The Prediction of Adverse Outcomes Following Major Non-Cardiac Surgery

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Dedication

To my wife Carol
And my two beautiful girls Eilidh and Rosie

Declaration

This thesis represents original research carried out in the Department of Surgery, Gartnavel General Hospital, in collaboration with the Department of Cardiology at the Western Infirmary, Glasgow.

I have undertaken all of the data collection, patient follow-up, analysis of data and manuscript preparation. Assistance with patient recruitment and sample collection in the early part of the study came from other members of the research team. Biochemical analyses were performed by Dr J Morton, Department of Biochemistry, Western Infirmary. Funding for sample analyses was provided from the research funds of the Departments of Surgery and Cardiology.

None of the work presented in the thesis has been previously submitted for any other degree. All of the studies were carried out following ethical approval from the West of Scotland Research Ethics Committee and all patients provided written consent prior to inclusion.

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Summary

The prediction of adverse outcomes following major non-cardiac surgery is complex. Clinical variables and risk factors, functional status, electrocardiography and non-invasive cardiac investigations can all be used to assess and stratify the risk of post-operative cardiac morbidity or mortality. Multiple factors can be combined into bed-side scoring systems. Increasingly, cardiac biomarkers such as b-type natriuretic peptide (BNP) have been shown to predict heart failure and mortality in non-surgical populations.

In the studies in this thesis, I have investigated the incidence of peri-operative cardiac morbidity and mortality in patients undergoing major non-cardiac surgery and identified clinical variables that predicted adverse outcomes. I have tested the utility of BNP for prediction of cardiac complications. I have investigated the long-term survival of the patients in the cohort to identify predictors of reduced survival. I have examined the predictive value of the pre-operative 12-lead ECG for adverse outcomes. I have also studied the utility of a commonly used risk scoring system, the revised cardiac risk index (RCRI), for prediction of cardiac events.

The study was a prospectively performed observational study of consecutive patients undergoing major surgery. The cohort consisted of patients undergoing aortic surgery (25.8%), lower limb bypass surgery (29.8%), amputation (25.2%) and laparotomy (20.0%). The patients underwent post-operative screening for myocardial infarction; consisting of serial ECG and troponin measurement. The end-points were major adverse cardiac event (MACE), defined as myocardial infarction or cardiac death and all-cause mortality. Long term follow-up was performed following discharge.

Three hundred and forty-five patients were recruited to the trial. Forty-six patients (13.3%) suffered a peri-operative MACE and twenty-seven patients (7.8%) died in the post-operative period (six weeks). Independent predictors of peri-operative MACE were pre-operative anaemia, urgent surgery, a history of hypertension and age > 70 years. Pre-operative BNP was significantly higher in patients who subsequently went on to have a peri-operative MACE, compared with those who did not. An elevated BNP was an independent predictor of both

MACE and peri-operative mortality on multivariate analysis. A low BNP was highly indicative of an uneventful post-operative period, with a negative predictive value of 96% for MACE and 95% for all-cause mortality. Traditional clinical markers of heart disease, such as past history of ischaemic heart disease, prior myocardial infarction, cerebro-vascular disease or history of cardiac failure provided no predictive utility for either MACE or mortality.

The mortality rate at 1 year was 19.1%. The median follow-up period was 953 days (IQR 661-1216 days). Age > 70 years, diabetes, hypertension, renal impairment, a history of left ventricular failure, anaemia and urgent surgery were associated with reduced long-term survival. A BNP concentration of 87.5 pg/ml provided the best combined sensitivity and specificity for prediction of long-term mortality. Patients with an elevated BNP (>87.5 pg/ml) had a significantly reduced survival and BNP >87.5 pg/ml independently predicted reduced survival on Cox regression analysis. Urgent surgery and anaemia were also independent predictors of reduced long-term survival.

An abnormal ECG was observed in 41% of patients recruited. An abnormal ECG was associated with an increased peri-operative MACE and mortality rate. Ventricular strain and prolonged QTc (>440ms) were ECG abnormalities that predicted MACE on multivariate analysis. Patients with an abnormal ECG, but no prior cardiac history, represent a high risk group that may benefit from optimisation.

