12 (14.4%)	120 (8.9%)
Comorbidities			
COPD/Asthma	202 (15.9%)	22 (26.5%)	224 (16.6%)
Atrial fibrillation	179 (14.1%)	21 (25.5%)	200 (14.8%)
Hypertension	536 (42.3%)	31 (37.1%)	567 (42.0%)
Diabetes	170 (13.4%)	12 (14.5%)	182 (13.5%)
Cancer	105 (8.3%)	13 (15.6%)	118 (8.7%)
Renal failure	49 (3.9%)	19 (22.8%)	68 (5.0%)
Heart failure	320 (25.2%)	40 (48.2%)	360 (26.6%)
Stroke	184 (14.5%)	17 (20.5%)	201 (14.9%)

COPD=Chronic obstructive pulmonary disease

Table 50 Rate per (1000) of incident PAD with CHD

	Total population registered with GPs	Patients with PAD/CHD	Rate
Sex			
Men	792651	841	1.06
Women	807959	510	0.63
Age			
<45	950345	120	0.13
45-64	410998	302	0.73
65-74	133058	437	3.28
75-84	80828	491	6.07
85+	25381	91	3.59
Socio-economic			
Q1 Least deprived	305557	152	0.50
Q2	358497	139	0.39
Q3	401492	345	0.86
Q4	305760	310	1.01
Q5 Most deprived	266735	301	1.13
Years			
1999	227690	166	0.73
2000	226503	182	0.80
2001	225806	147	0.65
2002	227146	164	0.72
2003	228766	169	0.74
2004	232554	147	0.63
2005	232343	120	0.52

Prescribing of EBTs before and after first recorded diagnosis

Table 51 shows prescribing of EBTs before and after the first recorded diagnosis of PAD/CHD. The percentage of patients prescribed aspirin before first diagnosis of PAD/CHD was 64.0%, β-blockers 47.5%, CCB 44.3%, and statins 42.1%. After a first diagnosis, prescribing within 30 days was at a lower percentage than before diagnosis. However, prescribing at any time after diagnosis was at a higher level than before for all EBTs.

Table 51 Evidence based therapies prescribing for patients with incident diagnosis of PAD/CHD

Medicine	Prescribed drug before 1st diagnosis	Prescribed drug after 1st diagnosis at any time	Prescribed drug within 30 days after 1st diagnosis*
ACEI/ARB	38.6%	69.0%	20.1%
β-blockers	47.5%	61.8%	20.5%
CCB	44.3%	57.6%	20.5%
PVD	3.1%	9.0%	3.2%
Statins	42.1%	84.6%	27.1%
Aspirin	64.0%	82.7%	30.4%
Clopidogrel	6.1%	21.4%	3.7%
Oral anti-coagulant	9.0%	31.1%	4.2%

* This percentage is for patients alive 30 days after the 1st diagnosis, ACEI=Angiotensin converting enzyme inhibitor, ARBs=Angiotensin receptor blockers, CCB=calcium channel blockers. PVD=peripheral vasodilator

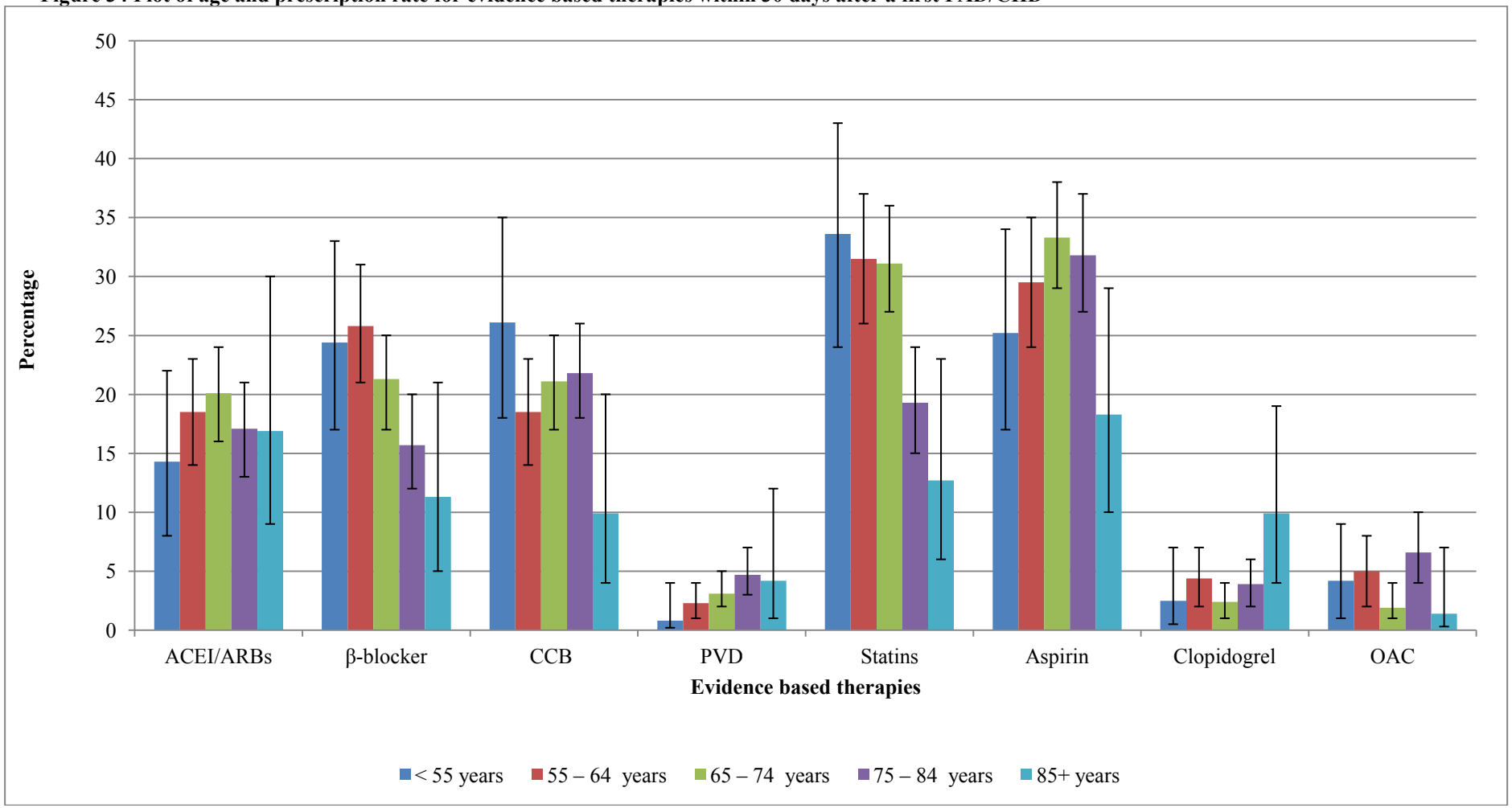
5.4.1 Differences in prescribing of evidence based therapies for PAD/CHD

5.4.1.1 Age differences in prescribing of evidence based therapies

Figure 34 shows that patients aged less than 55 years received proportionally more prescriptions of CCB and statins than the other age groups. Patients aged from 55-64 years received more prescriptions of β-blockers. Prescribing of ACEI/ARBs and aspirin was higher for age group 65-74 years than other groups. Patients aged between 75 and 84 years had the highest percentage of PVD and oral anticoagulants prescriptions than other age groups. Patients aged ≥ 85 years received proportionally more prescriptions of clopidogrel. The values of the percentages shown in Figure 34 are in Table 53. For example, proportion of prescribing CCBs for age group less than 55 years was 26.1% and 33.6% for statins compared to the other groups (Table 54). Age group 55-64 years received more prescriptions for β-blockers (25.8%). Proportions of prescribing ACEI (20.1%), aspirin (33.3%) were higher for patients in the age group 75-84 than others. Higher proportions for PVD (4.7%) and oral anticoagulants (6.6%) were for the age group between 75 and 84 years.

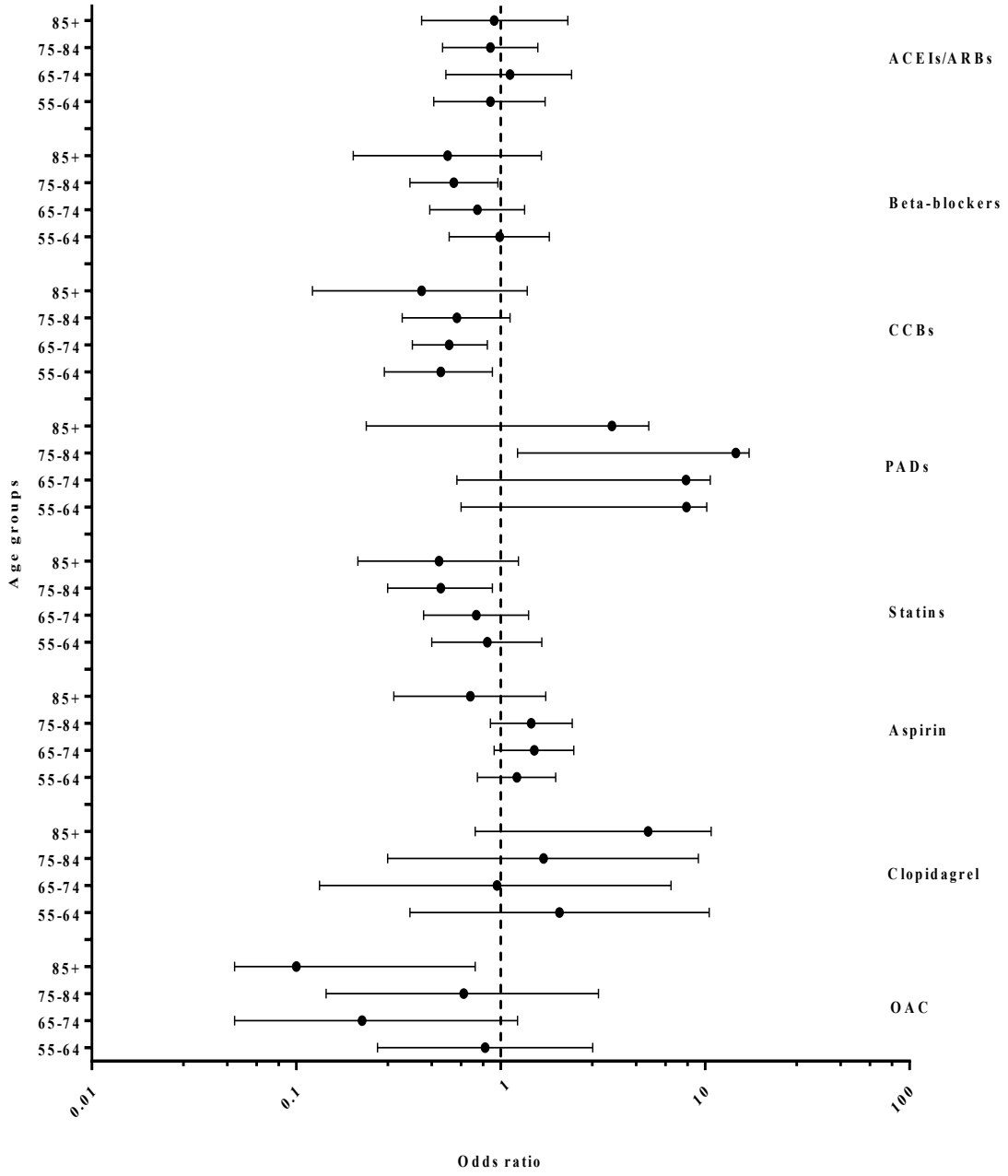
After adjustment using multivariable analysis compared to the youngest group <55, the eldest age group (≥ 85 years) were significantly less likely to receive oral anticoagulants (OR 0.07; 95%CI 0.01-0.75). The eldest patients had higher odds of being prescribed PVD (OR 3.50; 95%CI 0.22-53.88) and clopidogrel (OR 5.26; 95%CI 0.75-36.7); however, they had lower odds of being prescribed all other medications compared to the youngest patients (Figure 35 and Table 13 appendix 6).

Figure 34 Plot of age and prescription rate for evidence based therapies within 30 days after a first PAD/CHD



ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, PVD=Peripheral vasodilator, OAC=Oral anticoagulant

Figure 35 Forest plot of odds ratio of sex and prescribing evidence based therapies within 30 days after first diagnosis of peripheral arterial disease with CHD



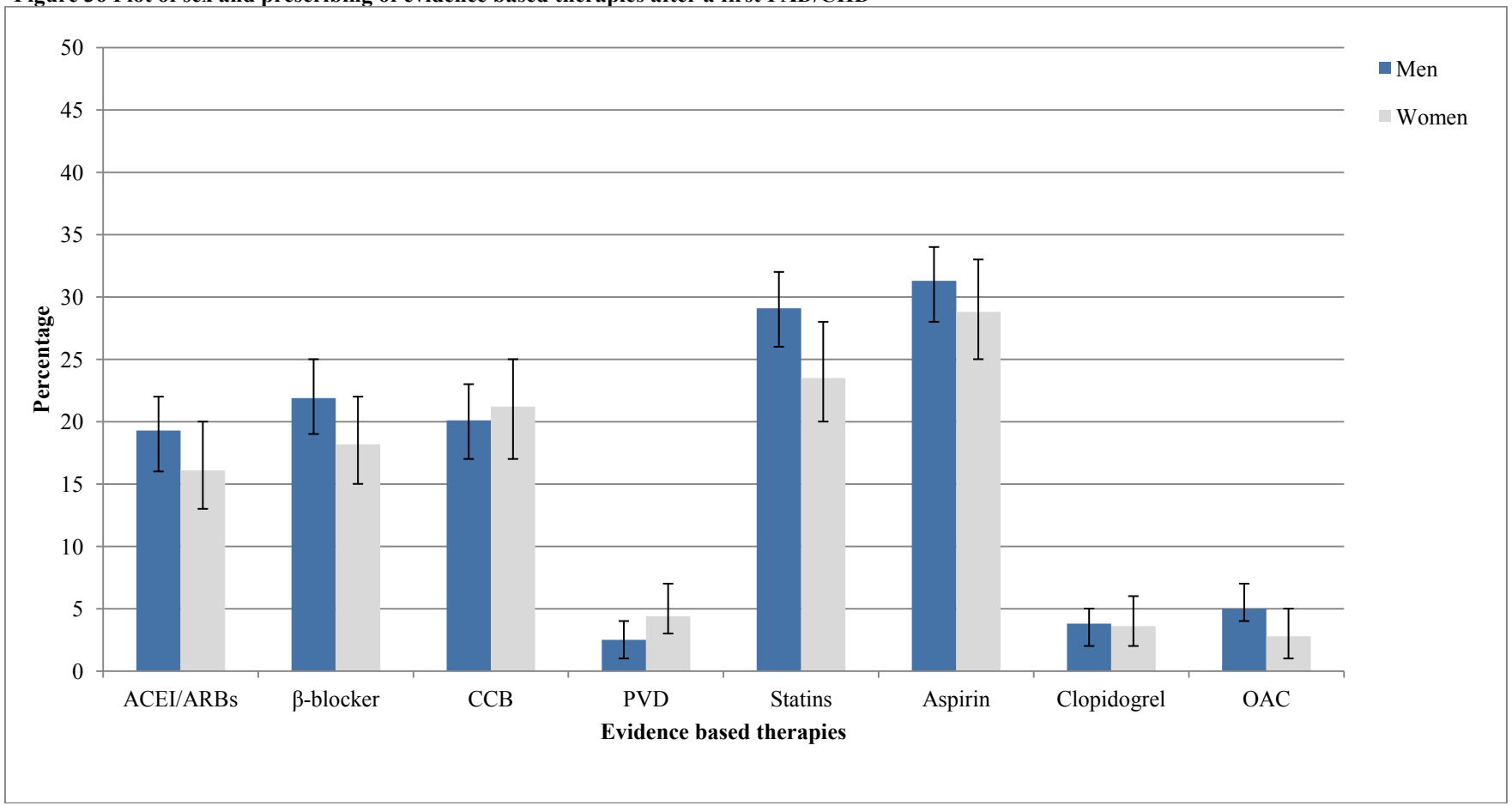
Patients aged <55 years are the reference category. Odds ratio adjusted for sex, socioeconomic status, year of diagnosis, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, clustered practices, and whether the drug was previously prescribed. Upper 95% CI for PVD has configured see table in the appendix.

ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, OAC= Oral anticoagulants.

5.4.1.2 Sex differences in prescribing of evidence based therapies

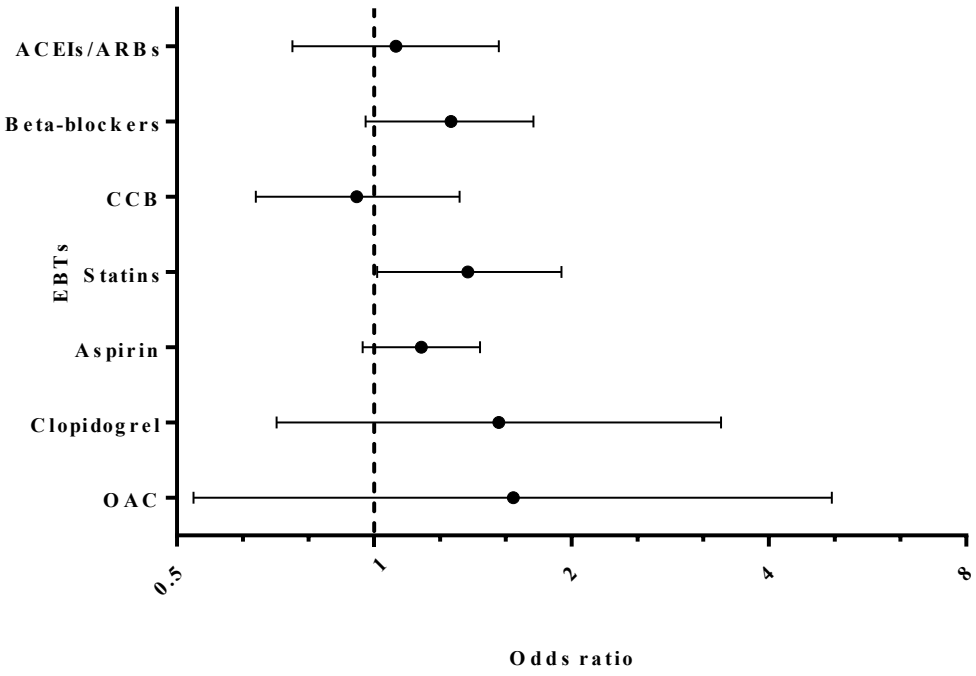
Prescribing of EBTs was higher in men compared with women for most EBT classes. Prescribing of ACEI/ARBs, β-blockers, statins, aspirin, clopidogrel and oral anticoagulant was higher in men compared with women, whereas women received more prescriptions for CCBs and PVD than men (Figure 36). The values of the percentages shown in Figure 36 are found in Table 54. ACEI/ARBs were prescribed for 19.3% of men vs. 16.1% for women, β-blockers 21.9% of men vs. 18.2% of women, statins 29.1% of men vs. 23.5% of women, aspirin 31.3% of men vs. 23.5% of women. After adjustment using multivariable analysis compared to women, there was a trend towards men being more likely to be prescribed β-blockers (OR 1.31; 95% CI 0.97-1.75, p=0.04), clopidogrel (OR 1.55; 95% CI 0.71-3.38, p=0.2), but these were not statistically significant. Men were statistically more likely to receive statins (OR 1.39; 95% CI 1.01-1.93, p=0.04). In contrast, they had lower odds to receive CCBs (OR 0.94; 95% CI 0.66-1.35, p=0.7) and PVD (OR 0.57; 95% CI 0.28-1.16, p=0.12) (Figure 37 and Table 14 appendix 6).