The studies in this thesis have identified that BNP, a simple pre-operative blood test, provides valuable information regarding the risk of both peri-operative morbidity and mortality, and long-term survival after major non-cardiac surgery. Improved risk stratification could allow targeted intervention and medical optimisation prior to surgery with the aim of modifying the risk of adverse outcomes.

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List of Abbreviations

ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
AF	Atrial Fibrillation
AHA	American Heart Association
APA	Antiplatelet Agent
ASA	American Society of Anaesthesiology
AUC	Area Under The Curve
BBB	Bundle Branch Block
BMT	Best Medical Therapy
BNP	B-type Natriuretic Peptide
CAD	Coronary Artery Disease
CABG	Coronary Artery Bypass Graft
CCF	Congestive Cardiac Failure
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPET	Cardiopulmonary Exercise Testing
CRP	C-Reactive Protein
cTn	Cardiac Troponin
CVD	Cerebrovascular Disease
DSE	Dobutamine Stress Echocardiography
DES	Drug Eluting Stent
DM	Diabetes Mellitus
ECG	Electrocardiograph
EDTA	Ethylenediaminetetraacetic Acid
ERAS	Enhanced Recovery After Surgery
ESC	European Society of Cardiology
ESHF	End Stage Heart Failure
EVAR	Endovascular Aneurysm Repair
GFR	Glomerular Filtration Rate
GP	General Practitioner
HES	Hospital Episode Statistics
HeS	Hydroxyethyl Starch
HR	Hazard Ratio

HR	Heart Rate
IDDM	Insulin Dependent Diabetes Mellitus
IHD	Ischaemic Heart Disease
IQR	Interquartile Range
LAD	Left Axis Deviation
LVAD	Left Ventricular Assist Device
LVH	Left Ventricular Hypertrophy
LVF	Left Ventricular Failure
LVSD	Left Ventricular Systolic Dysfunction
MACE	Major Adverse Cardiac Event
MET	Metabolic Equivalent
MDT	Multidisciplinary Team
MI	Myocardial Infarction
NCS	Non-Cardiac Surgery
NPV	Negative Predictive Value
NSQIP	National Surgical Quality Improvement Program
NT-proBNP	N-terminal Pro-B-type Natriuretic Peptide
OAA	Oral Antiplatelet Agent
OD	Oesophageal Doppler
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
PMI	Peri-Operative MI
PPV	Positive Predictive Value
PVC	Premature Ventricular Contraction
PVD	Peripheral Vascular Disease
RCRI	Revised Cardiac Risk Index
RCT	Randomised Controlled Trial
ROC	Receiver Operating Characteristic
TIA	Transient Ischaemic Attack
UK	United Kingdom
US	United States
VO_2	Oxygen Consumption

1 Introduction

1.1 Cardiac morbidity and mortality following major non-cardiac surgery – what is the scale of the problem?

Peri-operative cardiac events are the commonest cause of peri-operative mortality in the Western world.[1] Worldwide, it is estimated that over 200 million major surgical procedures are performed annually, with the majority of cases performed in developed countries.[2] This number will increase as health expenditure rises in developing countries, as will concerns about surgical safety peri-operative morbidity and mortality.[3] A very conservative estimation of between 500,000 and 900,000 patients worldwide will suffer a peri-operative cardiac event following non-cardiac surgery (NCS).[4] Cardiac morbidity presents a significant burden to both patients and healthcare providers. Furthermore, in the setting of an aging population, this will become a more pressing problem in the future.

Numerous studies have presented the rates of peri-operative major adverse cardiac events (MACE) and mortality in patients undergoing NCS. The results of many of these studies will be individually discussed later in this chapter. However, from the larger studies and meta-analyses, the reported incidence of major cardiac complications ranges from 1% to 28%.[5-8] Unsurprisingly, the observed MACE rate is very variable, especially when considering studies performed within different surgical subspecialties. For example, patients undergoing major vascular surgery have a high underlying incidence of overt and occult heart disease and accordingly a high rate of peri-operative events are found.[9] In a historical paper from the Cleveland Clinic Foundation, Hertzer and colleagues performed percutaneous coronary angiography on 1000 patients prior to elective vascular surgery.[10] Severe coronary artery disease (CAD), defined as coronary artery stenosis >70% in one or more vessel, was present in 60% of cases. Only 8% of patients had normal coronary arteries. A recent review found that the incidence of post-operative myocardial infarction (MI) amongst elective vascular patients was as high as 26%.[11]