Figure 36 Plot of sex and prescribing of evidence based therapies after a first PAD/CHD



ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blocker, PVD=Peripheral vasodilator, OAC=Oral anticoagulant

Figure 37 Forest plot of odds ratio of sex and prescribing evidence based therapies within 30 days after first diagnosis of peripheral arterial disease with CHD



Women are the reference category. Odds ratio adjusted for age group, socioeconomic, year of diagnosis, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, stroke, clustered practices, and whether the drug was previously prescribed.

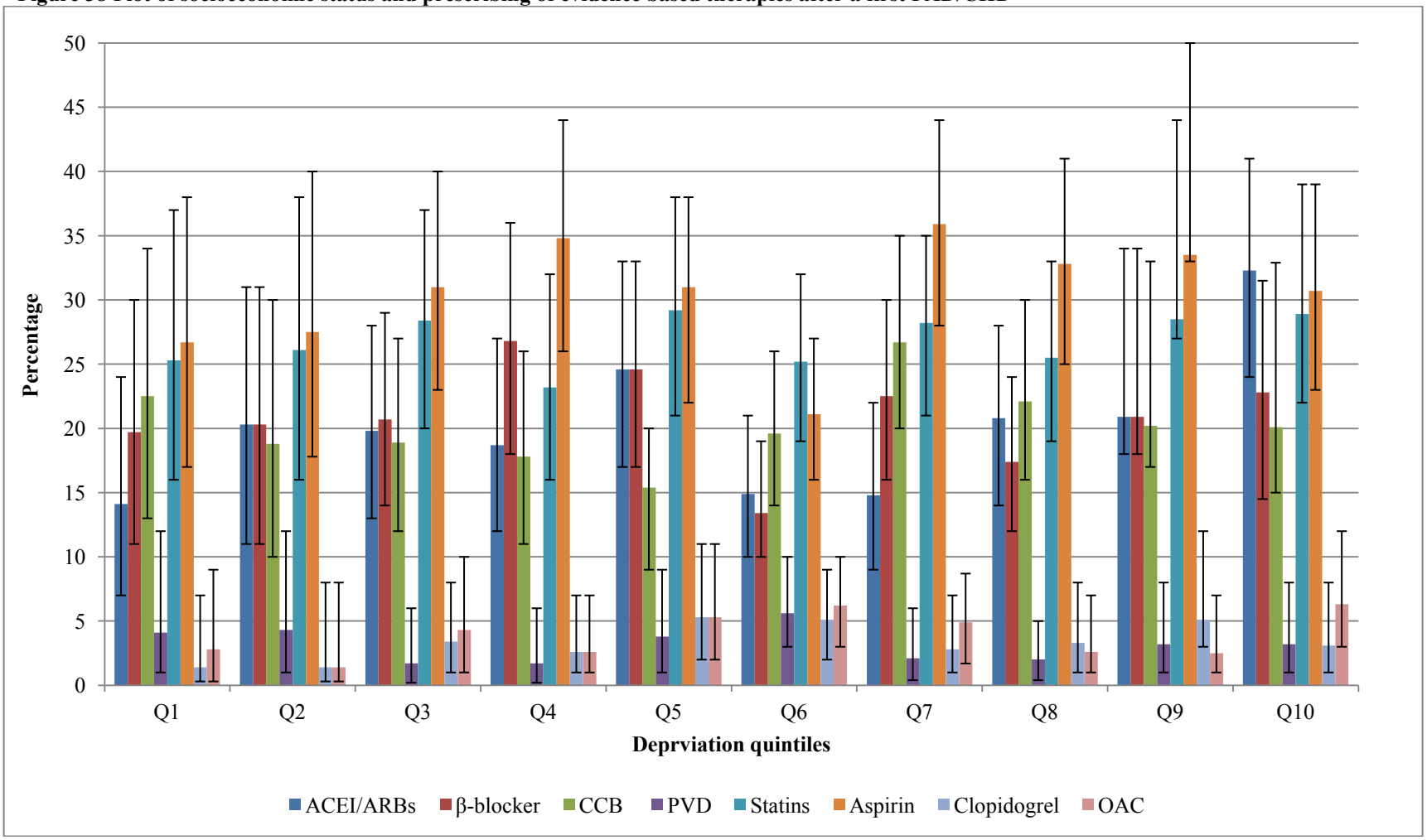
ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, OAC= Oral anticoagulants.

5.4.1.3 Socioeconomic differences in prescribing of evidence based therapies

Figure 38 shows the differences in prescribing of EBTs between the socioeconomic status groups. Small variations in the prescribing of EBTs between the deprivation groups were identified. Patients residing in the least deprived areas (Q1) received fewer prescriptions than those residing in the most deprived areas (Q10) for ACEI/ARBs (16.3% vs. 22.9%) and aspirin (27.3% vs. 32.4%) (Table 53). Generally, patients residing in the most deprived area (Q5) associated with higher percentage of EBTs prescriptions, particularly statins (28.9%) and aspirin (30.7%) than the least deprived area.

The multivariable analyses showed that after adjustment there was only evidence of differences in the odds of prescribing between the socioeconomic deprivation groups for ACEI/ARBs (0.03) (Table 54). Compared to those patients residing in the least deprived areas (Q1), patients living in the most deprived areas had lower odds of being prescribed β-blockers (OR 0.88; 95% CI 0.48-1.59), CCB (OR 0.54; 95% CI 0.25-1.18) and PVD (OR 0.69; 95% CI 0.13-3.57) although all these associations were not statistically significant (Figure 39 and Table 15, appendix 6).

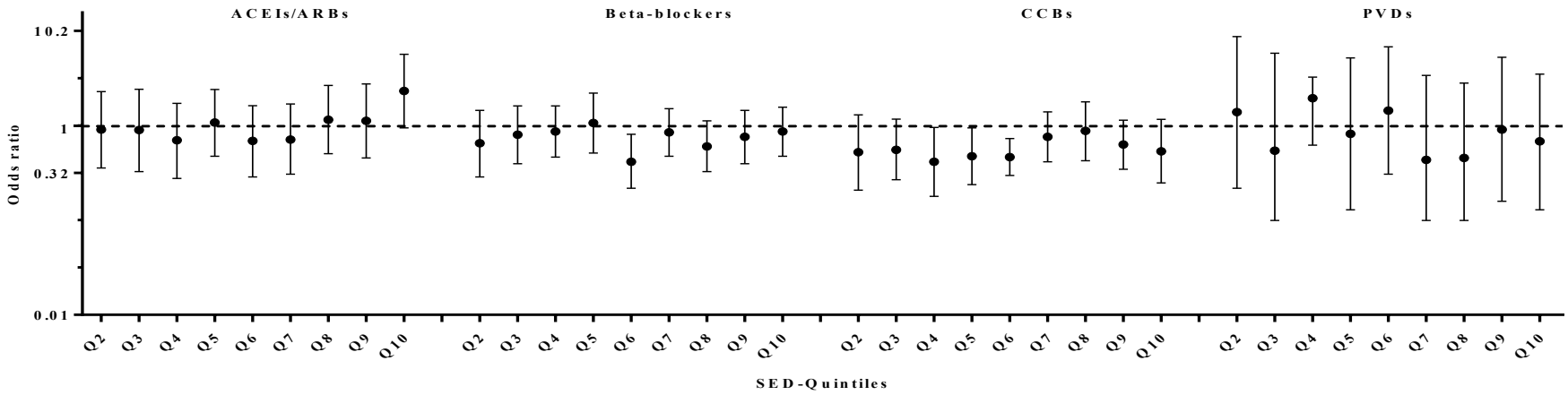
Figure 38 Plot of socioeconomic status and prescribing of evidence based therapies after a first PAD/CHD



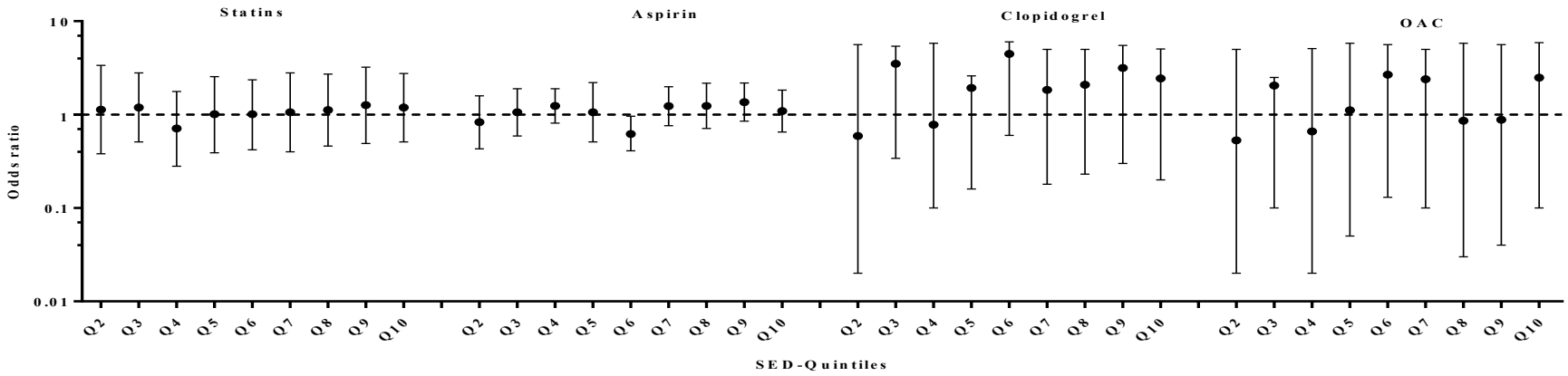
ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, PVD=Peripheral vasodilator

Figure 39 Forest plot of odds ratio of socioeconomic deprivation and prescribing evidence based therapies within 30 days after first diagnosis of peripheral arterial disease/CHD

A



B

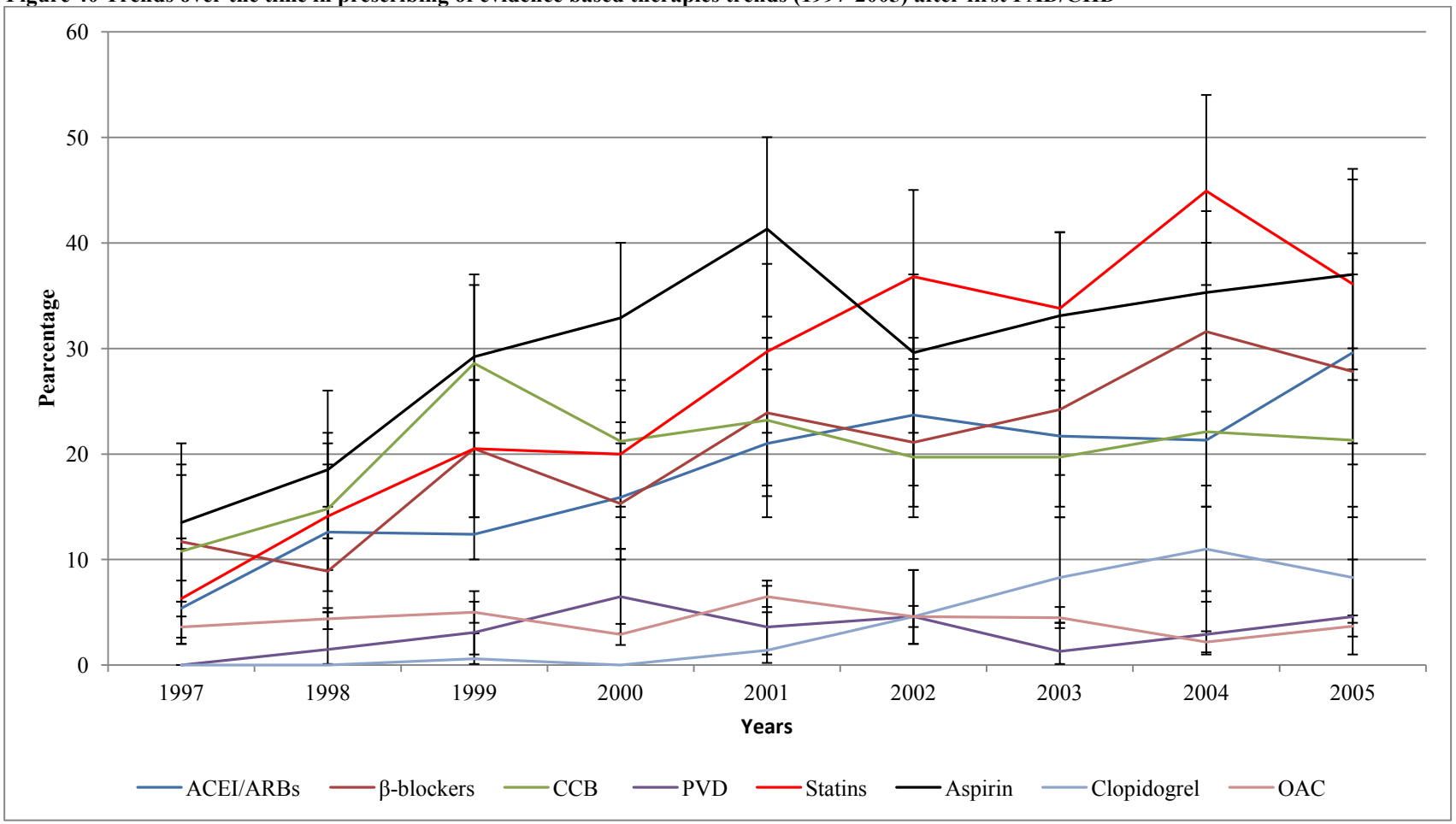


Quintile 1 (Q1) least deprived is a reference. Odds ratio adjusted for sex, age group, year of diagnosis, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, clustered practices, and whether the drug was previously prescribed. Upper 95% CI for clopidogrel and OAC has configured in the plot "see appendix. SED=Socioeconomic deprivation ACEI=Angiotensin converting enzyme inhibitors, ARBs=Angiotensin receptor blockers, CCB=Calcium channel blockers, OAC= oral anticoagulant.

5.4.1.4 Trends of prescribing EBTs from 1997 to 2005

Figure 40 shows trends of prescribing EBTs within 30 days after first diagnosis of PAD/CHD over the 9 years of the study. Although there is an overall increase in the trend of prescribing EBTs, there were variations in the association. Prescribing of clopidogrel, PVD and oral anticoagulants all slightly increased from 1997 to 2005. Aspirin and statins were associated with higher increases during the study period than other drugs. Although prescribing had generally increased, it declined between 2004 and 2005 for statins, β-blockers, CCB and clopidogrel. The trends of prescribing EBTs shown in Figure 40 are presenting as percentages in Table 54. For instance, there were increases in prescribing for ACEI/ARBs from 5.4% to 29.6%, β-blockers from11.7% to 27.8%, CCBs from10.8% to 21.3%, PVD from 0.0% to 4.6%, statins from 6.3% to 36.1%, aspirin from13.5% to 37.0%, and oral-anticoagulants from 3.6% to 3.7%. Compared to prescribing in 1997, patients in 2005 were significantly more likely to be prescribed ACEI/ARBs (OR 3.17; 95% CI 1.11-7.12), aspirin (OR 2.51; 95% CI 1.19-5.28) and clopidogrel (OR 13.6; 95% CI 1.65-11.2) (Figure 41 and Table 16, appendix 6).

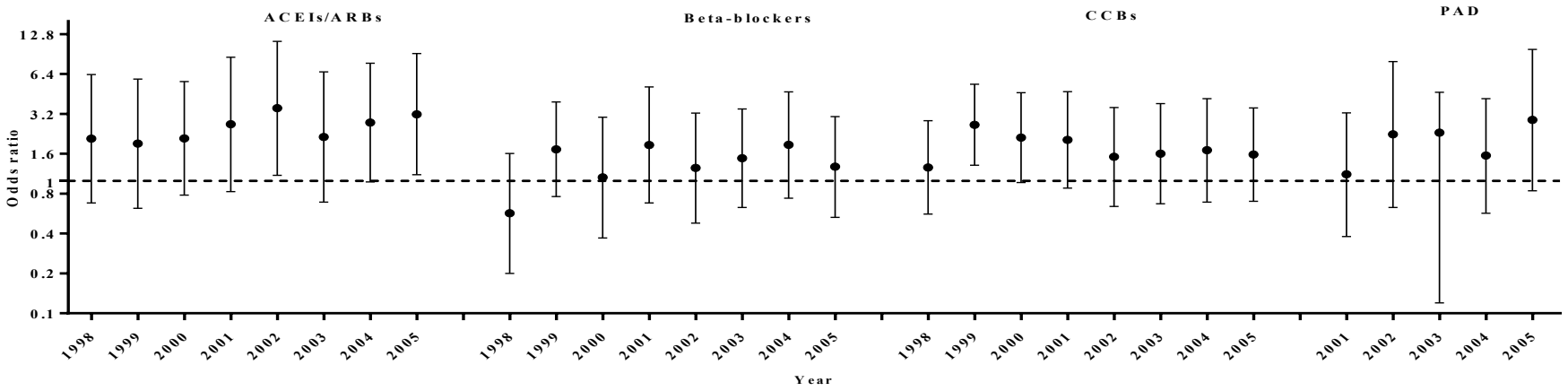
Figure 40 Trends over the time in prescribing of evidence based therapies trends (1997-2005) after first PAD/CHD



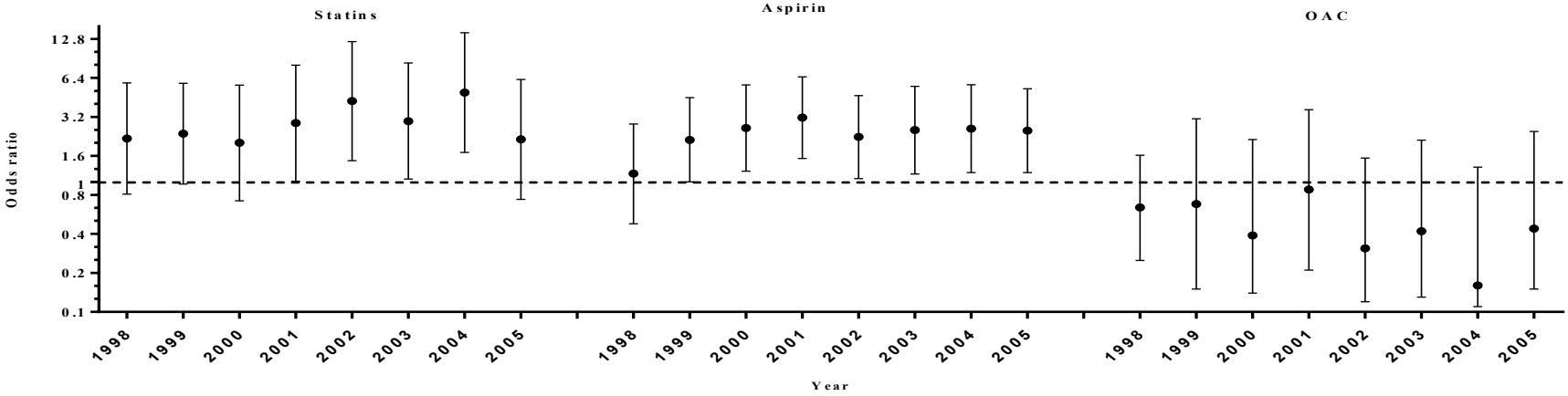
ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, PVD=Peripheral vasodilator, OAC=Oral anticoagulant

Figure 41 Forest plot of odds ratio of trends over time (1997-2005) and prescribing evidence based therapies within 30 days after first diagnosis of peripheral arterial disease/CHD.

A



B



Year 1997 is the reference. Adjusted for sex, age group, socioeconomic status, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, peripheral arterial disease, clustered practices, and whether the drug was previously prescribed. **2000 is the reference for clopidogrel. For clopidogrel result see table in the appendix.
ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, OAC= oral anticoagulants

5.4.1.5 Association between comorbidity and prescribing

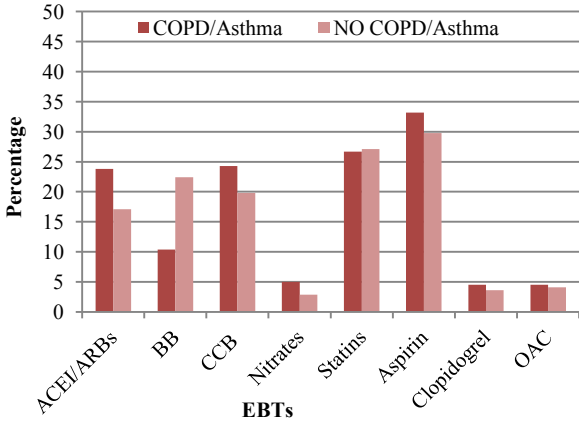
Figure 42b shows a stark difference in the prescribing of oral anti-coagulants for patients with and those without AF. Prescribing of EBTs was generally higher among patients with hypertension than those without hypertension (see Figure 42c). However, prescribing EBTs was generally lower among patients with cancer than those without cancer (see Figure 42e). Other concomitant diseases were associated with different patterns in the prescribing of EBTs.

Compared to patients without COPD/asthma, patients with COPD/asthma had lower percentage of prescriptions for β-blockers (10.4% vs. 22.4%). Patients with AF had a higher percentage for oral anticoagulant (71.3% vs. 2.0%), but lower for aspirin (32.1% vs. 19.6%) than those without AF. The largest difference between patients with hypertension compared to those without hypertension was for ACEI/ARBs (24.8% vs. 22.9) (Table 53).

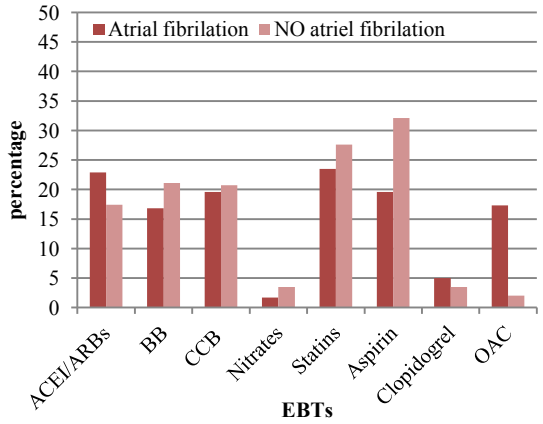
As can be seen in Table 52, after adjustment using multivariable analysis there were some statistically significant differences in the odds of prescribing and whether certain comorbidities were present or not. Patients with COPD/asthma were significantly less likely to receive β-blockers (OR 0.60; 95% CI 0.36-0.99). Patients with AF were more likely to be prescribed oral anticoagulants (OR 4.46; 95% CI 1.72-11.16), though they were significantly less likely to be prescribed aspirin (OR 0.50; 95% CI 0.31-0.81). Patients with hypertension were significantly more likely to be prescribed ACEI/ARBs (OR 1.53; 95% CI 1.05-2.29) and β-blockers (OR 1.39; 95% CI 1.01-1.92) than those without hypertension. Patients with diabetes were less likely to receive oral anticoagulant (OR 0.25; 95% CI 0.07-0.82) than those without diabetes. Patients with renal failure were significantly less likely to be prescribed CCB (OR 0.11; 95% CI 0.02-0.49) than those without renal failure.

Figure 42 Plot of comorbidities and prescribing of evidence based therapies

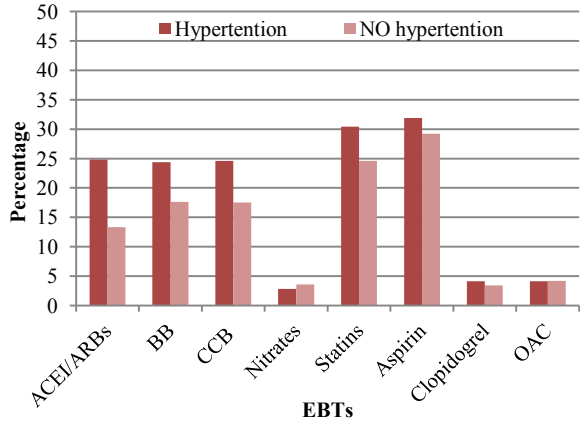
42a



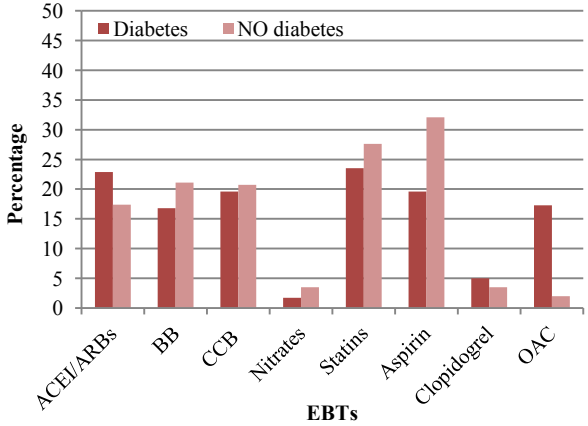
42b



42c



42d



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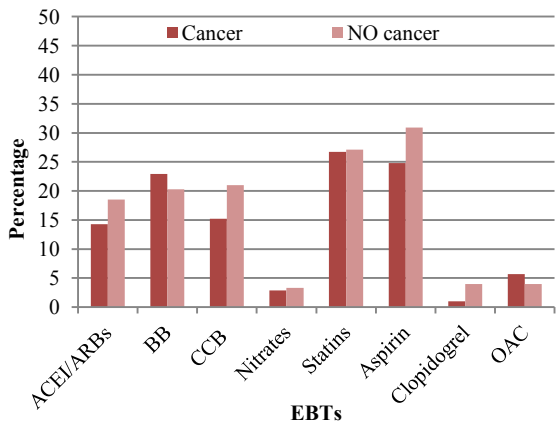

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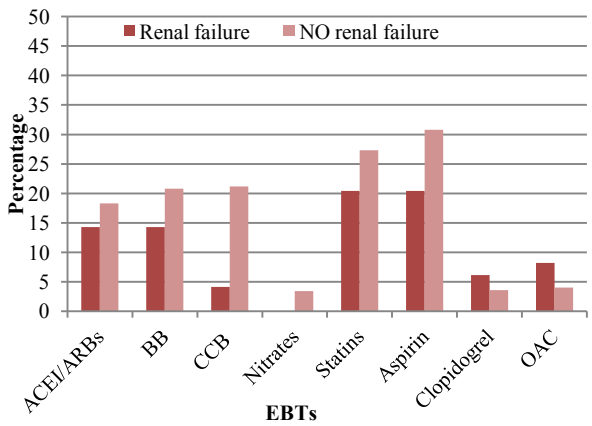

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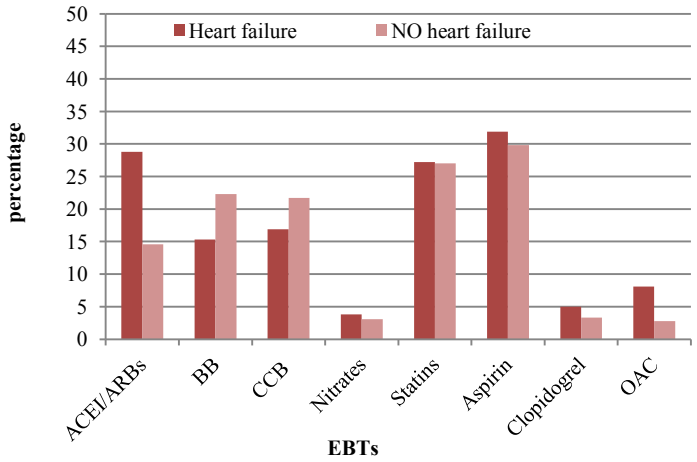

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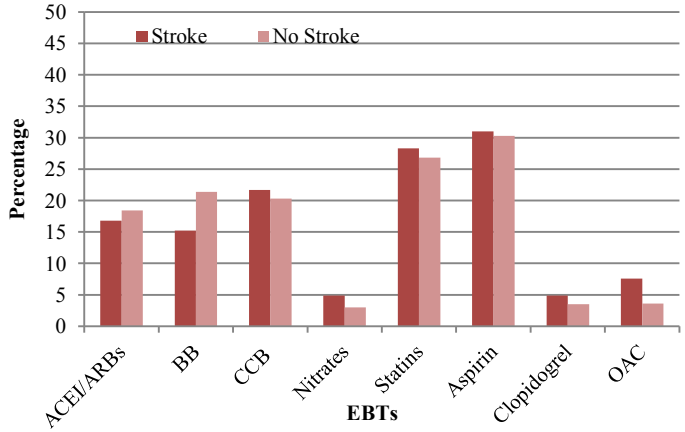


COPD= chronic obstructive pulmonary disease, ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, BB= beta blocker PVD= Peripheral vasodilator, OAC=Oral anticoagulant

Table 52 Association of comorbidities with prescribing EBTs for patients diagnosed with PAD/CHD (OR, 95% CI)

Adjusted OR, 95% CI, p value	ACEI/ARBs	β-blocker	CCB	PVD	Statins	Aspirin	Clopidogrel	Oral anti-coagulant
COPD	1.31 (0.88-1.95), 0.17	0.60 (0.36-0.99), 0.05	1.12 (0.72-1.74), 0.61	1.91 (0.91-4.00), 0.08	1.01 (0.67-1.52), 0.95	1.09 (0.76-1.56), 0.62	2.22 (1.01-4.94), 0.05	0.81 (0.31-2.09), 0.66
AF	0.82 (0.53-1.26), 0.37	0.75 (0.44-1.25), 0.27	1.23 (0.78-1.95), 0.36	0.41 (0.11-1.47), 0.17	0.91 (0.59-1.39), 0.66	0.50 (0.31-0.81), 0.01	8.70 (0.37-2.03), 0.75	4.46 (1.72-11.6), 0.01
HYP	1.53 (1.05-2.22), 0.03	1.39 (1.01-1.92), 0.05	1.14 (0.81-1.60), 0.44	0.55 (0.26-1.12), 0.10	1.16 (0.82-1.62), 0.38	0.93 (0.70-1.25), 0.66	1.21 (0.59-2.47), 0.58	1.09 (0.57-2.06), 0.79
Diabetes	0.81 (0.53-1.21), 0.30	1.03 (0.68-1.56), 0.87	1.05 (0.68-1.62), 0.80	0.11 (0.02-0.45), 0.01	0.77 (0.51-1.16), 0.22	1.07 (0.76-1.52), 0.66	0.75 (0.27-2.06), 0.58	0.25 (0.07-0.82), 0.02
Cancer	0.57 (0.32-1.02), 0.06	1.17 (0.68-2.01), 0.55	0.56 (0.30-1.06), 0.08	0.85 (0.29-2.48), 0.77	1.18 (0.82-1.69), 0.36	0.67 (0.43-1.06), 0.09	0.16 (0.01-2.18), 0.17	1.67 (0.64-4.35), 0.28
Renal failure	0.29 (0.11-0.72), 0.01	0.52 (0.21-1.31), 0.16	0.11 (0.02-0.49), 0.01	1.14 (0.23-5.47), 0.80	0.45 (0.22-0.92), 0.03	0.39 (0.21-0.74), 0.01	1.22 (0.29-5.07), 0.77	4.99 (1.38-17.9), 0.01
HF	1.19 (0.84-1.68), 0.31	0.87 (0.57-1.33), 0.54	0.80 (0.54-1.16), 0.24	1.32 (0.66-2.62), 0.42	1.17 (0.85-1.61), 0.33	1.21 (0.92-1.59), 0.15	1.11 (0.46-2.62), 0.81	1.14 (0.48-2.70), 0.75
Stroke	0.91 (0.55-1.51), 0.73	0.69 (0.43-1.11), 0.12	1.11 (0.71-1.75), 0.63	1.65 (0.64-4.22), 0.30	1.19 (0.78-1.82), 0.40	1.01 (0.68-1.46), 0.99	1.14 (0.42-3.08), 0.80	1.46 (0.69-3.08), 0.31

***** Adjusted for sex, age group, socioeconomic status, year of diagnosis, chronic obstructive pulmonary disease (COPD), asthma, atrial fibrillation (AF), hypertension (HTN), diabetes, cancer, renal failure, heart failure (HF), and stroke, whether the drug was previously prescribed.

ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers

NB: comparator for all comorbidities is No disease

5.4.1.6 Interactions by year of diagnosis

Where statistically significant findings were found in sections 5.4.1.1–5.4.1.3, the interaction between that factor and year was tested (Table 53). It can be seen that there was no significant interactions between sex, age groups, deprivation and year.

Table 53 Interaction between year of diagnosis and selected variables and therapies. Variables and medications selected on the basis of significant multivariable associations.

Factors	Medication	P for interaction
Age group		
	Oral anticoagulant	0.99
Sex		
	Statins	0.51
Socioeconomic deprivation		
	ACEI/ARBs	0.64

Table 54 Prescribing evidence based therapies within 30 days for patients who survived the first 30 days after a first diagnosis PAD/CHD (n=1268)

	ACEI/ARB	β-lockers	CCB	PVD	Statins	Aspirin	Clopidogrel	Oral anti coagulant
N (n=1268)	230 (18.1%)	260 (20.5%)	260 (20.5%)	41 (3.2%)	343 (27.1%)	385 (30.4%)	47 (3.7%)	53 (4.2%)
Male (n=796)	154 (19.3%)	174 (21.9%)	160 (20.1%)	20 (2.5%)	232 (29.1%)	249 (31.3%)	30 (3.8%)	40 (5.0%)
Female (n=472)	76 (16.1%)	86 (18.2%)	100 (21.2%)	21 (4.4%)	111 (23.5%)	136 (28.8%)	17 (3.6%)	13 (2.8%)
Age (years)								
< 55 (n=119)	17 (14.3%)	29 (24.4%)	31 (26.1%)	1 (0.8%)	40 (33.6%)	30 (25.2%)	3 (2.5%)	5 (4.2%)
55 – 64 (n=298)	55 (18.5%)	77 (25.8%)	55(18.5%)	7 (2.3%)	94 (31.5%)	88 (29.5%)	13 (4.4%)	15 (5.0%)
65 – 74 (n=418)	84 (20.1%)	89 (21.3%)	88 (21.1%)	13 (3.1%)	130 (31.1%)	139 (33.3%)	10 (2.4%)	8 (1.9%)
75 – 84 (n=362)	62 (17.1%)	57 (15.7%)	79 (21.8%)	17 (4.7%)	70 (19.3%)	115 (31.8%)	14 (3.9%)	24 (6.6%)
85+ (n=71)	12 (16.9%)	8 (11.3%)	7 (9.9%)	3 (4.2%)	9 (12.7%)	13 (18.3%)	7 (9.9%)	1 (1.4%)
Deprivation								
Q1 (n=71)	10 (14.1%)	14 (19.7%)	16 (22.5%)	3 (4.1%)	18 (25.3%)	19 (26.7%)	1 (1.4%)	2 (2.8%)
Q2 (n=69)	14 (20.3%)	14 (20.3%)	13 (18.8%)	3 (4.3%)	18 (26.1%)	19 (27.5%)	1 (1.4%)	1 (1.4%)
Q3 (n=116)	23 (19.8%)	24 (20.7%)	22 (18.9%)	2 (1.7%)	33 (28.4%)	36 (31.0%)	4 (3.4%)	5 (4.3%)
Q4 (n=112)	21 (18.7%)	30 (26.8%)	20 (17.8%)	2 (1.7%)	26 (23.2%)	39 (34.8%)	3 (2.6%)	3 (2.6%)
Q5 (n=130)	32 (24.6%)	32 (24.6%)	20 (15.4%)	5 (3.8%)	38 (29.2%)	39 (31.0%)	7 (5.3%)	7 (5.3%)
Q6 (n=194)	29 (14.9%)	26 (13.4%)	38 (19.6%)	11 (5.6%)	49 (25.2%)	41 (21.1%)	10 (5.1%)	12 (6.2%)
Q7 (n=142)	21 (14.8%)	32 (22.5%)	38 (26.7%)	3 (2.1%)	40 (28.2%)	51 (35.9%)	4 (2.8%)	7 (4.9%)
Q8 (n=149)	31 (20.8%)	26 (17.4%)	33 (22.1%)	3 (2.01%)	38 (25.5%)	49 (32.8%)	5 (3.3%)	4 (2.6%)
Q9 (n=128)	33 (20.9%)	33 (20.9%)	32 (20.2%)	5 (3.2%)	45 (28.5%)	53 (33.5%)	8 (5.1%)	4 (2.5%)
Q10 (n=127)	41 (32.3%)	29 (22.8%)	28 (20.1%)	4 (3.2%)	38 (28.9%)	39 (30.7%)	4 (3.1%)	8 (6.3%)