The study methodology will also affect the observed MACE rate. Reporting of cardiac events is often higher in prospectively collected cardiac outcome studies with active screening for peri-operative cardiac events, than from retrospective studies relying on clinical variables and outcomes gathered from databases.[12]

For example, Davenport and colleagues analysed a prospectively collected National Surgical Quality Improvement Program (NSQIP) database from 142 North American institutions.[8] They included over 180,000 patients undergoing a variety of surgical procedures, including major abdominal (39%) and vascular (16%) surgery, and more minor procedures, such as hernia surgery (25%). This large study revealed a modest 1.29% unscreened cardiac event rate. Interestingly, of the patients who suffered an event, 59% went on to die on that admission. This high same admission mortality rate following a peri-operative MI has been identified in other studies.[4,13] Prospective screening for cardiac events post-operatively will inevitable identify a number of 'silent' cardiac events.[14] Evidence suggests that clinically unrecognised MI carries a similar prognosis to patients with a clinically apparent MI.[15]

Large studies examining peri-operative cardiac morbidity and mortality in the United Kingdom and, in particular, Scotland are lacking. National English database analysis studies exist that present mortality figures for elective and emergency NCS, however little qualitative details about cardiac morbidity can be extracted from these studies.[16,17] Accurate data regarding the scale of the problem locally, and information for clinicians to allow risk stratification, is crucial.

I have found this literature review of peri-operative cardiac morbidity challenging from a number of perspectives. The following issues were encountered frequently while writing this chapter;

- Diverse study methodology,
- Variable or unclear endpoints,
- Heterogeneous populations,
- Rapidly evolving technologies, both surgical and medical.

Finally, and perhaps most notable, are the shocking allegations of research fraud directed at the chief investigator of one the world's leading research institutes into peri-operative cardiac morbidity. This will be discussed at the end of this chapter.

1.2 Pathophysiology of post-operative myocardial infarction (PMI)

A universal definition of myocardial infarction has been published by the joint task force from the European Society of Cardiology (ESC), the American College of Cardiology (ACC), the American Heart Association (AHA) and the World Heart Federation. The criteria for the diagnosis of acute myocardial infarction are detailed in Figure 1.1.

Figure 1.1 Criteria for diagnosis of acute myocardial infarction

Criteria for Acute Myocardial Infarction (MI), adapted from[18]

The term MI should be used when there is evidence of myocardial necrosis in a setting consistent with myocardial ischaemia. Any of the following criteria meets the diagnosis of myocardial infarction.

- Detection of the rise and fall of cardiac biomarkers (preferably troponin) together with evidence of myocardial ischaemia with one of the following:
  - Ischaemic symptoms,
  - ECG changes suggesting acute ischaemia (new ST-T changes or new left bundle branch block),
  - Development of pathological Q waves on ECG,
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Sudden, unexpected cardiac death, involving cardiac arrest with symptoms suggestive of myocardial ischaemia and accompanied by ischaemic ECG changes.
- For patients undergoing percutaneous coronary intervention (PCI) with normal baseline troponin, elevations of cardiac biomarkers are indicative of necrosis. Elevations of biomarkers 3x99th percentile of upper reference limit (URL) define PCI-related MI .
- For coronary bypass grafting (CABG) with normal baseline troponin, elevation of biomarkers greater than 5x99th percentile of (URL) define CABG-related MI.
- Post-mortem findings of acute myocardial infarction .

The post-operative patient is subjected to a variety of adverse physiological events; haemodynamic instability, pro-inflammatory response, deranged coagulation, hypothermia and immobility. Accordingly, it is no surprise that these patients are exposed to a higher risk of cardiac events. Although the peri-operative period can be likened to the ultimate myocardial stress test, in fact it is very unlike a stress test. Peri-operative stress can be gradual, variable and prolonged, with no fixed end-point, rather than the controlled, rapidly increasing cardio-respiratory stress of an exercise tolerance test.

There are no standardised criteria for the diagnosis of post-operative myocardial infarction (PMI). There are 2 suggested mechanisms of evolution for the PMI, based on the classification of different types of myocardial infarction.[18]

A. Acute coronary syndrome (Type 1 PMI)

Rupture of an unstable coronary artery plaque due to the systemic inflammatory response to surgery leads to thrombus formation and arterial occlusion.[18]

B. Oxygen supply-demand imbalance (Type 2 PMI)

Tachycardia and increased ventricular workload in the presence of pre-existing coronary artery disease results in an oxygen supply / demand mismatch leading subendocardial hypoperfusion and subsequent infarct.[13] These events may be potentiated by peri-operative anaemia, arrhythmias and hypotension.[19]

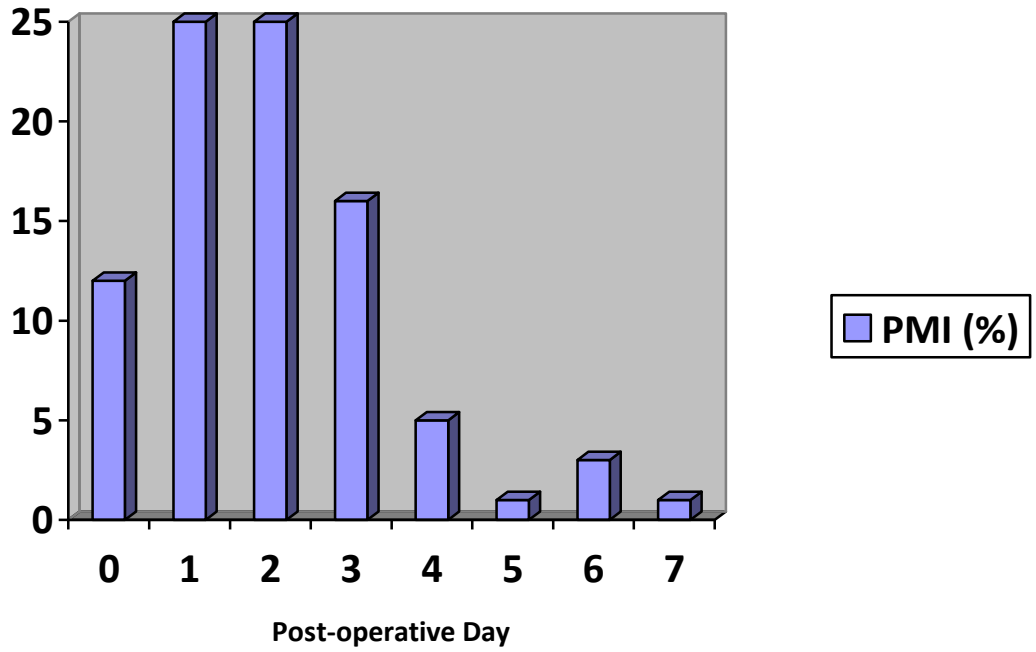
The exact aetiology of PMI compared with MI in the non-surgical patient is unclear. Evidence to support type 1 PMI comes from cadaveric data. A post-mortem study by Dawood and colleagues found evidence of coronary plaque rupture or haemorrhage in 55% of patients, who had suffered a fatal MI within 30 days of NCS.[20] This is confirmed by Cohen and colleagues, who studied the post-mortem coronary arteries of twenty six patients who had undergone a variety of NCS procedures complicated by a fatal MI.[21] They demonstrated a 46% rate of plaque disruption in this cohort.

The association between peri- and post-operative ST-segment depression, subendocardial ischaemia and PMI was explored by Landesberg and colleagues.[22]

They demonstrated that prolonged periods of ST-segment depression (>2 hours) on continuous monitoring was significantly associated with cardiac events, and that this preceded 85% of MACE. Similarly, Fleisher and colleagues performed continuous peri-operative ECG monitoring of 145 high risk surgical patients.[23] In the patients who suffered a PMI, 78% had preceding ST depression that lasted longer than 30 minutes. In this study, ST depression was a stronger predictor of MACE than any collected pre-operative variables.