Year		ACEI/ARB	β-lockers	CCB	PVD	Statins	Aspirin	Clopidogrel	Oral-anti coagulant
1997 (n=111)		6 (5.4%)	13 (11.7%)	12 (10.8%)	0 (0.0%)	7 (6.3%)	15 (13.5%)	0 (0.0%)	4 (3.6%)
1998 (n=135)		17 (12.6%)	12 (8.9%)	20 (14.8%)	2 (1.5%)	19 (14.1%)	25 (18.5%)	0 (0.0%)	6 (4.4%)
1999 (n=161)		20 (12.4%)	33 (20.5%)	46 (28.6%)	5 (3.1%)	33 (20.5%)	47 (29.2%)	1 (0.6%)	8 (5.0%)
2000 (n=170)		27 (15.9%)	26 (15.3%)	36 (21.2%)	11 (6.5%)	34 (20.0%)	56 (32.9%)	0 (0.0%)	5 (2.9%)
2001 (n=138)		29 (21.0%)	33 (23.9%)	32 (23.2%)	5 (3.6%)	41 (29.7%)	57 (41.3%)	2 (1.4%)	9 (6.5%)
2002 (n=152)		36 (23.7%)	32 (21.1%)	30 (19.7%)	7 (4.6%)	56 (36.8%)	45 (29.6%)	7 (4.6%)	7 (4.6%)
2003 (n=157)		34 (21.7%)	38 (24.2%)	31 (19.7%)	2 (1.3%)	53 (33.8%)	52 (33.1%)	13 (8.3%)	7 (4.5%)
2004 (n=136)		29 (21.3%)	43 (31.6%)	30 (22.1%)	4 (2.9%)	61 (44.9%)	48 (35.3%)	15 (11.0%)	3 (2.2%)
2005 (n=108)		32 (29.6%)	30 (27.8%)	23 (21.3%)	5 (4.6%)	39 (36.1%)	40 (37.0%)	9 (8.3%)	4 (3.7%)
Comorbidities									
COPD/Asthma									
	Yes (202)	48 (23.8%)	21 (10.4%)	49 (24.3%)	10 (5.0%)	54 (26.7%)	67 (33.2%)	9 (4.5%)	9 (4.5%)
	No (1066)	182 (17.1%)	239 (22.4%)	211 (19.8%)	31 (2.9%)	289 (27.1%)	318 (29.8%)	38 (3.6%)	44 (4.1%)
Atrial fibrillation									
	Yes (179)	41 (22.9%)	30 (16.8%)	35 (19.6%)	3 (1.7%)	42 (23.5%)	35 (19.6%)	9 (5.0%)	31 (17.3%)
	No (1089)	189 (17.4%)	230 (21.1%)	225 (20.7%)	38 (3.5%)	301 (27.6%)	350 (32.1%)	38 (3.5%)	22 (2.0%)
Hypertension									
	Yes (536)	133 (24.8%)	131 (24.4%)	132 (24.6%)	15 (2.8%)	163 (30.4%)	171 (31.9%)	22 (4.1 %)	22 (4.1%)
	No (732)	97 (13.3%)	129 (17.6%)	128 (17.5%)	26 (3.6%)	180 (24.6%)	214 (29.2%)	25 (3.4%)	31(4.2%)

		ACEI/ARB	β-lockers	CCB	PVD	Statins	Aspirin	Clopidogrel	Oral-anti coagulant
Diabetes									
	Yes (170)	41 (22.9%)	30 (16.8%)	35 (19.6%)	3 (1.7%)	42 (23.5%)	35 (19.6%)	9 (5.0%)	31 (17.3%)
	No (1116)	189 (17.4%)	230 (21.1%)	225 (20.7%)	38 (3.5%)	301 (27.6%)	350 (32.1%)	38 (3.5%)	22 (2.0%)
Cancer									
	Yes (105)	15 (14.3%)	24 (22.9%)	16 (15.2%)	3 (2.9%)	28 (26.7%)	26 (24.8%)	1 (1.0%)	6 (5.7%)
	No (1163)	215 (18.5%)	236 (20.3%)	244 (21.0%)	38 (3.3%)	315 (27.1%)	359 (30.9%)	46 (4.0%)	47 (4.0%)
Renal failure									
	Yes (49)	7 (14.3%)	7 (14.3%)	2 (4.1%)	0 (0.0%)	10 (20.4%)	10 (20.4%)	3 (6.1%)	4 (8.2%)
	No (1219)	223 (18.3%)	253 (20.8%)	258 (21.2%)	41 (3.4%)	333 (27.3%)	375 (30.8%)	44 (3.6%)	49 (4.0%)
Heart failure (HF)									
	Yes (320)	92 (28.8%)	49 (15.3%)	54 (16.9%)	12 (3.8%)	87 (27.2%)	102 (31.9%)	16 (5.0%)	26 (8.1%)
	No (948)	138 (14.6%)	211 (22.3%)	206 (21.7%)	29 (3.1%)	256 (27.0%)	283 (29.8%)	31 (3.3%)	27 (2.8%)
Stroke									
	Yes (184)	31 (16.8%)	28 (15.2%)	40 (21.7%)	9 (4.9%)	52 (28.3%)	57 (31.0%)	9 (4.9%)	14 (7.6%)
	No (1084)	199 (18.4%)	232 (21.4%)	220 (20.3%)	32 (3.0%)	291 (26.8%)	328 (30.3%)	38 (3.5%)	39 (3.6%)

* Proportions for each cell represent the number of those who are prescribed an EBT e.g. ACEI/ARBs for each category e.g. men. For example, the proportion for men who are prescribed ACEI/ARBs within 30 days after 1st diagnosis is 154, the total men who survived 30 days after 1st diagnosis 796 (prescribed and not prescribed ACEI/ARBs): 154/796 x 100=19.3%. For the same drug and category, those not prescribed ACEI/ARBs 642: 642/796 x 100=80.7%.

5.4.1.7 Slope index of inequalities (SII) and relative index of inequalities (RII)

In this study SII and RII were used to measure the socioeconomic relationship between the prescribing of EBTs within 30 days after hospital discharge of PAD/CHD.

As can be seen in Tables 55 and 56, most of the absolute and relative index of inequalities are small in magnitude across the classes of EBTs (values close to 0 and 1, respectively) and not statistically significant, indicating not much evidence of inequality in the prescribing of EBTs in terms of socioeconomic deprivation. However, ACEI/ARBs are statistically significant in the absolute and relative index of inequality, which indicates inequality in prescribing this drug group.

Table 55 Relative index of inequality (RII) for PAD/CHD

	RII (95% CI)	P value
ACEI/ARBs	1.59 (1.07-2.37)	0.02
β-blockers	0.94 (0.63-1.41)	0.8
CCB	1.09 (0.76-1.55)	0.6
PAV	0.8 (0.32-2.07)	0.6
Statins	1.14 (0.81-1.61)	0.4
Aspirin	1.20 (0.92-1.56)	0.2
Clopidogrel	1.65 (0.74-3.62)	0.2
Oral anticoagulant	1.31 (0.44-3.94)	0.6

Table 56 Slope index of inequality (SII) for PAD/CHD

	SII (95% CI)	P value
ACEI/ARBs	0.08 (0.02-0.15)	0.01
β-blockers	-0.01 (-0.1-0.06)	0.7
CCB	0.03 (-.04-0.11)	0.4
PVD	0.01 (-0.02-0.04)	0.5
Statins	0.01 (-0.08-0.11)	0.7
Aspirin	0.05 (-0.01-0.12)	0.1
Clopidogrel	0.02 (-0.03-0.06)	0.4
Oral anticoagulant	0.01 (-0.03-0.63)	0.5

5.4.1.8 Goodness of fit tests for PAD/CHD

As can be seen in Table 57, the majority of ROC values for the EBTs ranged between 0.7 and 0.9 which shows acceptable and good discrimination. The Hosmer-Lemeshow test p value was >0.05 for all medications indicating good model fit for all of the medications for those with PAD and CHD. Furthermore, sensitivity analyses (using 10 groups for the test) showed good model fit as well.

Table 57 ROC and Hosmer-Lemeshow

	ROC P value	Hosmer-Lemeshow group (5) P value	Hosmer-Lemeshow group (10) P value
ACEI/ARBs	0.85	0.40	0.85
β-blockers	0.82	0.87	0.89
CCB	0.83	0.41	0.24
PVD	0.85	0.74	0.66
Statins	0.83	0.42	0.30
Aspirin	0.72	0.19	0.50
Clopidogrel	0.91	0.24	0.40
Oral anticoagulant	0.90	0.25	0.14

5.4.2 Summary

5.4.2.1 Incidence of peripheral arterial disease

A study from Edinburgh[417] was conducted in 1988 and randomly recruited 1592 subjects aged 55-74 years from 10 general practices. Patients were followed up prospectively to 5 years. The Edinburgh artery study was associated with higher incidence rate of intermittent claudication (15.5/1000) compared to the most matched year of this study "1999" (2.05/1000).

5.4.2.2 Age differences in prescribing EBTs after a first PAD, PAD/CHD

In the isolated PAD group, prescribing of β-blockers, statins and aspirin was significantly influenced by age. However, with CHD it was only significant for oral anticoagulants. Two studies, using unadjusted analysis, examined age differences in prescribing EBTs for PAD. The Paquet *et al.* study[336] showed higher proportion of ACEI, antiplatelet and statins among young compared to old patients, however, another study (n=89)[337] had a conflicting result for statins (old 33% vs. 13.0% for young). In this study the percentage of prescribing statins was higher among young than old patients, whereas it was similar for ACEI/ARBs.

5.4.2.3 Sex association in prescribing EBTs after first PAD, PAD/CHD

In this study, for most EBT classes, the odds of prescribing for patients with isolated PAD are lower in men than in women, but were only statistically significant for statins (OR 0.73; 95% CI 0.57 to 0.95, p=0.01). In contrast, in patients diagnosed with CHD, men were associated with higher odds of being prescribed most EBTs than women, Table 24 and Table 33. Men with CHD were significantly more often prescribed statins than women (OR 1.41; 95% CI 1.02-1.93, p=0.03). In the earlier sections for MI and angina men were more likely to receive EBTs which can explain the difference here between isolated and non-isolated PAD. Few studies, using unadjusted analysis, examined sex differences in prescribing EBTs for PAD.[338,339] In this study, the proportion of prescribing EBTs in patients with isolated PAD was higher among women than men, except for anticoagulants. Three studies were congruent with this study and showed that prescribing of statins or LLD was higher among women than men,[338,339] however, one reported that men had higher proportions of statin prescriptions than women.[336]

5.4.2.4 Socioeconomic status association in prescribing EBTs after first PAD, PAD/CHD

This study found that there was evidence for significant differences in prescribing PVD by socioeconomic deprivation status for isolated PAD and in prescribing ACEI/ARBs for PAD/CHD. Although the percentage differences in prescribing PVD for isolated PAD were small, it was relatively significant (0.03) after adjustment. On the other hand, there was no evidence for significant differences in prescribing by socioeconomic deprivation status for other EBTs. Only one study,[340] using adjusted analysis, matched these results and showed no significant difference in prescribing antiplatelet and statins between low and high socioeconomic status. However, unadjusted RR showed that the risk of being prescribed antiplatelet and statins was significantly lower among low than high socioeconomic status.

5.4.2.5 Trends of prescribing EBTs after a first PAD, PAD/CHD over time

Prescribing was increased over the study period for all EBTs in both isolated PAD or in PAD/CHD. In this study, prescribing of ACEI/ARBs and β-blockers for PAD was lower than two previous studies,[316,341] however it was higher for statins.[316,336,341] One study showed a higher increase of statins prescriptions over the years than this study.[343] Subherwal *et al.*'s study[342] described prescribing of cardioprotective medication in patients diagnosed with PAD alone, PAD with CHD and CHD alone. Trends of prescribing (within the first 3 months after diagnosis for Subherwal *et al.*'s study and within 30 days after diagnosis for this study) over the period for both studies were increased in all study groups. In my study the use of statins in isolated PAD group increased from 1.1% in 1997 to 31.2% in 2005 (30.1% change over the years, $P<0.001$), and in the PAD/CHD group from 6.3% in 1997 to 36.1% in 2005 (29.8% change over the years, $P=0.006$). In the Subherwal *et al.* study prescribing of statins for isolated PAD increased from 9% in 2000 to 56% in 2007 (47% change, $P<0.0001$), and approximately from 28% in 2000 to 72% for PAD/CHD.

5.4.2.6 Comorbidities association in prescribing EBTs after first PAD, PAD/CHD

In my analyses, several concomitant diseases have been included to identify their influence in prescribing EBTs after angina. Only one previous study examined the influence of comorbidities in prescribing EBTs after PAD. It showed that, from unadjusted analysis, the percentage of prescribing for statins was higher in patients with hypertension and diabetes than those without relevant disease. Concomitant CHD with other comorbidities in patients recently diagnosed with PAD can alter the choice of drug, such as β-blockers, which was significant in patients with CHD (OR 1.39; 95% CI 1.01-1.93), however, it disappeared in isolated PAD (OR 1.00; 95% CI 0.69-1.45).

Summary

Prescribing EBTs within 30 days after a first PAD and PAD/CHD improved over the time, however it remains suboptimal. Sex differences in prescribing EBTs associated with conflicting results between isolated and concomitant CHD analysis. Influence of socioeconomic status has been seen with PAD analysis; however, this was not found in MI and angina patient groups. Prescribing of statins and aspirin are associated with greatest increases since 1997. Concomitant CHD may influence the choice of drug in PAD treatment.

6.0 Overall discussion

Summary of key findings

Several studies have investigated the prescribing of EBTs after a diagnosis of MI. These studies show conflicting results for the nature of the association between prescribing EBTs and age, sex, socioeconomic status and comorbidities. However, all studies have demonstrated that prescribing of EBTs has improved over time. This is the first study to examine the association between prescribing EBTs and age, sex, socioeconomic status, comorbidities and trends over time in one single population. This study also adjusted for many covariates and prescribing for all recommended, evidence-based, secondary prevention was examined. Prescribing within 30 days post MI was examined to ensure that all patients had enough time to collect their prescriptions from their GPs. I also examined prescribing after a first event so as to get clarity about prescribing for a particular episode and avoid confusion as to whether recommended treatments might have been given for another event.

This study aimed to describe the associations between prescribing EBTs (within 30 days after first diagnosis with MI, angina and PAD) and several factors including sex, age, socioeconomic status and concomitant disease, as well as examining the trend of prescribing EBTs over the study period. Prescribing of EBTs has improved over time in Scotland. Prescribing over the study period (1997-2005) showed a steady increase for most of EBTs for all conditions examined. However, although prescribing has improved, it remains low. To illustrate, the most commonly prescribed EBTs for MI was β-blockers (19.2%) and in 2005 the percentage of prescribing was (43.4%). Factors (sex, age, socioeconomic status and comorbidities) have been examined to identify their association with prescribing EBTs. Sex, age, socioeconomic status and comorbidities were examined in relation to prescribing EBTs after first diagnosis for MI, angina, PAD and PAD/CHD. Older age (≥ 85years old) was associated with lower rate of being prescribed EBTs compared to younger patients. Male sex was associated with higher prescription EBTs than female sex, however, differences were not always significant. Socioeconomic status had little influence on prescribing of EBTs across all patient categories. However, comorbidities were associated with varied differences in prescribing EBTs for all conditions.

Patient selection bias

This study was subject to selection bias as I have excluded those who died within 30 days and had a prescription of EBTs after first diagnosis of MI, angina or PAD. Although bias may affect the validity of the result, the number of patients excluded from the analyses was acceptably low (857 for MI, 99 for angina, 147 for isolated PAD and 83 for those with PAD and CHD). These tables (19, 29, 40 and 49) showed that the number of patients who died before getting a prescription is higher than those who died and had had a prescription. Therefore excluding those who died did not exclude people who had also had a prescription. Therefore, the decision made to exclude these patients is likely to have very little effect on the absolute rates and relative rates described in the thesis.

6.1 Prescribing of EBTs

The differences in prescribing EBTs after first diagnosis of MI, angina, isolated PAD and PAD/CH varied according to the factors that have been examined in this study. In the previous studies there was a wide variability in time of determining prescribing EBTs, for example, some studies used three months, or six months to examine prescribing inequality. In this study I have used 30 days after first diagnosis as time frame to examine prescribing EBTs inequality for sex, age, socioeconomic status and comorbidities. The rationales behind that were, firstly, because all guidelines recommended that patients diagnosed with these diseases should be discharged from hospital with a prescription for EBTs, unless contraindicated, to control symptoms, reduce progression, reduce the risk for further cardiovascular disease, and to reduce the risk of morbidity and mortality. Secondly, to get as many patients considering it might take them a while to fill the prescription and get on these therapies. Furthermore, because I have restricted the analysis to those who survived for 30 days to avoid losing more patients due to mortality, I have examined prescribing EBTs within 30 days after first diagnosis. One more reason is that these therapies can be prescribed for any other cardiovascular disease, so using a different time point may increase the chance of being prescribed for other diseases.

Age groups were examined in this study to identify whether age differences in prescribing EBTs is evident. This study shows similar results to the majority of the prior literature in suggesting that older patients are less commonly prescribed EBTs than younger patients. This fact has been recognised for all cohorts included in this study, i.e. MI, angina, PAD, PAD/CHD. There was a dramatic difference between younger and older patients in prescribing β-blockers and statins, however, this not the case with ACEI/ARBs (appendix

7). This can be due to a specific comorbidity, for example patients with HF can establish treatment just when their disease becomes stable. Increase in age is associated with an increased risk of multiple comorbidities which consequently may decrease the opportunity of being prescribed EBTs due to contraindications. This is one hypothesis for fewer EBTs prescriptions for older patients, however, in the current study, for all cohorts, the results were adjusted for several "common" associated comorbidities. Increased comorbidities with age associated with a high chance of using different drug groups, consequently this increased the risk of drug–drug interaction. Older patients were more likely to be treated therapeutically rather than surgically, so they should benefit from the EBTs secondary preventive therapy. The lower use of some EBTs in older patients with CHD (e.g. statins) has been explained as due to prescriber perception that statins are less effective or less cost effective in older patients.

Similar to most prior literature, rates of prescribing EBTs for women were less common compared to men for all cohorts (appendix 7). This can be interpreted as that women with CHD tend to be 7 to 10 years older than men, i.e. age effect. Also women are more sensitive than men and tend to not tolerate side effects. In this study the difference in prescribing EBTs between men and women was narrowed after adjustment. Men were significantly more likely to receive β-blockers, ACEI/ARBs and statins than women in MI, angina and PAD/CHD, respectively. Although guidelines and clinical trials showed that both sexes benefit from the EBTs secondary preventive therapy, inequalities exist. In this study I did not have any information about the disease severity. Angina and PAD are commonly diagnosed in GPs, so may lack the most recent updated information in practitioners attributed to prescribing discrepancies.

Scottish Index of Multiple Deprivation (SIMD) score was used in this study to examine inequalities in prescribing EBTs between the most and least deprived patients recently diagnosed with MI, angina or PAD. Generally no significant differences were found in prescribing EBTs across deprivation quintiles in Scotland. This is matched to the report of Simpson *et al.* which showed no differences in prescribing EBTs between the most and least deprived CHD patients. Simpson *et al.*[223] used CMR data sets, which are a part of the datasets I used in my research, however, he analysed all patients diagnosed with CHD, irrespective of whether it was a first event or recurrent diagnosis. Furthermore, prescribed medications were assessed at any time point after diagnosis. The similarity in prescribing EBTs among all deprivation quintiles may be attributed to the Scottish health care system. This provided free prescriptions to those who were on low incomes or with chronic

diseases. The provision of these free prescriptions (or lower cost prescriptions through the use of a pre-payment scheme) may be why there was little difference in prescribing rates across socioeconomic groups. Influence of socioeconomic status was obvious in countries that do not provide free drug prescriptions for patients diagnosed with chronic disease.

In this study numerous comorbidities were included in the model to examine their influence in prescribing EBTs after first diagnosis, whereas most previous studies involved fewer numbers of comorbidities. Most of the included comorbidities were associated to different tendencies in prescribing EBTs. These associations may affect positively in prescribing EBTs such as ACEI/ARBs in patients with a history of HF, while some other comorbidities may influence prescribing negatively due to certain medication contraindication such as β-blockers with airway obstructive disease. Previous studies showed similar influence of examined comorbidities in prescribing EBTs.