Bicard and Rodseth have performed a review of the pathophysiology of PMI.[24] In their review of post mortem studies, pre-operative coronary angiography studies and peri-operative myocardial ischaemia trials, they concluded that type 1 PMI and type 2 PMI occur with approximately equal frequency. However, hypoperfusion infarcts (type 2 PMI) form the majority of early events (within the first 4 days following surgery), while type 2 events are more randomly distributed throughout the post-operative period. Figure 1.2 shows the chronological distribution of PMI. The authors noted that more than 80% of hypoperfusion events occur in patients with pre-existing CAD.

Figure 1.2. Distribution of post-operative myocardial infarction



Reproduced with publisher's permission [24].

The diagnosis of PMI is further complicated by the masking of the classical features of myocardial infarction during the immediate post-operative period by wound pain as well as regional anaesthetic techniques and systemic opiate therapy. Mangano and colleagues studied 474 high risk males undergoing NCS. They found two thirds of PMIs were clinically undetectable.[25] Badner and colleagues intensively measured serial post-operative cardiac enzymes (troponin-T and creatinine kinase) in high risk patients undergoing NCS.[14] They found only 17% of PMI cases had typical chest pain symptoms.

Several studies have examined the incidence of post-operative serum troponin elevation. Troponins are myofibrillar contractile proteins found in both skeletal and cardiac muscle. The cardiac troponin (cTn) subunits, cTn-I and cTn-T, are specific to the myocardium and can be distinguished from skeletal isoforms using immunological techniques.[26,27] Cardiac troponins are highly sensitive and specific markers of myocardial injury.[28,29] Patients presenting with acute coronary syndrome in the non-operative setting have an increased mortality if raised cTn is evident.[30] Elevation of cardiac troponins is integral to the diagnosis of myocardial infarction.[18]

Post-operative troponin elevation is common. Landesberg and colleagues investigated over 500 consecutive high risk patients undergoing vascular surgery with serial post-operative serum cTn analysis.[31] They identified a raised cTn in 23.1% of patients, with only 2.3% having a clinically detectable MI (troponin elevation and chest pain or ECG changes). Kim and colleagues demonstrated a 12% rate of post-operative cTn elevation in an unselected vascular cohort of over two hundred patients.[32] Similarly, results from the Erasmus Centre at Rotterdam have also demonstrated a 14% rate of asymptomatic post-operative cTn elevation.[33]

1.3 Implications of post-operative myocardial infarction (PMI)

Patients who suffer a peri-operative MI (PMI) have a poorer outcome than those who do not suffer a cardiac event.[1] As previously discussed, there are no universally accepted criteria for PMI. Several different definitions of peri-operative cardiac injury have been used in peri-operative cardiac morbidity studies; however, the most commonly used is the definition of a non-fatal MI published by The Joint European Society of Cardiology/American College of Cardiology Committee[34]: a typical rise and gradual fall of cTnI with at least one of the following: ischaemic symptoms, development of pathological Q waves on the ECG, ECG changes indicative of ischaemia (ST segment elevation or depression) or coronary artery intervention.

Studies consistently show that patients suffering a PMI have a poorer post-operative course,[25] and a higher same admission mortality rate.[35] For example, Devereaux and colleagues showed that PMI was an independent risk factor for post-operative mortality (OR 3.45, 95% CI 2.20-5.41).[5] Similarly, patients who have had a PMI have a higher rate of cardiac morbidity following discharge. Mangano and colleagues studied 444 patients undergoing mixed NCS.[36] They found a 28-fold increase in the incidence of subsequent MACE within 6 months of surgery in PMI patients compared with those patients who did not have a PMI.[36] Table 1.1 shows the reported incidence of peri-operative MACE in a selection of larger RCTs, observational trials and database analysis studies.

Vascular patients are at a particularly high risk of PMI. Sprung and colleagues reviewed 8 years of vascular surgery at Cleveland Clinic, Ohio and found that of those patients who had a peri-operative MI, 20.6% went on to have a cardiac death in the same admission.[37] Le Manach and colleagues performed post-operative troponin surveillance on over one thousand consecutive patients undergoing aortic surgery.[38] They found a PMI rate of 5%. Patients who suffered a PMI had a significantly higher in-hospital mortality rate than those who did not (22% vs. 3%, $p<0.001$).

Albaladejo and colleagues reported the results of the RECO study, which examined the post-operative outcomes of 1134 patients who had previous

percutaneous coronary intervention (PCI) and stent insertion.[39] They found that despite previous revascularisation the MACE rate was 10.9%, and the 30 day mortality in the MACE group was 14.5%. McFalls and colleagues found that patients with evidence of coronary artery disease on angiography, undergoing elective vascular surgery, had an 8.4% MACE rate.[40] Poldermans and colleagues investigated over 400 patients with multiple risk factors for IHD prior to vascular surgery.[41] Dobutamine stress echocardiography demonstrated extensive ischaemia in 101 patients. The PMI rate in these patients was 32.7%, and the one year mortality was 24.7%.

In summary, there is a considerable variation in the reported incidence of PMI depending on the patient group studied and the use or not of post-operative screening for MI.

Table 1.1 Incidence of peri-operative major adverse cardiac events (MACE) in selected randomised control trials, observational studies and database analyses published within the last 15 years

Author	Year of Recruiting	Year of Reporting	Cohort Size	Study Population	Screened for MI?	MACE rate	Mortality Rate
Randomised Controlled Trials							
Brady[42]	2001-2004	2005	103	Vascular Surgery	Yes	31.1%	3.9%
Mackey[43]	2003-2004	2006	236	Vascular Surgery	No	17.8%	3.4%
Devereaux[5]	2002-2007	2008	8,351	High risk for IHD, mixed NCS	Yes	6.4%	2.7%
Dunkelgrun[44]	2004-2008	2009	1,066	Intermediate risk for IHD, mixed NCS	No	4.0%	2.3%
Oscarsson[45]	2005-2008	2010	220	High or intermediate risk surgery	Yes	5.4%	2.0%
Observational Studies							
Lee[6]	1989-1994	1999	4,315	Mixed NCS	Yes	2.9%	Not documented
Gilbert[46]	1995-1997	2000	2,035	Mixed NCS	No	6.4%	2.4%

Author	Year of Recruiting	Year of Reporting	Cohort Size	Study Population	Screened for MI?	MACE rate	Mortality Rate
Kumar[47]	1992-1995	2001	1,121	Known or suspected heart disease - mixed NCS	Yes	8.1%	Not documented
Boersma[48]	1996-1999	2001	1,351	Vascular Surgery	No	3.3%	Not documented
Aziz[49]	1996-2001	2003	365	EVAR	N/A	14.2%	2.7%
Albaladejo[39]	2007-2009	2011	1,134	Patients with previous coronary stents	No	10.9%	Not documented
Sabate[35]	2007-2008	2011	3,387	Intermediate – high risk NCS	No	4.3%	1.9%
Orcutt[50]	2008-2011	2012	1,182	Vascular Surgery	No	4.9%	Not documented
Database Analyses							
Davenport[8]	2002-2004	2007	183,069	Mixed NCS	N/A	1.3%	Not reported
Kheterpal[51]	2002-2006	2009	7,740	Mixed NCS	N/A	1.1%	Not reported
Bertges[52]	2003-2008	2010	10,081	Vascular Surgery	N/A	6.3%	Not reported

Abbreviations; MACE - major adverse cardiac event, MI - myocardial infarction, IHD - ischaemic heart disease, NCS - non-cardiac surgery, EVAR - endovascular aneurysm repair.

1.3.1 Raised post-operative cardiac troponin (cTn)

There are currently over 200 publications examining the incidence and significance of peri-operative cTn rise. Several cardiac markers have been studied and a wide variety of study designs have been employed. For the purposes of this chapter, I will discuss a selection of representative studies.