Prescribing over the study time was increased for almost all medications, albeit with different trend patterns. Statins were the drug associated with the highest increase of prescribing from 1997 to 2005. This finding is similar to most of the previous studies. This huge increase in prescribing of statins can be related to the influence of clinical trials such as 4S trials. Generally most of the prior studies reported different rates of improvement in prescribing of EBTs for CHD, MI, angina and PAD, however the rates remained low. The rate of prescribing EBTs within 30 days is lower in this study compared to others, however, prescribing rates at any time point (e.g. for MI) show much better trends and are similar to the prior studies (Appendix 8).

CHD is one of the main causes of death in many Western countries such as Scotland. Studies have demonstrated that mortality rates for men due to CHD have fallen from 460 per 100,000 population in 1979 to 136 per 100,000 population in 2010, and fallen for women from 208 to 64 per 100,000 population.[418] A number of studies have suggested that 45-75% of these falls in mortality are due to declines in the major risk factors for CHD such as smoking and hypertension. Furthermore, they also suggest that the use of EBTs decreased death rates by 25-55%.[417] In Scotland, Hotchkiss *et al.* reported that the death rate due to CHD declined in adults aged 25 years and more by 43% between 2000 and 2010. Improvement in medical treatment use was attributed as causing a 40% reduction in CHD mortality in Scotland. Lipid lowering drugs, particularly statins, are attributed to 13% of the fall in total CHD mortality, followed by the use of secondary prevention therapies after MI (9%).[417] Hotchkiss *et al.*[417] and O'Flaherty *et al.*[418] demonstrated that the mortality rate due to CHD is higher among the most deprived compared to the least

deprived. One study examined the variation of death from CHD by day in Scotland.[419] This study showed a significant day of the week variation in death due to CHD ($p < 0.001$), with higher rate on Monday (3.1% above the daily average).

The prescribing of primary and secondary preventative medications has improved over time. This has occurred as the result of key randomised controlled clinical trials being published that have led to a change in practice. A number of key trials were published during the period leading up to and during the study period. These are listed in Table 58. While many of these medications were used in the treatment of CVD prior to the publication of these trials, as can be seen, the role of each of these medications was confirmed by trials prior to the period of the study. Therefore, there is likely to be little influence on the results as a consequence of new evidence.

Table 58 Major primary and secondary prevention trials for MI, angina and PAD

	Antiplatelet	**β-blockers**	**ACEI**	**Statins**
MI	CAPRIE (1996) CURE (2000) SIS2 (1987)	NMS (1985) BHAT (1982) ISIS1 (1986)	SAVE (1992) AIRE (1993)	4S (1994) CARE (1991) LIPD (1998)
Angina	SAPAT (1992)	ASIST (1994)	HOPE (2000) EUROPA (2003)	HPS (2002) LIPD (1998)
PAD	CAPRIE	----	HOPE (2000)	4S (1994) HPS (2002) WOSCOPS (1995) AFCAPS/ TexCAPS (1998)

Other external influences could have made an impact on the changes in prescribing practice reported here. The Quality Outcomes Framework was introduced to incentivize general practices to adhere to certain standards, including prescribing standards. The impact of the QOF is likely to be minimal in the data used in this thesis as the first QOF exercise was conducted in April 2004, at the end of the study period. I did not observe any large step changes in prescribing practice in the period preceding this or around that time that would suggest that the introduction of QOF influenced the trends in prescribing observed.

Finally, changes in the methods of diagnosis may have influenced the results reported here. The diagnosis of angina and PAD has not changed dramatically over the time period studied. However, towards the end of the study period new biomarkers were introduced to detect MI. The troponin assay is a much more sensitive and specific marker of MI than the previous biomarker of creatinine kinase (CK) and cardiac mitochondrial creatinine kinase

(CK-MB). The use of troponin has made it possible to detect smaller MIs but they were only widely used at the end of the study period from 2001 onwards in Scotland. While the inclusion of more cases with less severe infarction may lead to the inclusion of individuals less likely to receive treatment would decrease rates. I found the opposite trend rates increased over this period and there was no major change in the prescribing of drugs at this time during the study period.

Prescribing of EBTs was modestly higher after first diagnosis with MI, however, it was lower in patients with angina and PAD. Patients with angina and PAD are more likely to be diagnosed for the first time in the GP and this may explain why this group of patients are associated with a lower rate of secondary preventions EBTs. Also, this theory may be supported by looking at the prescribing at any time (appendix 7) where it is shown that all EBTs prescriptions were increased at least twofold, this may be related to either these patients developing other cardiovascular diseases or being referred to a specialist. This study highlighted a very important public health message in prescribing of secondary prevention EBTs for patients with isolated PAD as these recommended medications were poorly prescribed compared to other cardiovascular diseases. Patients with isolated PAD are at risk of developing any other cardiovascular diseases so they should be prescribed prophylactic EBTs. As mentioned above, this group is mostly diagnosed in GP, so this tendency may be due to a lack of practitioners' information for updated guidelines in the management of these diseases (e.g. PAD affects their decisions on prescribing EBTs).

Study implications

Although clinical trials have shown that these EBTs reduce morbidity and mortality, they are still underused as demonstrated in these analyses. This has a number of implications for patients and the health care professionals looking after them. The most important implication of my findings is for patients who are not receiving appropriate secondary preventative therapies. This means that a large number of people are not benefiting from a potential reduction in risk with appropriate medication. This leads to potentially preventable morbidity and mortality. The reasons for this sub optimal prescribing rate will be due to a number of patient and health care professional related factors. While a number of patients will have a contra-indication to certain medications, the large proportion of patients not on particular EBTs, and the variation by diagnosis, suggests that other factors are involved in the low rate of prescription. These factors cannot be determined from this study but may be due to patient choice as patients may be unwilling to take another medication on top of those that they already take. They may also experience side effects that mean that they are unable to tolerate the drug. Such factors are hard to change except for educating patients as to the potential benefits of particular EBTs. Whatever the patient factors are for the low rate of prescribing they are undoubtedly not the only factor – health care provider related factors are certainly a cause as well. The results of this study have greater implications for health care providers and prescribers as they are responsible for suggesting the correct EBTs for a patient.

Although prescribing rates rose during the period studied suggesting that improvements have occurred, the rates are still low. This gap in prescribing suggests that there is still much to be done in improving prescribing practice. Improving prescribing can be achieved through a number of mechanisms. Use of electronic records that prompt physicians to prescribe certain drugs for a certain diagnosis can be effective.[421] Training and education is also potentially useful, especially in the setting of smaller practices.[422]. Using pharmacists in the community to help increase prescribing and optimise dosing may also be used.[423] However, whether these interventions translate into improvements in outcomes are uncertain.[423]

Increased prescribing of EBTs may have beneficial effects on morbidity and mortality, however, there may be unintended consequences of more prescribing. Prescribing of more drugs may increase the rate of side effects experienced by patients. There may also be a rise in the number of significant drug interactions that occur as a result of more

medications being prescribed. The rate of adverse events with EBTs may also increase, for example bleeding in patients receiving an anticoagulant. However, these are not reasons to avoid prescribing but rather employ good prescribing practice such as checking for known drug interactions and monitoring for adverse effects. Similarly, the risk of adverse effects such as bleeding with anticoagulants can be reduced by the use of scores to identify high risk patients.[424]

7.0 Strengths and Limitations

This cohort study included a large sample of patients with a first diagnosis of a CVD (MI, angina and PAD). I used this linked dataset of primary and secondary care, which allowed me to follow patients in primary care after hospital discharge. The linked dataset also provided a longitudinal study design so the first (incident) diagnosis could be identified and patients could then be followed forwards and backwards for analysis. Furthermore, linkage to the GROS allowed those patients who died shortly after a first diagnosis to be removed from further analysis. The majority of prior studies that have examined prescribing inequalities were restricted to either primary or secondary care datasets, limiting their size. They were therefore also unable to find the first diagnosis irrespective of whether this happened in primary or secondary care in contrast to my analyses where this time point could be identified.

A further strength of the dataset that I analysed was that data on prescriptions was taken directly from the electronic system. This removed the potential for recall-bias. Prior studies in the literature have relied on patient self-reported prescribing data. These studies are therefore prone to recall-bias and the accuracy of the results can be questioned.

In my research I examined the influence of several factors on prescribing of EBTs, which has not been done before. Several variables were included in the model for statistical analysis (age sex, socioeconomic status, time, comorbidities and previous prescribing) to minimise confounding. I adjusted for the following comorbidities: a history of COPD/asthma, AF, hypertension, diabetes, cancer, renal failure, HF, PAD, stroke and angina. In contrast, a number of prior studies either did not adjust their analyses for comorbidities or restricted their adjustment to one or two comorbidities such as diabetes or renal failure only.[267,269] However, many diseases can confound the prescribing of EBTs due to contraindications such as ACEIs in patients with renal failure. Therefore, a strength of this study in comparison to the prior literature is that I have included a wide range of

comorbidities to adjust for these confounding diagnoses that may have influenced prescribing patterns.

Another strength of this study is that it included all recommended secondary prevention therapies. Many studies have focused on only one or two therapies.[219,221,227] This study describes the wide range of medications used in the secondary prevention of MI, angina and PAD. A further strength in comparison to the prior literature is that I examined prescribing in relation to a number of cardiovascular diseases in the same cohort. This allowed me to make comparisons between different diagnoses. Prior studies have focussed on one diagnosis at a time, making comparisons difficult.[326,328]

This study, like any work, has some points of weakness. The Secondary Care data set (SMR) does not provide patients' medications at time of discharge, which can only be obtained from the Primary Care datasets "GPs". Therefore, actual data users do not know what patients were prescribed at the point of hospital discharge. On another hand, for chronic serious diseases, such as MI, patients are at high risk of death, which may lead to miss some patients in the analysis if they died before a GP visit. Although MI is an emergency case and would usually be diagnosed and treated in hospital, in this study a number of patients were recorded as being diagnosed in the Primary Care. There is no marker for disease severity, and only ICD/Read codes classifications are available. There is also uncertainty regarding incidence of diagnosis for the early study period because I have no data available before 1997. Although this study adjusted for most common cardiovascular disease, further confounders may be missed such as prescriber and the rationales behind non-prescribed EBTs. Another limitation is that multiple tests have been conducted in this research and because of the well recognised multiple comparisons problem, some of the statistically significant associations could be spurious. The majority of patients with angina and PAD were diagnosed in GPs and not necessarily confirmed by definitive investigations.

As I have discussed in relation to the previously published literature, bias is inherent in any observational study. The present analyses are no exception to this. To study prescribing at a time point patients naturally need to survive to this point. This leads to a survivor bias. As I have shown the patients who survived to 30 days were similar to those who died without a prescription and the numbers were small, limiting this bias. There is also the possibility of recording bias. Prescriptions may have been incorrectly recorded. However, prior audits have reported that the accuracy of prescribing data in CMR is practically 100%.[366] Case ascertainment bias is perhaps the largest bias in this study. While the

accuracy of cardiovascular diagnoses is high in SMR and CMR it is not 100%. Therefore bias caused by case ascertainment is present though it is low, given that the accuracy of cardiovascular diagnoses is high.

One limitation of the dataset is that I could not account for the type of practices included. For example as discussed in section 4.1.3.2 Validity of the CMR datasets, a number of practices are likely to have been training practices or have Practices Accreditation (PA) or a Quality Practice Award (QPA). Although I used clustered standard errors in the analysis to try to account for this I was unable to fully adjust for these differences.

Unfortunately, Hosmer-Lemeshow tests demonstrated that the logistic regression models were not always well calibrated, and sensitive to choice of number of groups used in the test. Calibration was best for PAD/CHD models and worst for angina models. The poor lack of fit for angina may be due to angina diagnosis being more heterogeneous in terms of severity, i.e. how severe is the angina. Furthermore, results in this study adjusted for limited variables.

One assumption made during this thesis is that the baseline characteristics represent a lifetime risk. I have examined prescribing in a relatively short time period. Therefore there is little expectation that important baseline characteristics will change to a degree to affect the results. However, in future studies, it must be remembered that characteristics can change over time and these changes may influence the results. I did not have any data on smoking or lifestyle factors to adjust for in the models. These data are not recorded by CMR.

In this study patients that did not survive 30 days after hospital discharge was excluded from the analysis, which certainly led to selection bias. I have discussed and justified this issue early in this study.

8.0 Future research

This study can be used as a basis for further analysis. More work to identify the influence of the used factors in prescribing EBTs for other chronic disease such as HF, atrial fibrillation or stroke can be established. Further factors that may influence prescribing can also be included such as race, physicians' gender or speciality, and physicians' years of experience. Since this study was focused on identifying the existence of prescribing inequality, the reasons behind that should be investigated in future. Further prospective studies can be useful to follow patients from the time of hospital admission to the day of discharge. In such studies investigators can obtain medications at time of discharge, severity of disease and ensure a thorough medical history for a particular disease is obtained. More analysis should be carried out to examine whether the prescribed drug doses match the doses used in the clinical trials. In addition, reasons for not prescribing any recommended EBTs should be detailed and records should be kept of any prescribed – if any – alternative therapy.

9.0 Conclusion

This study shows that inequalities of prescribing EBTs exist in Scotland. Prescribing within 30 days varied by sex, age and comorbidities but not by socioeconomic status.

Although clinical trials have demonstrated the efficacy of a number of EBTs in preventing events after a MI irrespective of the age, older patients, particularly those aged over 85 years, were significantly less commonly prescribed EBTs, e.g. β-blockers and ACEIs. Furthermore, they were less commonly prescribed risk lowering drugs such as statins. Lower prescribing of EBTs for older patients (≥ 85 years) was also seen after a patient had a diagnosis of angina or PAD. Although older individuals are more likely to have multiple comorbidities, I found that these age inequalities persisted even after adjusting for a number of comorbidities.

Prescribing of EBTs was higher in men compared to women after a first MI, angina and PAD/CHD. However, these differences were statistically significant for only a few medications. In patients with a MI or angina men were significantly more likely to be prescribed β-blockers and ACEI/ARBs, respectively. However, in contrast, the prescribing of EBTs was lower among men than women after diagnosis of PAD. The prescribing of statins after a diagnosis of PAD was significantly less common in men than women, however, there was no significant differences between men and women in prescribing of other EBTs.

My review of the literature found numerous studies reporting that there were differences in prescribing of EBTs in the least and most deprived patients in several countries. I did not find any evidence of a significant difference in the prescribing of EBTs by socioeconomic status, i.e. between least and most deprived patients, after first diagnosis of MI, angina, PAD and PAD/CHD. This may be due to the National Health Service in Scotland and the availability of free health care in comparison to other countries where socioeconomic differences in prescribing rates have been reported.

In this study I adjusted for a number of comorbidities. These included a history of COPD/asthma, AF, hypertension, diabetes, cancer, renal failure, HF, PAD, stroke and angina which are all known confounders of prescribing patterns as they may increase or decrease the rate of prescribing due to positive indications or contraindications respectively. I have shown that comorbidity influences the prescribing of different EBTs. Prescribing of drugs that also lower blood pressure, e.g. β-blockers or ACEI/ARBs after a

first diagnosis of MI or angina was higher in patients with hypertension. However, prescribing of β-blockers or ACEI/ARBs declined in patients with asthma or renal failure, respectively as these are contraindications to their use. I also found that some comorbidities may lead to the use of an alternative drug, for example patients with AF were more likely to be prescribed an oral anticoagulant (warfarin) instead of aspirin.

This study examined the prescribing trend of EBTs from 1997 to 2005. The results suggest that prescribing EBTs within 30 days after first diagnosis, although increasing over time, remains low. However, further studies are required to determine whether these trends have continued and whether further efforts to improve prescribing are needed.

This study highlighted an important and neglected disease. Although PAD is associated with significant morbidity and mortality, the rate of prescribing of EBTs was very low. Further studies are required to understand why this population are so under-prescribed EBTs and how we might change this finding.

Finally, the results of this study would suggest that more studies examining other chronic diseases such as HF, atrial fibrillation and asthma should be conducted to examine prescribing inequalities and trends. The low rates of prescribing and inequalities in prescribing that I have described need to be addressed. The information from these analyses can be used to identify those patients who are least likely to receive appropriate EBTs, e.g. the elderly, women and those with comorbidities. This may help prescribers identify such patients so that they can be specifically targeted for review of their medications to ensure they are on as many EBTs as indicated or tolerated. The information could also be used by public health care professionals to target interventions or resources such as community pharmacists to these groups of patients to maximise prescribing of EBTs. Through identifying those at risk of low prescribing rates or EBTs, I hope that prescribing rates can improve generally which will hopefully translate to improved outcomes for these patient populations.