The implication of asymptomatic cTn elevation was investigated in 297 patients undergoing aortic or lower limb vascular surgery, of whom 28 (12%) patients had an elevated post-operative cTn-I.[32] This was associated with a 6-fold increased risk of 6-month all cause mortality (OR 5.9: 95% CI, 1.6-22.4) and a 27-fold increase in PMI (OR 27.1; 95% CI, 5.2-142.7). The authors also noted a dose-response relationship between cTn-I and outcome. For example patients with a markedly elevated cTn-I (>3.0 ng/ml) had significantly poorer 6 month mortality than the group of patients with only a modestly elevated cTn-I (≤0.35 ng/ml) (OR, 4.9; 95% CI, 1.3-19.0). Oscarrson and colleagues studied a group of 211 patients undergoing urgent NCS (defined as surgery required within 4 days of an unplanned admission).[53] An elevated post-operative cTn was observed in as many 33% of patients, and these patients had a higher 30-day mortality than those patients without an elevated cTn (23% vs. 7%, p=0.003).

Furthermore, cTn elevation remains predictive of poorer outcome when patients who have had a peri-operative MACE are excluded. Lopez-Jimenez and colleagues studied the 6-month outcome of 772 patients undergoing major NCS (defined as expected hospital stay of >2days).[54] Patients with a peri-operative MACE were not included in the study. An asymptomatic cTn elevation was observed in 12% of patients. These patients had a higher rate of MACE during the 6 month follow-up period (RR 5.4, 95% CI 2.2-13, p=0.001).

Recently, the results of a large prospective multicentre study examining the association between raised post-operative cTnT and post-operative outcomes have been reported.[55] The trial recruited over 15000 patients undergoing NCS and demonstrated that peak post-operative cTnT independently predicted 30-day mortality. The higher the cTnT value, the higher the risk of mortality; 1.0% for cTnT value of <0.01 ng/ml, 4.0% for 0.02 ng/ml, 9.3% for 0.03-0.29 ng/ml and 11.6% for cTnT value of >0.30 ng/ml.

In summary, elevation in serum cardiac troponin post-operatively is a powerful predictor of outcome, and this appears to be the case for both patients who meet the criteria for MI, and those with an asymptomatic troponin rise.

1.3.2 Long term survival

Patients suffering a peri-operative cardiac event have poorer long term outcomes than those that do not.

Orcutt and colleagues investigated the long-term outcomes following 1,182 vascular procedures performed in a single North American institution.[50] A peri-operative cardiac event was associated with a significantly higher long-term mortality following multivariate Cox regression analysis (HR 5.30 (95% CI 1.77-15.96), p=0.003). Renal disease and COPD were clinical variables that remained significant after multivariate analysis. Similarly, McFalls and colleagues found an improved long term survival in patients that did not suffer a peri-operative MACE in 115 patients undergoing vascular surgery.[56] Virgilio and colleagues demonstrated, in patients undergoing EVAR, that a non-fatal MI was associated with a significantly shorter median survival (95 days vs. 2265 days, p<0.001).[57] Similarly, Archan and colleagues showed that patients suffering a PMI following EVAR had a one year mortality rate of 35.7%.[58] At a median follow-up of 2.1 years, 71.4% of PMI patients had died.

A raised post-operative troponin also has implications for longer term survival. Oscarsson and colleagues prospectively observed 546 elderly patients (>70 years) undergoing mixed NCS, and found an elevated cTn-T in 9.7% of patients.[59] Only 11.0% of patients with an elevated cTn-T had clinical signs or symptoms of cardiac ischaemia. At 1-year after surgery, patients with an elevated cTn-T had a significantly higher mortality (32.1% vs. 4.6%, p<0.001). Kertai and colleagues demonstrated a significantly higher all cause mortality during a 4-year follow-up period in patients with an elevated post-operative cTn-T compared with patients without a raised cTn-T (41% vs. 17%, p<0.001).[33]

1.3.3 Implications for health economics

Cardiac complications have economic implications for health-care providers. Fleischmann and colleagues studied nearly 4000 patients undergoing NCS.[60] A markedly increased hospital stay was seen in patients with peri-operative MACE (11 days, 95% CI: 9-12 days) compared with patients without complications (4 days, 95% CI: 3-4 days). Likewise, Sabate and colleagues noted a higher ICU utilisation (64% vs. 2%) and a longer median length of hospital stay (12 vs. 6 days) in patients who suffered a MACE compared with those that had no cardiac complications.[35]