Appendices

Appendix 1

Searching literature key words

Key words	Main word	Synonyms
1- Factors	Age	Older, young
	Sex	Gender, male, female, men, women
	Socioeconomic	Poor, low income, lower income
	Time	Time trends, temporal, decade, trends
	Comorbidities	
Result of search	2787266 English articles	
2- Evidence based	Evidence based	Heart protection, cardiac protective, cardio protective, therapy, secondary prevention, pharmacotherapy, beta blocker, calcium channel blocker, statins, angiotensin converting enzyme inhibitors, angiotensin receptor blocker, ACEI, ARBs, aspirin, clopidogrel, anticoagulant, Warfarin, cilostazol, naftidrofuryl, pentoxifylline, loop diuretics, thiazide diuretics, statins, lipid lowering drugs
Result of search	1037318 English articles	
3- Prescribing	Prescribing	Missed opportunity, lower use, lower prescribing, use, utilisation, utilization, prescription, inequalities, underuse
Result of search	69202 English articles	
4- Myocardial infarction	MI	myocardial infarction, heart attack, cardiac arrest
Result of search	129064 English articles	
5- Angina	Angina	Angina, angina pectoris, stable coronary artery disease
Result of search	33106 English articles	
6- Peripheral artery disease (PAD)	Peripheral artery disease	peripheral arterial disease, PAD, peripheral vascular disease, PVD, intermittent claudication, peripheral artery disease, lower extremity peripheral artery disease, lower limb peripheral arterial disease, lower extremity peripheral arterial disease, lower limb peripheral arterial disease
Result of search	25179 English articles	
7- Coronary heart disease (CHD)	CHD	Coronary heart disease[Title/Abstract] OR Ischemic

		heart disease, ischaemic heart disease, coronary artery disease, acute coronary syndrome
Result of search	100304 English articles	
8- Comorbidities		chronic obstructive pulmonary disease, COPD, asthma, hypertension, atrial fibrillation, diabetes, diabetes mellitus, heart failure, cancer, renal failure
Result of search	1429789 English articles	

Key words:

1- Factors2

((((((((((age[Title/Abstract] OR older[Title/Abstract]) OR young[Title/Abstract]) OR sex[Title/Abstract]) OR gender[Title/Abstract]) OR male[Title/Abstract]) OR female[Title/Abstract]) OR men[Title/Abstract]) OR women[Title/Abstract]) OR socioeconomic[Title/Abstract]) OR poor[Title/Abstract]) OR low income[Title/Abstract]) OR lower income[Title/Abstract]) OR low income[Title/Abstract] OR temporal[Title/Abstract] OR time trends[Title/Abstract] OR decade[Title/Abstract] OR trends[Title/Abstract] OR comorbidities[Title/Abstract] OR mortality[Title/Abstract]

English (2787266)

2- Evidence based 2

((((((((((((((((((((((evidence based[Title/Abstract] OR heart protection[Title/Abstract]) OR cardioprotective[Title/Abstract]) OR cardiac protective[Title/Abstract]) OR therapy[Title/Abstract]) OR secondary prevention[Title/Abstract]) OR pharmacotherapy[Title/Abstract]) OR beta blocker[Title/Abstract]) OR calcium channel blocker[Title/Abstract]) OR aspirin[Title/Abstract]) OR statins[Title/Abstract]) OR angiotensin converting enzyme inhibitors[Title/Abstract]) OR angiotensin receptor blockers[Title/Abstract]) OR ARBs[Title/Abstract]) OR ACEI[Title/Abstract]) OR clopidogrel[Title/Abstract]) OR anticoagulant[Title/Abstract]) OR warfarin[Title/Abstract]) OR CILOSTAZOL[Title/Abstract]) OR naftidrofuryl[Title/Abstract]) OR PENTOXIFYLLINE[Title/Abstract]) OR loop diuretics[Title/Abstract]) OR thiazide diuretics[Title/Abstract]) OR lipid lowering drugs[Title/Abstract]) OR peripheral vasodilators[Title/Abstract]) OR beta blockers[Title/Abstract] OR calcium channel blockers[Title/Abstract]

English (1037318)

3- Prescribing2

(((prescribing[Title/Abstract] OR missed opportunity[Title/Abstract]) OR lower use[Title/Abstract]) OR lower prescribing[Title/Abstract]) OR use[Title/Abstract] OR prescription[Title/Abstract] OR inequalities[Title/Abstract] OR utilisation[Title/Abstract] OR underuse[Title/Abstract]

English (69202)

4- Myocardial infarction (MI)

((myocardial infarction[Title/Abstract] OR heart attack[Title/Abstract]) OR cardiac arrest[Title/Abstract]) OR MI[Title/Abstract]

English (129064)

5- Angina

(angina[Title/Abstract] OR angina pectoris[Title/Abstract]) OR stable coronary artery disease[Title/Abstract]

English (33106)

6- Coronary heart disease (CHD)

(((Coronary heart disease[Title/Abstract] OR Ischemic heart disease[Title/Abstract]) OR ischaemic heart disease[Title/Abstract]) OR coronary artery disease[Title/Abstract]) OR acute coronary syndrome[Title/Abstract]

English (100304)

7- Peripheral artery disease (PAD2)

(((((((peripheral arterial disease[Title/Abstract] OR PAD[Title/Abstract]) OR peripheral vascular disease[Title/Abstract]) OR PVD[Title/Abstract]) OR intermittent claudication[Title/Abstract]) OR peripheral artery disease[Title/Abstract]) OR lower extremity peripheral artery disease[Title/Abstract]) OR lower limb peripheral arterial disease[Title/Abstract]) OR lower extremity peripheral arterial disease[Title/Abstract]) OR lower limb peripheral arterial disease[Title/Abstract]

English (25179)

8- Comorbidities

(((((((chronic obstructive pulmonary disease[Title/Abstract] OR COPD[Title/Abstract]) OR asthma[Title/Abstract]) OR hypertension[Title/Abstract]) OR atrial fibrillation[Title/Abstract]) OR diabetes[Title/Abstract]) OR diabetes mellitus[Title/Abstract]) OR heart failure[Title/Abstract]) OR cancer[Title/Abstract]) OR renal failure[Title/Abstract]

English (1429789)

9- MI+Angina+CHD

((((((((((Coronary heart disease[Title/Abstract] OR ischaemic heart disease[Title/Abstract]) OR Ischemic heart disease[Title/Abstract]) OR coronary artery disease[Title/Abstract]) OR acute coronary syndrome[Title/Abstract]) OR angina[Title/Abstract]) OR angina pectoris[Title/Abstract]) OR stable coronary artery disease[Title/Abstract]) OR myocardial infarction[Title/Abstract]) OR cardiac arrest[Title/Abstract]) OR heart attack[Title/Abstract]) OR MI[Title/Abstract]

English (223980)

10- MI+Angina+CHD+PAD

((((((((((((((((((Coronary heart disease[Title/Abstract] OR Ischemic heart disease[Title/Abstract]) OR ischaemic heart disease[Title/Abstract]) OR coronary artery

disease[Title/Abstract]) OR disease[Title/Abstract]) OR stable coronary artery disease[Title/Abstract]) OR acute coronary syndrome[Title/Abstract]) OR angina pectoris[Title/Abstract]) OR angina[Title/Abstract]) OR cardiac arrest[Title/Abstract]) OR heart attack[Title/Abstract]) OR myocardial infarction[Title/Abstract]) OR MI[Title/Abstract]) OR peripheral arterial disease[Title/Abstract]) OR peripheral vascular disease[Title/Abstract]) OR PVD[Title/Abstract]) OR peripheral artery disease[Title/Abstract]) OR lower extremity peripheral artery disease[Title/Abstract]) OR lower limb peripheral arterial disease[Title/Abstract]) OR lower extremity peripheral arterial disease[Title/Abstract]) OR lower limb peripheral arterial disease[Title/Abstract]) OR intermittent claudication[Title/Abstract]

English (1725700)

Search strategy and combinations of key words

1- All keys with comorbidities

1&2&3&4&5&6&7&8= 2 (1) 1&2&3&10&8= 1045 (937)

2- All keys NO comorbidities

1&2&3&4&5&6&7= 2 (1) 1&2&3&10= 2311 (2051)

3- Main keys (factors+ evidence based+ prescribing) AND (MI+ Angina+ CHD)

1&2&3&4&5&6= 30 (24) 1&2&3&9= 808 (709)

4- Main keys and MI

1&2&3&4= 402

5- Main keys and angina

1&2&3&5= 82

6- Maine keys and CHD

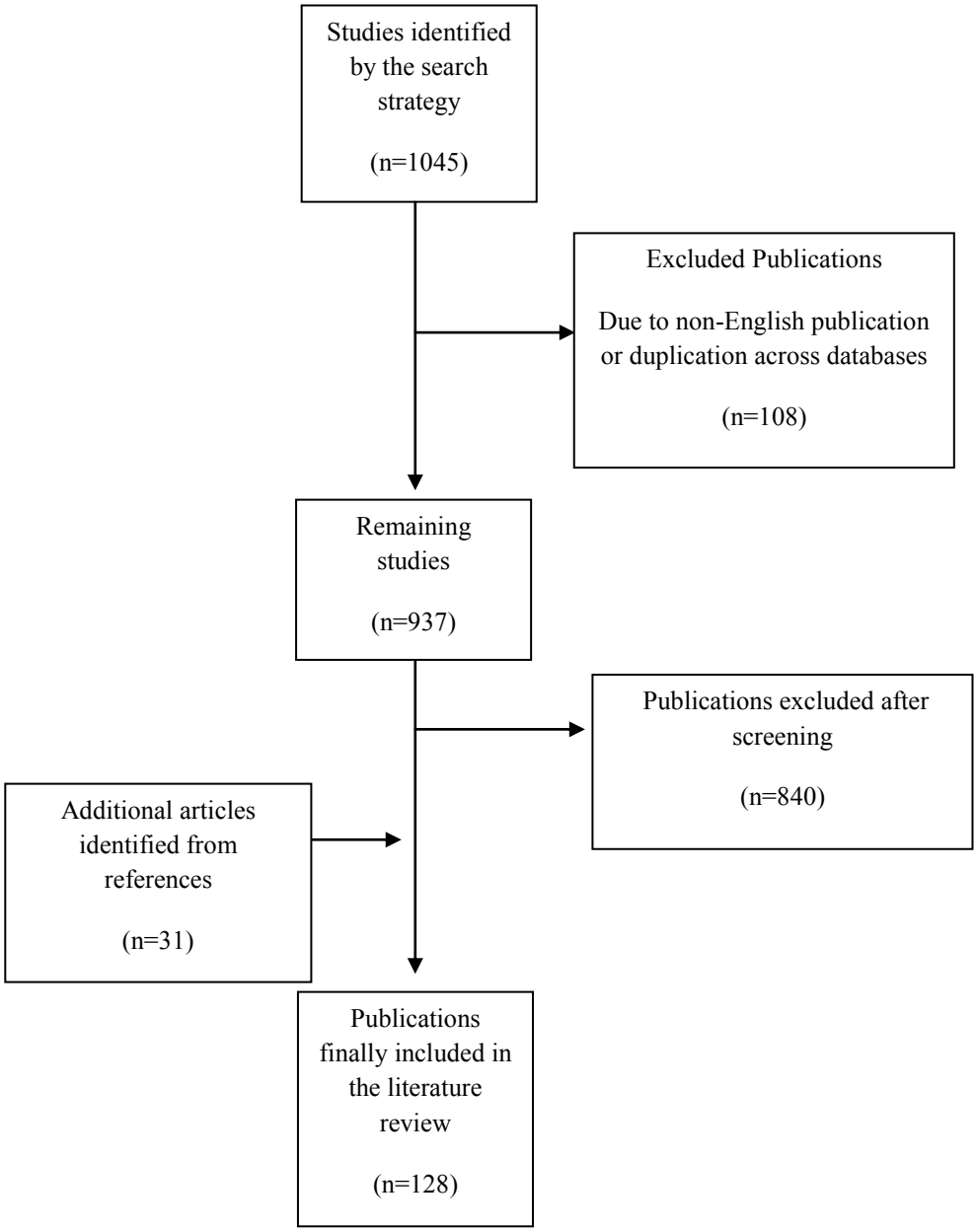
1&2&3&6= 389

7- Main keys and PAD

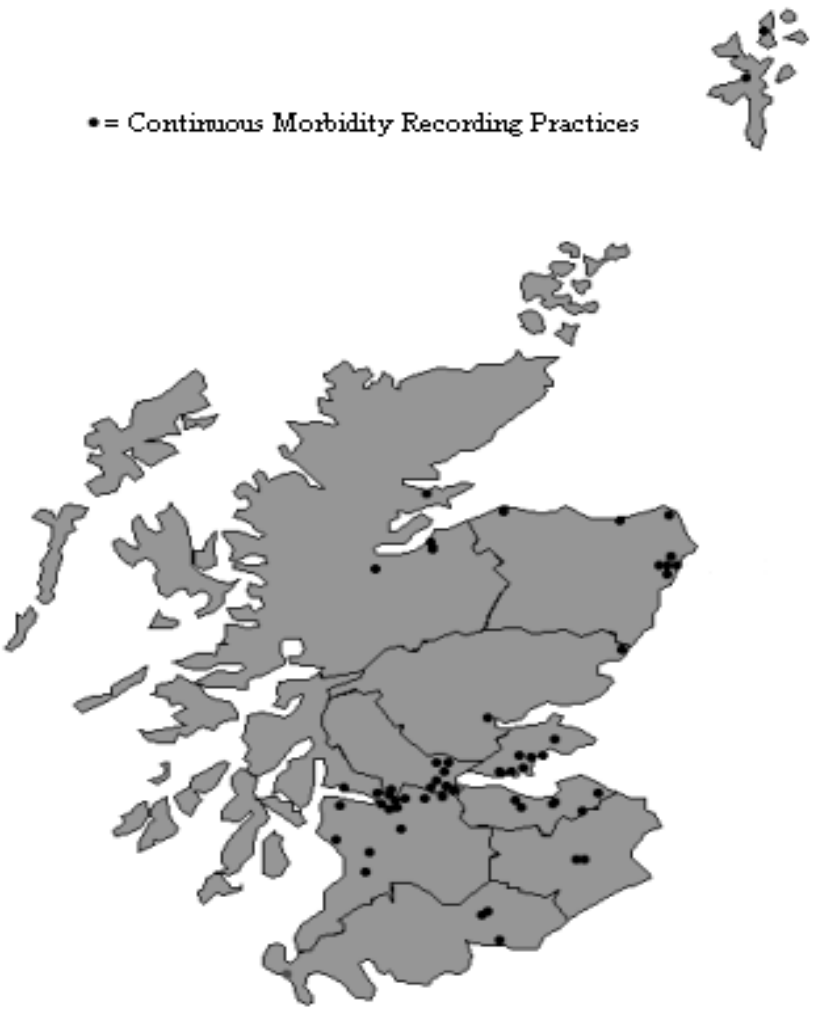
1&2&3&7= 40

Appendix 2

PRISMA flow diagram of the literature included in the review.



Appendix 3



Appendix 4

Diseases	Read cods	ICD9	ICD10
Angina	((c.readcode like 'G311.%')or (c.readcode like 'G33%') or(c.readcode like 'Gyu30%'))	413 Angina pectoris or 411	I20 or I24.9
Myocardial infarction	((c.readcode like 'G30%')or (c.readcode like 'G35%') or (c.readcode like 'G38%')or(c.readcode like 'Gyu34%'))	410	I21 or I22
PAD	c.readcode like 'G73%	440.2, 440.8, 440.9, 443.9, 444.22, 444.8-444.9	I70.2, I70.8, I70.9, I73.9, I74.3-9

In the read code symbol of % means e.g. G3% means all G3 and below.

Comorbidities read codes, ICD9 and ICD10 Diseases	Read cods	ICD9	ICD10
Asthma	(c.readcode like 'H33%') and ((readcode not like 'H333%') or(readcode not like 'H33z1%'))	493.0, 493.1, 493.2, 493.9	J45.1, J45.8, J45.9
COPD	H36.., H37.., H38.., H39.., H3y1.,	496	J44.1, J44.9
Atrial fibrillation	((c.readcode like 'G573.') or (c.readcode like 'G5730') or (c.readcode like 'G5731') or(c.readcode like 'G5732') or(c.readcode like 'G5733') or(c.readcode like 'G573z')) and (c.readcode not like '212R')	427.3	I48
Hypertension	((c.readcode like 'G2...%') or (c.readcode like 'G20%') or (c.readcode like 'G24..%') or(c.readcode like 'G2y%') or(c.readcode like 'G2z%'))	401	I10-I13

Diabetes	c.readcode like 'C10%'	250	E10-E14)
Cancer	B0... - B32z., B34.. - B6z0., Byu.. - Byu41, Byu5. - ByuE0	140-208	C00 – C99
Chronic kidney disease	((c.readcode like '14D..')or (c.readcode like '14D1.')or (c.readcode like '14V2.') or (c.readcode like 'P7690')or (c.readcode like 'K05..')or (c.readcode like 'K050.')or (c.readcode like 'K0D..') or (c.readcode like 'K138z')or (c.readcode like '1Z1..')or (c.readcode like '1Z10.')or (c.readcode like '1Z11.') or (c.readcode like '1Z12.')or (c.readcode like '1Z13.')or (c.readcode like '1Z14.')or (c.readcode like '8L50.') or (c.readcode like 'ZV451')or (c.readcode like 'G22..')or (c.readcode like 'G220.')or (c.readcode like 'G221.') or (c.readcode like 'G222.')or (c.readcode like 'G22z.')or (c.readcode	585, 586, 587	**N18,N19**

	like 'K07..')or (c.readcode like 'K070.') or (c.readcode like 'K071.')or (c.readcode like 'K072.')or (c.readcode like 'K07z.')or (c.readcode like 'G701.') or (c.readcode like '7L1A.')or (c.readcode like '7L1A0')or (c.readcode like '7L1A1')or (c.readcode like '7L1A2') or (c.readcode like 'G703.')or (c.readcode like 'PD1..')or (c.readcode like 'PD11.')or (c.readcode like 'PD12.') or (c.readcode like 'PD13.')or (c.readcode like 'PD1y.')or (c.readcode like 'PD1z.')or (c.readcode like '7B063') or (c.readcode like 'D215.')or (c.readcode like 'ZV560')or (c.readcode like 'C10E0')or (c.readcode like 'C10F0') or (c.readcode like 'K0B..')or (c.readcode like 'K0B1.')or (c.readcode like 'K0B2.')or (c.readcode like 'K0B3.') or (c.readcode like 'K0B4.')or		

	(c.readcode like 'K0B5.')or (c.readcode like 'K0B6.')or (c.readcode like 'G233.') or (c.readcode like '7L1B.')or (c.readcode like 'TA020')or (c.readcode like 'G232.')or (c.readcode like 'K09..') or (c.readcode like 'K090.')or (c.readcode like 'K091.')or (c.readcode like 'K09z.')or (c.readcode like 'K0C..') or (c.readcode like 'K0C0.')or (c.readcode like 'K0C1.')or (c.readcode like 'K0C2.')or (c.readcode like 'K0C3.') or (c.readcode like 'K0C4.')or (c.readcode like 'D3101')or (c.readcode like 'K03..') or (c.readcode like 'K031.')or (c.readcode like 'K032.') or (c.readcode like 'K06%'))		

Appendix 5

Drugs class	BNF code	Description
Angiotensin converting enzyme inhibitors	2.5.5.1	
Angiotensin II receptor antagonist	2.5.5.2	
Beta blocker	2.4	
Calcium channel blocker	2.6.2	
Nitrates	2.6.1	
Other anti-anginal drugs	2.6.3	Nicorandil and ivabradine
Antiplatelet	2.9	Aspirin and clopidogrel
Lipid regulating drugs	2.12	Statins
Oral anticoagulant	2.8.2	Warfarin
Peripheral vasodilators	2.6.4	Cilostazol, naftidrofuryl oxalate, pentoxifylline (oxpentifylline)

Appendix 6

Table 1 Association between age and prescribing of evidence based therapies after a first myocardial infarction (age < 55 years reference group)

	ACEI/ ARBs	β-blockers	CCB	Statins	Aspirin	Clopidogrel	Oral anticoagulant
Adjusted OR*, 95% CI 55-64	1.18 (0.95-1.47)	1.01 (0.85-1.21)	1.05 (0.74-1.49)	0.98 (0.83-1.15)	1.07 (0.90-1.28)	1.01 (0.81-1.26)	0.95 (0.54-1.67)
Adjusted OR, 95% CI 65-74	1.04 (0.81-1.33)	0.93 (0.73-1.18)	0.98 (0.66-1.45)	0.84 (0.66-1.07)	1.07 (0.87-1.32)	0.83 (0.63-1.09)	0.95 (0.52-1.71)
Adjusted OR, 95% CI 75-84	0.82 (0.62-1.08)	0.64 (0.51-0.80)	1.13 (0.76-1.67)	0.54 (0.43-0.68)	0.86 (0.70-1.05)	0.67 (0.51-0.88)	1.10 (0.56-2.17)
Adjusted OR, 95% CI ≥ 85	0.46 (0.32-0.67)	0.38 (0.26-0.54)	0.89 (0.52-1.53)	0.21 (0.13-0.32)	0.66 (0.47-0.92)	0.51 (0.31-0.85)	0.33 (0.11-1.07)
Adjusted^{+} overall P-value	<0.001	<0.001	0.0.85	<0.001	0.002	0.01	0.14

* Patients aged <55 years are the reference category, $^{+}$Adjusted for sex, socioeconomic status, year of diagnosis, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, peripheral arterial disease, angina, clustered practices, and whether the drug was previously prescribed.

ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers

Table 2 Association between sex (male vs. female) and prescribing of evidence based therapies after first myocardial infarction

	Adjusted OR (95% CI)*	Adjusted[+] p-value
ACEI/ ARBs	1.12 (0.91-1.39)	0.27
β-blockers	1.18 (1.04-1.33)	0.01
CCB	1.02 (0.81-1.28)	0.9
Statins	1.09 (0.94-1.25)	0.20
Aspirin	1.09 (0.96-1.24)	0.15
Clopidogrel	1.09 (0.88-1.36)	0.41
Oral anticoagulant	0.79 (0.55-1.15)	0.29

Women are the reference category, [+]Adjusted for age group, socioeconomic, year of diagnosis, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, stroke, peripheral arterial disease, angina, clustered practices, and whether the drug was previously prescribed.

ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers

Table 3 Association between socioeconomic deprivation and prescribing of evidence based therapies within 30 days after a first myocardial infarction (quintile Q1 least deprived reference)

Adjusted OR*, (95% CI)	ACEI/ARBs	β-blocker	CCB	Statins	Aspirin	Clopidogrel	Oral anticoagulant
Q2	1.43 (1.00-2.03)	1.00 (0.60-1.42)	1.00 (0.39-2.03)	1.00 (0.88-2.31)	0.96 (0.58-1.57)	1.32 (0.7-2.31)	0.96 (0.32-2.84)
Q3	1.12 (0.63-1.99)	1.09 (0.61-1.95)	0.96 (0.45-2.06)	1.38 (0.65-2.94)	1.13 (0.60-2.12)	1.34 (0.81-2.23)	1.38 (0.58-3.23)
Q4	2.00 (0.84-2.97)	1.17 (0.65-2.12)	0.83 (0.39-1.76)	1.38 (0.60-3.14)	1.00 (0.59-2.25)	1.57 (1.02-2.53)	0.50 (0.11-2.16)
Q5	1.21 (0.62-2.37)	1.04 (0.57-1.89)	0.81 (0.38-1.69)	1.41 (0.67-2.97)	1.14 (0.56-2.32)	1.28 (0.83-2.05)	2.42 (1.01-5.82)
Q6	1.19 (0.66-2.16)	1.08 (0.64-1.83)	1.03 (0.52-2.01)	1.25 (0.61-2.54)	1.17 (0.63-2.14)	1.27 (0.85-2.03)	1.53 (0.61-3.81)
Q7	1.07 (0.57-2.01)	0.87 (0.48-1.56)	0.95 (0.46-1.96)	1.20 (0.59-2.45)	1.03 (0.52-2.07)	1.25 (0.77-2.22)	1.54 (0.60-3.95)
Q8	1.22 (0.63-2.35)	0.97 (0.52-1.81)	1.28 (0.63-2.59)	1.20 (0.56-2.57)	1.107 (0.54-2.24)	1.60 (0.98-2.80)	1.36 (0.55-3.36)
Q9	1.22 (0.63-2.37)	1.17 (0.63-2.17)	1.015 (0.51-1.98)	1.41 (0.68-2.94)	1.25 (0.59-2.66)	1.42 (0.88-2.39)	1.22 (0.37-4.02)
Q10	1.09 (0.54-2.18)	0.86 (0.44-1.67)	1.02 (0.51-2.05)	1.18 (0.54-2.57)	1.11 (0.53-2.30)	1.35 (0.79-2.32)	1.01 (0.29-3.49)
Adjusted^{+} overall P-value	0.24	0.35	0.86	0.5	0.81	0.84	0.11

* Adjusted for sex, age group, year of diagnosis, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, peripheral arterial disease, angina, clustered practices, and whether the drug was previously prescribed.
ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers

Table 4 Trends over time (1997-2005) in prescribing of evidence based therapies within 30 days after a first myocardial infarction (1997 reference)

	ACEI/ARBs	β-blocker	CCB	Statins	Aspirin	Clopidogrel**	Oral anticoagulant
Adjusted OR, 95% CI 1998*	1.32 (0.79-2.18)	1.43 (1.01-2.04)	0.73 (0.42-1.25)	2.36(1.55-3.59)	1.32 (1.02-1.72)		3.84 (0.80-18.37)
Adjusted OR, 95% CI 1999	1.54 (1.01-2.3)	2.22 (1.61-3.07)	1.10 (0.61-1.99)	3.74 (2.43-5.75)	1.85 (1.34-2.56)		3.11 (0.58-16.69)
Adjusted OR, 95% CI 2000	2.52 (1.66-3.82)	2.77(1.97-3.89)	1.41 (0.81-2.47)	4.33 (3.03-6.20)	1.89 (1.43-2.49)		3.43 (0.99-11.86)
Adjusted OR, 95% CI 2001	3.36 (2.17-5.21)	3.11 (2.15-4.51)	1.30 (0.66-2.55)	5.17 (3.51-7.60)	1.73 (1.25-2.39)	9.1 (4.9-17.1)	5.06 (0.94-27.06)
Adjusted OR, 95% CI 2002	4.11 (2.68-6.27)	2.93 (2.06-4.15)	1.07 (0.59-1.94)	7.23 (4.67-11.17)	2.23 (1.56-3.19)	20.1 (11.7-30.1)	2.82 (0.55-14.33)
Adjusted OR, 95% CI 2003	3.38 (2.21-5.21)	2.59 (1.77-3.81)	1.07 (0.64-1.81)	7.21 (4.59-11.30)	2.04 (1.41-2.94)	25.8 (14.4-46.4)	3.11 (0.80-12.02)
Adjusted OR, 95% CI 2004	3.81 (2.30-6.11)	3.41 (2.20-5.29)	0.92 (0.52-1.63)	11.74 (7.24-19.04)	2.33 (1.66-3.27)	48.6 (28.5-82.8)	5.72 (1.18-27.69)
Adjusted OR, 95% CI 2005	5.25 (3.40-8.11)	3.60 (2.49-5.20)	0.88 (0.50-1.57)	11.11 (6.70-18.42)	2.81 (1.90-4.15)	68.4 (38.5-121)	5.91 (1.15-30.37)
Adjusted over all p-value	<0.001	<0.001	0.27	<0.001	<0.001	<0.001	0.10

Adjusted for sex, age group, socioeconomic status, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, peripheral arterial disease, angina, clustered practices, and whether the drug was previously prescribed. **2000 is the reference for clopidogrel,

ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers

Table 5 Association between age and prescribing of evidence based therapies after a first angina (age < 55 years reference group)

	ACEI/ ARBs	β-blockers	CCB	Nitrates	Statins	Aspirin	Clopidogrel	Other anti-anginal
Adjusted OR*, 95% CI 55-64	1.06 (0.86-1.30)	1.07 (0.89-1.24)	1.06 (0.87-1.32)	1.07 (0.93-1.23)	0.99 (0.85-1.15)	1.20 (1.05-1.37)	0.81 (0.61-1.09)	0.66 (0.45-0.97)
Adjusted OR, 95% CI 65-74	1.12 (0.90-1.38)	0.91 (0.77-1.03)	1.03 (0.86-1.25)	1.21 (1.04-1.40)	0.80 (0.70-0.92)	1.16 (1.02-1.32)	0.63 (0.46-0.87)	0.75 (0.51-1.11)
Adjusted OR, 95% CI 75-84	0.97 (0.75-1.26)	0.78 (0.63-0.92)	1.00 (0.75-1.34)	1.21 (1.06-1.39)	0.52 (0.42-0.63)	0.95 (0.81-1.12)	0.58 (0.37-0.91)	0.59 (0.39-0.91)
Adjusted OR, 95% CI ≥ 85	0.87 (0.56-1.35)	0.34 (0.25-0.46)	0.91 (0.58-1.42)	1.29 (1.05-1.59)	0.19 (0.12-0.33)	1.16 (0.94-1.44)	0.39 (0.19-0.77)	0.65 (0.34-1.20)
Adjusted+ overall P-value	0.5	<0.001	0.9	0.03	<0.001	0.01	0.02	0.18

* Adjusted for sex, socioeconomic status, year of diagnosis, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, peripheral arterial disease, angina, and whether the drug was previously prescribed.

ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blocker.

Table 6 Association between sex (male versus female) and prescribing of evidence based therapies after first angina

	Adjusted OR (95%,CI)*	Adjusted+ p-value
ACEI/ARBs	1.26 (1.05-1.47)	0.01
β-blockers	1.08 (0.93-1.22)	0.25
CCB	1.01 (0.85-1.18)	0.92
Nitrates	1.03 (0.93-1.14)	0.55
Statins	1.09 (0.95-1.25)	1.60
Aspirin	1.05 (0.95-1.15)	0.3
Clopidogrel	1.27 (0.98-1.64)	0.06
Other anti-angina	1.01 (0.75-1.36)	0.93

*Women are the reference, +Adjusted for age group, socioeconomic status, year of diagnosis, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, peripheral arterial disease, angina, and whether the drug was previously prescribed.

Table 7 Association between socioeconomic status and prescribing of evidence based therapies within 30 days after a first angina (Quintile Q1 least deprived reference)

Adjusted OR*, (95% CI)	ACEI/ARBs	β-blocker	CCB	Nitrates	Statins	Aspirin	Clopidogrel	Other anti-anginal
Q2	1.35 (0.93-1.96)	0.97 (0.71-1.32)	0.93 (0.60-1.44)	0.88 (0.64-1.21)	1.09 (0.81-1.48)	1.14 (0.87-1.49)	0.94 (0.51-1.74)	1.01 (0.49-2.07)
Q3	1.04 (0.67-1.62)	0.83 (0.62-1.13)	0.95 (0.74-1.22)	0.91 (0.75-1.11)	0.91 (0.65-1.27)	0.97 (0.75-1.24)	1.05 (0.54-2.06)	0.85 (0.43-1.69)
Q4	1.18 (0.65-2.15)	0.97 (0.72-1.37)	1.12 (0.79-1.60)	0.93 (0.76-1.13)	0.96 (0.69-1.33)	1.17 (0.84-1.63)	0.94 (0.54-1.63)	0.78 (0.41-1.48)
Q5	1.09 (0.70-1.68)	0.93 (0.70-1.23)	0.95 (0.67-1.35)	0.97 (0.79-1.21)	1.01 (0.69-1.49)	1.22 (0.93-1.61)	0.69 (0.37-1.29)	0.79 (0.42-1.46)
Q6	1.29 (0.81-2.05)	0.79 (0.61-1.02)	1.11 (0.83-1.46)	0.96 (0.77-1.21)	1.04 (0.71-1.51)	1.14 (0.86-1.49)	0.88 (0.51-1.51)	0.71 (0.35-1.43)
Q7	1.34 (0.89-2.02)	0.91 (0.67-1.20)	0.71 (0.49-1.02)	0.86 (0.70-1.05)	1.01 (0.73-1.39)	1.17 (0.93-1.47)	0.75 (0.41-1.36)	0.59 (0.32-1.07)
Q8	1.04 (0.68-1.59)	0.79 (0.58-1.03)	0.92 (0.64-1.33)	0.81 (0.66-1.01)	0.92 (0.64-1.30)	1.08 (0.83-1.39)	0.88 (0.47-1.63)	0.56 (0.28-1.12)
Q9	0.87 (0.59-1.28)	0.76 (0.58-1.00)	0.96 (0.70-1.32)	0.92 (0.72-1.19)	0.85 (0.62-1.17)	1.07 (0.84-1.36)	0.69 (0.38-1.27)	0.93 (0.48-1.82)
Q10	1.13 (0.71-1.80)	0.71 (0.48-1.01)	0.86 (0.55-1.35)	0.93 (0.66-1.32)	0.87 (0.59-1.27)	1.20 (0.90-1.60)	0.88 (0.47-1.63)	0.87 (0.44-1.72)
Adjusted[+] overall P-value	0.20	0.12	0.14	0.85	0.77	0.56	0.8	0.6

* Adjusted for sex, age group, year of diagnosis, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, peripheral arterial disease, angina, and whether the drug was previously prescribed.

ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers

Table 8 Trends over time (1997-2005) in prescribing of evidence based therapies within 30 days after a first angina (1997 reference)

	ACEI/ARBs	β-blocker	CCB	Nitrates	Statins	Aspirin	Clopidogrel**	Other antianginal
Adjusted OR, 95% CI 1998*	1.18 (0.79-1.76)	1.30 (0.98-1.72)	1.15 (0.82-1.61)	0.97 (0.81-1.17)	1.71 (1.27-2.31)	1.40 (1.12-1.75)		1.67 (0.53-5.22)
Adjusted OR, 95% CI 1999	1.42 (0.92-2.19)	2.23 (1.75-2.86)	1.44 (1.15-1.80)	1.31 (1.05-1.63)	2.95 (2.27-3.82)	2.06 (1.65-2.56)		1.46 (0.63-3.35)
Adjusted OR, 95% CI 2000	2.18 (1.25-3.81)	3.21 (2.40-4.31)	1.48 (1.07-2.03)	1.51 (1.23-1.85)	3.67 (2.79-4.83)	2.53 (1.99-3.21)		2.53 (0.96-6.67)
Adjusted OR, 95% CI 2001	2.48 (1.55-3.97)	4.00 (2.86-5.48)	1.73 (1.28-2.35)	1.75 (1.34-2.29)	3.91 (2.80-5.46)	2.85 (2.30-3.55)	7.78 (4.4-13.6)	3.40 (1.42-8.14)
Adjusted OR, 95% CI 2002	2.61 (1.68-4.05)	3.38 (2.54-4.49)	1.72 (1.25-2.38)	1.91 (1.45-2.50)	4.37 (3.35-5.70)	2.99 (2.24-4.00)	14.44 (7.9-26.2)	4.49 (1.86-10.8)
Adjusted OR, 95% CI 2003	3.12 (2.06-4.72)	4.48 (3.10-6.41)	1.28 (0.86-1.89)	2.12 (1.55-2.89)	6.51 (4.83-8.78)	3.44 (2.65-4.48)	22.74 (12.2-42.4)	6.36 (2.67-15.1)
Adjusted OR, 95% CI 2004	2.75 (1.82-4.16)	4.77 (3.41-6.49)	1.15 (0.81-1.64)	1.68 (1.36-2.08)	8.73 (6.49-11.75)	2.85 (2.30-3.55)	33.54 (19.1-58.9)	10.6 (4.54-25.2)
Adjusted OR, 95% CI 2005	3.71 (2.46-5.58)	4.75 (3.26-6.73)	1.31 (0.95-1.79)	1.77 (1.32-2.38)	8.11 (5.89-11.15)	2.99 (2.24-4.00)	22.74 (12.2-42.4)	7.69 (3.03-19.5)
Adjusted over all p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

* Adjusted for sex, age group, socioeconomic status, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, peripheral arterial disease, angina, and whether the drug was previously prescribed. **2000 is the reference for clopidogrel,

ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers

Table 9 Association between age and prescribing of evidence based therapies after a first PAD (age < 55 years reference group)

Adjusted OR*, 95% CI	ACEI/ ARBs	β-blockers	CCB	PVD	Statins	Aspirin	Clopidogrel	Oral anticoagulant
Adjusted OR, 95% CI 55-64	0.81 (0.52-1.24)	0.47 (0.22-0.99)	1.45 (0.66-3.20)	1.49 (0.74-2.99)	0.71 (0.47-1.06)	1.16 (0.84-1.61)	1.98 (0.55-7.03)	0.63 (0.26-1.52)
Adjusted OR, 95% CI 65-74	0.73 (0.45-1.21)	1.06 (0.61-1.84)	1.57 (0.70-3.52)	1.99 (1.01-3.93)	0.89 (0.59-1.32)	1.41 (1.01-1.97)	3.13 (1.03-9.48)	0.53 (0.21-1.39)
Adjusted OR, 95% CI 75-84	0.53 (0.28-1.01)	0.80 (0.45-1.41)	1.71 (0.78-3.73)	2.32 (1.32-4.06)	0.55 (0.34-0.88)	1.16 (0.81-1.67)	1.14 (0.25-5.11)	0.47 (0.15-1.43)
Adjusted OR, 95% CI ≥ 85	0.36 (0.17-0.78)	0.60 (0.20-1.82)	0.95 (0.36-2.53)	1.25 (0.50-3.14)	0.06 (0.01-0.28)	0.84 (0.53-1.31)	3.98 (0.99-16.0)	0.29 (0.08-1.07)
Adjusted+ overall P-value	0.07	0.01	0.16	0.06	<0.001	0.05	0.12	0.41

***** Adjusted for sex, socioeconomic status, year of diagnosis, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, whether the drug was previously prescribed.

ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, PVD=peripheral vasodilator

Table 10 Association between sex (male versus female) and prescribing of evidence based therapies after first PAD

	Adjusted OR (95%,CI)*	Adjusted[+] p-value
ACEI/ARBs	0.84 (0.60-1.17)	0.3
β-blockers	1.07 (0.76-1.51)	0.6
CCB	1.00 (0.74-1.33)	0.9
PVD	1.02 (0.77-1.36)	0.8
Statins	0.73 (0.59-0.91)	0.004
Aspirin	0.88 (0.71-1.08)	0.2
Clopidogrel	0.85 (0.46-1.55)	0.6
Oral anticoagulant	0.79 (0.38-1.62)	0.5

*Women are the reference, [+]Adjusted for age group, socioeconomic status, year of diagnosis, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, stroke, Whether the drug was previously prescribed.

CCB= Calcium channel blocker, PVD= Peripheral vasodilator

Table 11 Association between socioeconomic status and prescribing of evidence based therapies within 30 days after a first PAD (Quintile Q1 least deprived reference)

Adjusted OR*, (95% CI)	ACEI/ARBs	β-blocker	CCB	PVD	Statins	Aspirin	Clopidogrel	Oral anticoagulant
Q2	1.12 (0.47-2.63)	0.29 (0.08-1.04)	0.91 (0.45-1.83)	2.22 (0.41-11.8)	1.01 (0.52-1.93)	0.56 (0.35-0.90)	3.23 (0.46-22.4)	0.61 (0.11-3.39)
Q3	1.07 (0.58-1.97)	1.62 (0.68-3.83)	1.68 (0.89-3.17)	4.26 (1.32-13.7)	0.97 (0.55-1.68)	0.81 (0.57-1.16)	3.41 (0.38-28.2)	1.81 (0.84-3.91)
Q4	1.12 (0.61-2.05)	0.39 (0.15-0.97)	0.85 (0.39-1.84)	3.66 (0.86-15.4)	0.76 (0.42-1.38)	0.84 (0.55-1.27)	3.53 (0.35-35.3)	2.51 (1.18-5.34)
Q5	0.79 (0.34-1.83)	0.98 (0.49-1.95)	1.54 (0.66-3.58)	4.41 (1.15-16.8)	0.87 (0.41-1.83)	0.85 (0.58-1.25)	1.56 (0.14-16.7)	0.83 (0.25-2.70)
Q6	1.06 (0.58-1.94)	1.45 (0.80-2.64)	1.21 (0.58-2.51)	4.47 (1.36-14.6)	1.06 (0.61-1.85)	0.87 (0.64-1.20)	2.69 (0.29-24.6)	0.85 (0.28-2.56)
Q7	0.56 (0.29-1.11)	0.74 (0.39-1.42)	0.63 (0.31-1.29)	2.81 (0.72-10.8)	0.98 (0.54-1.76)	0.61 (0.41-0.91)	2.06 (0.21-20.3)	2.20 (0.78-6.20)
Q8	0.88 (0.42-1.84)	0.83 (0.34-2.03)	0.94 (0.45-1.96)	2.41 (0.59-9.81)	0.93 (0.52-1.68)	0.91 (0.63-1.31)	1.53 (0.10-23.6)	1.53 (0.49-4.72)
Q9	0.87 (0.38-1.99)	0.97 (0.43-2.16)	1.04 (0.52-2.07)	2.68 (0.69-10.4)	0.62 (0.38-1.02)	0.69 (0.47-1.01)	1.34 (0.24-7.54)	1.41 (0.64-3.05)
Q10	0.72 (0.35-1.49)	0.69 (0.24-1.97)	1.44 (0.76-2.73)	4.17 (1.03-16.8)	0.71 (0.39-1.27)	0.55 (0.37-0.83)	3.02 (0.24-37.9)	1.06 (0.30-3.70)
Adjusted[+] overall P-value	0.6	0.002	0.04	0.14	0.6	0.09	0.5	0.48

* Adjusted for sex, age group, year of diagnosis, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, whether the drug was previously prescribed.

ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, PVD=peripheral vasodilator

Table 12 Trends over time (1997-2005) in prescribing of evidence based therapies within 30 days after a first PAD (1997 reference)

	ACEI/ARBs	β-blocker	CCB	PVD	Statins	Aspirin	Clopidogrel**	Oral anticoagulant
Adjusted OR, 95% CI 1998*	1.18 (0.53-2.63)	0.58 (0.23-1.44)	0.81 (0.35-1.87)	1.37 (0.41-4.55)	1.63 (0.49-5.39)	1.34 (0.85-2.11)		0.46 (0.11-1.89)
Adjusted OR, 95% CI 1999	1.16 (0.50-2.69)	1.53 (0.68-3.45)	1.38 (0.69-2.78)	1.56 (0.72-3.38)	4.09 (1.49-11.2)	1.98 (1.33-2.95)		0.72 (0.24-2.13)
Adjusted OR, 95% CI 2000	1.46 (0.69-3.11)	1.04 (0.46-2.37)	1.30 (0.69-2.45)	3.15 (1.43-6.92)	4.97 (1.89-13.1)	2.39 (1.70-3.37)		1.28 (0.55-2.96)
Adjusted OR, 95% CI 2001	2.23 (0.90-5.53)	1.14 (0.61-2.10)	1.61 (0.81-3.20)	4.93 (2.35-10.35)	5.96 (2.51-14.2)	2.29 (1.61-3.24)	2.46 (0.64-9.39)	0.35 (0.11-1.13)
Adjusted OR, 95% CI 2002	1.59 (0.68-3.67)	1.26 (0.57-2.77)	1.11 (0.52-2.36)	4.06 (1.64-10.06)	9.34 (3.98-21.9)	3.40 (2.28-5.07)	0.75 (0.10-5.26)	0.92 (0.32-2.68)
Adjusted OR, 95% CI 2003	2.34 (1.05-5.18)	1.68 (0.91-3.13)	1.32 (0.59-2.95)	2.38 (0.97-5.81)	12.92 (5.3-31.7)	2.41 (1.58-3.68)	5.23 (1.38-19.7)	0.40 (0.15-1.02)
Adjusted OR, 95% CI 2004	1.11 (0.53-2.33)	1.03 (0.49-2.15)	0.80 (0.37-1.73)	3.49 (1.34-9.05)	10.61 (3.9-28.2)	3.21 (2.18-4.74)	2.58 (0.53-12.4)	0.78 (0.24-2.49)
Adjusted OR, 95% CI 2005	1.16 (0.56-2.39)	1.39 (0.56-3.44)	1.43 (0.72-2.80)	4.71 (1.98-11.21)	20.22 (8.7-46.9)	4.06 (2.62-6.29)	3.44 (0.78-15.0)	0.37 (0.10-1.42)
Adjusted over all p-value	0.08	0.34	0.23	<0.001	<0.001	<0.001	0.02	0.25

* Adjusted for sex, age group, socioeconomic status, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, whether the drug was previously prescribed. **2000 is the reference for clopidogrel,

ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, PVD= Peripheral vasodilator

PAD/CHD

Table 13 Association between age and prescribing of evidence based therapies after a first PAD/CHD (age < 55 years reference group)

Adjusted OR*, 95% CI	ACEI/ ARBs	β-blockers	CCB	PVD	Statins	Aspirin	Clopidogrel	Oral anticoagulant
Adjusted OR, 95% CI 55-64	0.89 (0.47-1.65)	0.99 (0.56-1.73)	0.51 (0.27-0.91)	8.11 (0.64-102)	0.86 (0.46-1.59)	1.20 (0.77-1.86)	1.94 (0.36-10.47)	0.84 (0.25-2.82)
Adjusted OR, 95% CI 65-74	1.11 (0.54-2.22)	0.77 (0.45-1.31)	0.56 (0.37-0.86)	8.07 (0.61-106)	0.76 (0.42-1.37)	1.46 (0.93-2.28)	0.96 (0.13-6.82)	0.21 (0.03-1.21)
Adjusted OR, 95% CI 75-84	0.89 (0.52-1.52)	0.59 (0.36-0.97)	0.61 (0.33-1.11)	14.1 (1.21-164)	0.51 (0.28-0.91)	1.41 (0.89-2.24)	1.62 (0.28-9.26)	0.66 (0.14-3.01)
Adjusted OR, 95% CI ≥ 85	0.93 (0.41-2.13)	0.55 (0.19-1.58)	0.41 (0.12-1.35)	3.50 (0.22-53.8)	0.50 (0.20-1.22)	0.71 (0.30-1.66)	5.26 (0.75-36.7)	0.07 (0.01-0.75)
Adjusted+ overall P-value	0.84	0.2	0.2	0.03	0.08	0.13	0.12	0.03

* Adjusted for sex, socioeconomic status, year of diagnosis, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, whether the drug was previously prescribed.

ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, PVD=Peripheral vasodilator

Table 14 Association between sex (male versus female) and prescribing of evidence based therapies after PAD/CHD

	Adjusted OR (95%,CI)*	Adjusted[+] p-value
ACEI/ARBs	1.08 (0.75-1.55)	0.6
β-blockers	1.31 (0.97-1.75)	0.07
CCB	0.94 (0.66-1.35)	0.7
PVD	0.57 (0.28-1.16)	0.1
Statins	1.39 (1.01-1.93)	0.04
Aspirin	1.18 (0.96-1.45)	0.1
Clopidogrel	1.55 (0.71-3.38)	0.2
Oral anticoagulant	1.63 (0.53-4.99)	0.4

*Women are the reference, [+]Adjusted for age group, socioeconomic status, year of diagnosis, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, stroke. Whether the drug was previously prescribed.

ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, PVD=Peripheral vasodilator

Table 15 Association between socioeconomic status and prescribing of evidence based therapies within 30 days after first PAD/CHD (Quintile Q1 least deprived reference)

Adjusted OR*, (95% CI)	ACEI/ARBs	β-blocker	CCB	PVD	Statins	Aspirin	Clopidogrel	Oral anticoagulant
Q2	0.92 (0.36-2.33)	0.66 (0.29-1.47)	0.53 (0.21-1.32)	1.41 (0.22-8.89)	1.13 (0.38-3.37)	0.83 (0.43-1.59)	0.59 (0.02-15.6)	0.53 (0.02-10.0)
Q3	0.91 (0.33-2.46)	0.81 (0.40-1.64)	0.56 (0.27-1.19)	0.55 (0.05-5.94)	1.19 (0.51-2.79)	1.06 (0.59-1.89)	3.49 (0.34-35.4)	2.05 (0.07-52.9)
Q4	0.71 (0.28-1.75)	0.88 (0.47-1.64)	0.42 (0.18-0.97)	0.63 (0.11-3.32)	0.71 (0.28-1.77)	1.24 (0.81-1.89)	0.78 (0.06-8.84)	0.66 (0.02-25.1)
Q5	1.09 (0.48-2.45)	1.08 (0.52-2.24)	0.48 (0.24-0.96)	0.83 (0.13-5.29)	1.01 (0.39-2.55)	1.06(0.51-2.20)	1.93 (0.16-22.6)	1.11 (0.05-23.8)
Q6	0.70 (0.29-1.65)	0.42 (0.22-0.82)	0.47 (0.30-0.74)	1.46 (0.31-6.95)	1.01 (0.42-2.36)	0.62 (0.41-0.96)	4.47 (0.60-32.9)	2.67 (0.13-51.6)
Q7	0.72 (0.31-1.72)	0.86 (0.48-1.53)	0.77 (0.42-1.42)	0.44 (0.05-3.45)	1.06 (0.40-2.80)	1.23 (0.76-1.99)	1.84 (0.18-18.9)	2.39 (0.08-63.9)
Q8	1.17 (0.51-2.71)	0.61 (0.33-1.14)	0.89 (0.43-1.81)	0.46 (0.07-2.87)	1.12 (0.46-2.71)	1.24 (0.71-2.17)	2.09 (0.23-18.7)	0.86 (0.03-22.1)
Q9	1.14 (0.46-2.81)	0.77 (0.40-1.47)	0.64 (0.35-1.16)	0.92 (0.16-5.38)	1.26 (0.49-3.22)	1.36 (0.85-2.18)	3.15 (0.3-25.46)	0.88 (0.04-17.2)
Q10	2.36 (0.96-5.77)	0.88 (0.48-1.59)	0.54 (0.25-1.18)	0.69 (0.13-3.57)	1.19 (0.51-2.76)	1.09 (0.65-1.83)	2.44 (0.2-22.05)	2.49 (0.09-65.1)
Adjusted^{+} overall P-value	0.03	0.2	0.4	0.6	0.9	0.1	0.4	0.4

* Adjusted for sex, age group, year of diagnosis, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, whether the drug was previously prescribed.

ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers, PVA=Peripheral vasodilator

Table 16 Trends over time (1997-2005) in prescribing of evidence based therapies within 30 days after a first PAD/CHD (1997 reference)

	ACEI/ARBs	β-blocker	CCB	PVD	Statins	Aspirin	Clopidogrel**	Oral anticoagulant
Adjusted OR, 95% CI 1998*	2.08 (0.68-6.33)	0.57 (0.20-1.61)	1.26 (0.56-2.84)		2.18 (0.81-5.86)	1.17 (0.48-2.82)		0.64 (0.25-1.62)
Adjusted OR, 95% CI 1999	1.91 (0.62-5.85)	1.73 (0.76-3.93)	2.65 (1.31-5.35)		2.38 (0.97-5.82)	2.13 (1.01-4.51)		0.68 (0.15-3.10)
Adjusted OR, 95% CI 2000	2.09 (0.78-5.61)	1.06 (0.37-3.02)	2.12 (0.97-4.62)		2.02 (0.72-5.64)	2.63 (1.22-5.66)		0.39 (0.07-2.14)
Adjusted OR, 95% CI 2001	2.67 (0.83-8.57)	1.86 (0.68-5.12)	2.04 (0.88-4.71)	1.12 (0.38-3.26)	2.87 (1.02-8.04)	3.16 (1.53-6.52)	9.25 (0.8-97.98)	0.88 (0.21-3.64)
Adjusted OR, 95% CI 2002	3.54 (1.10-11.3)	1.25 (0.48-3.25)	1.52 (0.64-3.57)	2.24 (0.63-7.95)	4.24 (1.47-12.2)	2.24 (1.07-4.68)	14.8 (1.9-115.6)	0.31 (0.06-1.54)
Adjusted OR, 95% CI 2003	2.14 (0.69-6.64)	1.48 (0.63-3.49)	1.60 (0.67-3.82)	4.66 (0.09-2.31)	2.97 (1.06-8.34)	2.53 (1.16-5.52)	18.9 (2.4-144.2)	0.42 (0.08-2.12)
Adjusted OR, 95% CI 2004	2.75 (0.98-7.71)	1.87 (0.74-4.70)	1.70 (0.69-4.17)	1.55 (0.57-4.17)	4.94 (1.70-14.3)	2.60 (1.19-5.67)	43.02 (5.21-135)	0.16 (0.02-1.31)
Adjusted OR, 95% CI 2005	3.17 (1.11-9.12)	1.28 (0.53-3.05)	1.58 (0.70-3.55)	2.88 (0.84-9.83)	2.15 (0.74-6.22)	2.51 (1.19-5.28)	13.6 (1.65-112)	0.44 (0.07-2.47)
Adjusted over all p-value	0.2	0.04	0.25	0.004	0.003	0.004	<0.001	0.5

* Adjusted for sex, age group, socioeconomic, chronic obstructive pulmonary disease, asthma, atrial fibrillation, hypertension, diabetes, cancer, renal failure, heart failure, and stroke, peripheral arterial disease, angina, whether drug was previously prescribed. **2000 is the reference for clopidogrel,

ACEI= Angiotensin converting enzyme inhibitors, ARBs= Angiotensin receptor blockers, CCB= Calcium channel blockers.

Appendix 7

Prescribing EBTs before first diagnosis for MI, angina, PAD or PAD/CHD

	ACEI/ARBs	β-blockers	CCB	Statins	Aspirin	Clopidogrel	Oral-anticoagulant
MI	19.0%	24.1%	22.1%	15.6%	30.3%	2.6%	3.9%
Angina	22.3%	33.2%	23.2%	22.1%	39.7%	3.5%	
PAD	16.5%	18.7%	16.4%	10.8%	23.0%	1.1%	3.8%
PAD/CHD	38.6%	47.5%	44.3%	42.1%	64.0%	6.1%	9.0%

Prescribing EBTs within 30 days after first diagnosis of MI, angina, PAD or PAD/CHD

	ACEI/ARBs	β-blockers	CCB	Statins	Aspirin	Clopidogrel	Oral-anticoagulant
MI	30.2%	35.5%	9.0%	36.1%	42.8%	11.6%	3.3%
Angina	15.3%	30.5%	16.1%	23.7%	34.1%	4.9%	
PAD	8.9%	5.8%	9.5%	10.9%	19.2%	1.2%	2.2%
PAD/CHD	20.1%	20.5%	20.5%	27.1%	30.4%	3.7%	4.2%

Prescribing EBTs at any time point after first diagnosis of MI, angina, PAD or PAD/CHD

	ACEI/ARBs	β-blockers	CCB	Statins	Aspirin	Clopidogrel	Oral-anticoagulant
MI	72.4%	72.4%	36.4%	83.5%	83.1%	29.3%	91.4%
Angina	58.7%	72.4%	54.1%	83.8%	85.2%	22.8%	
PAD	43.0%	29.0%	36.7%	59.8%	63.7%	11.9%	8.8%
PAD/CHD	69.0%	61.8%	57.6%	84.6%	82.7%	21.4%	31.1%

Sex differences in prescribing EBTs within 30 days after first diagnosis of MI, angina, PAD or PAD/CHD

	ACEI/ARBs	β-blocker	CCB	Statins	Aspirin	Clopidogrel	Oral anticoagulant
MI							
Male	31.3%	38.2%	8.6%	38.4%	44.2%	12.4%	2.9%
Female	28.4%	31.4%	9.6%	32.6%	40.5%	10.3%	4.0%
Angina							
Male	16.6%	32.1%	15.6%	26.0%	34.8%	5.8%	
Female	13.8%	28.4%	16.6%	20.9%	33.3%	3.8%	
PAD							
Male	8.4%	5.3%	8.9%	9.5%	18.2%	1.2%	2.4%
Female	9.4%	6.4%	10.3%	12.5%	20.5%	1.3%	2.0%
PAD/CHD							
Male	19.3%	21.9%	20.1%	29.1%	31.3%	3.8%	5.0%
Female	16.1%	18.2%	21.2%	23.5%	28.8%	3.6%	2.8%

Age (older vs. younger patients) differences in prescribing EBTs within 30 days after first diagnosis of MI, angina, PAD or PAD/CHD

Age (years)/ disease	ACEI/ARBs	β-blocker	CCB	Statins	Aspirin	Clopidogrel	Oral anticoagulant
MI							
< 55	28.6%	40.6%	6.7%	41.0%	44.2%	12.7%	2.0%
85+	19.9%	19.2%	7.4%	14.1%	33.3%	7.7%	2.0%
Angina							
< 55	13.4%	33.5%	13.9%	28.5%	32.1%	6.2%	
85+	14.9%	14.0%	14.3%	5.8%	35.6%	2.4%	
PAD							
< 55	5.4%	5.8%	4.2%	11.8%	14.0%	0.7%	2.2%
85+	5.7%	3.3%	7.1%	0.9%	18.0%	1.9%	2.4%
PAD/CHD							
< 55	14.3%	24.4%	26.1%	33.6%	25.2%	2.5%	4.2%
85+	16.9%	11.3%	9.9%	12.7%	18.3%	9.9%	1.4%

Appendix 8

Studies examined prescribing trends in the UK for CHD

	ACEI/ARBs	β-blockers	CCB	Statins	Aspirin	Clopidogrel	Antiplatelet
DeWilde et al[257] UK, 1994 vs. 2005	13.5 vs. 57.0	29.0 vs.55.0		4.00 vs. 80.0			31.0 vs. 75.0
	12.0 vs. 51.0	25.0 vs. 48.0		3.00 vs. 70.0			37.0 vs. 74.0
Ryan et al[258] England-Wales, 1994 vs. 1998				4.2 vs. 29.0	46.3 vs. 61.5		
EUROASPIRE I & II[259] 9 countries 1995-2000	29.5 vs. 42.7	53.7 vs. 66.4		18.5 vs. 57.7			81.2 vs. 83.9

Studies examined prescribing trends in the UK and Denmark for MI

	ACEI/ARBs	β-blockers	CCB	Statins	Aspirin	Clopidogrel
Carey et al[294] **UK, 2005-2006 6 months**, GP				46.7 vs.94.4		
Hardoon et al[322] **UK, 1991 vs. 2002 (GP 90 days)**	11.0 vs. 71.0	26.0 vs. 68.0				
Gasse et al[316] **Denmark 1997 vs. 2003 6 months, post di**	35.0 vs. 52.7	74.0 vs. 76.2		17.0 vs. 70.5	38.0 vs. 83.0	
Gislason et al[287] **Denmark, 1995 vs. 2002 30 days**	24.5 vs. 35.5	38.1 vs. 67.9				

This Study **Scotland** **1997-2005** **30 days**	12.3 vs. 46.5	19.2 vs. 43.4	6.6 vs. 8.7	9.7 vs. 54.7	28.9 vs. 53.3	0.0 vs. 35.1

Studies examined prescribing trends in Denmark for PAD

	ACEI/ARBs	β-blockers	CCB	Statins	Aspirin	Clopidogrel
Gasse et al **Denmark** **1997-2003** **6 months**	23.0 vs. 41.0	9.00 vs. 15.0		3.00 vs. 22.0		
Subherwal et al **Denmark** **2000-2007** **3 months**	11.0 vs. 17.0			9.00 vs. 56.0		
This Study **Scotland** **1997-2005** **30 days**	3.5 vs. 14.6	3.5 vs. 8.5		1.1 vs. 31.2		

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