Mackey and colleagues performed a secondary analysis of a pharmacoeconomic study of 236 high risk patients undergoing vascular surgery in a North American institution.[43] A peri-operative MACE rate of 17.8% was observed. Patients who suffered a MACE had a higher mean critical care bed use (6.6 days vs. 3.7 days, $p=0.009$), longer mean length of stay (16.8 days vs. 10.0 days ($p<0.001$) and higher re-admission rate (23.8% vs. 10.3%, $p=0.02$) compared to patients without cardiac complications. Published in 2006, the authors used a national cost-of-living index to estimate an increased cost to the healthcare provider of $9980 per patient who suffered a MACE. The authors then extrapolated these figures to a national level. They estimated the annual cost of peri-operative cardiac morbidity for vascular surgical patients alone at $444 million.

1.4 Pre-operative prediction of peri-operative morbidity and mortality

Patient and clinical variables, laboratory tests and pre-operative investigations are available to assist the assessment of patients prior to NCS. Many studies have examined the predictive value of these various factors.

1.4.1 Clinical variables

1.4.1.1 Age

The risk of peri-operative MACE and mortality rises with age, as demonstrated across many observational studies. Davenport and colleagues, using NSQIP data from over 180,000 patients, showed that the mean age in the MACE group was significantly higher than in the non-MACE group (69.3±11.5 years vs. 60.2±14.3 years, $p<0.0001$).[8]

Polanczyk and colleagues prospectively studied 4315 patients undergoing major NCS.[61] They grouped patients by age; 50-59, 60-69, 70-79 and 80 years and over and found the respective combined mortality and major morbidity were 4.3%, 5.7%, 9.6% and 12.5% ($p<0.001$). Increasing age was significantly associated with post-operative heart failure, MI and ventricular arrhythmias. Similarly, Kaafarani and collegues observed a prospectively collected cohort of 1238 patients undergoing major NCS.[62] In patients aged >56 years, they found a higher 30-day mortality (0% vs. 1.4%, $p=0.0021$) and a higher 1-year mortality (1.65% vs. 3.89%, $p=0.020$).

Fazio and colleagues presented the outcomes of over 5000 patients undergoing colorectal resection at the Cleveland clinic.[63] Patients age 65-75 had an increased rate of mortality (OR 3.28, 95% CI 1.98–5.44, $p<0.001$) compared with patients aged less than 65 years. Patients older than 85 years had an even higher mortality (OR 9.49, 95% CI 4.53–19.90, $p<0.001$).[63] The findings of a significant association between increasing age and poor post-operative outcomes is supported by numerous other trials.[64-67]

1.4.1.2 Cardiac co-morbidity

A past history of cardiac disease is a commonly collected clinical variable in the assessment of cardiac risk. Sabate and colleagues have reported the results of the ANESCARDIOCAT study.[35] They performed a large, multicentre Spanish observational study of patients undergoing intermediate-to-high risk surgery, as defined by the ACC / AHA guidlines. They recruited 3387 patients, and observed a 4.3% MACE rate. They found a higher MACE rate in patients with a history of CAD (12.5% vs. 3.6%, $p<0.0001$), previous congestive heart failure (14.0% vs. 3.6%, $p<0.0001$) and previous revascularisation (PCI or CABG) (15.9% vs. 4.0%, $p<0.0001$).

Kheterpal and collegues performed a single centre analysis of NSQIP data for 7,740 patients. They found a significantly higher rate of MACE in patients with active heart failure ($p<0.001$), previous cardiac intervention ($p<0.001$) and hypertension requiring medication ($p<0.001$). Interestingly, there was no association between an MI within the preceding 6 months and peri-operative MACE.

Knowledge of a previous MI, and in particular the timing of the infarction prior to surgery, is an important consideration in pre-operative assessment. Kumar and colleagues prospectively studied over a thousand patients with known heart disease undergoing mixed major NCS.[47] An overall MACE rate of 8.1% was observed, although in the aortic surgery subgroup it was 23.8%. When considering a history of previous MI, both recent (<6 months before surgery) and earlier (>6 months before surgery) MI were univariate predictors of MACE. Likewise, both recent MI (OR 4.9, 95% CI 1.9-12.9) and earlier MI (OR 2.2, 95% CI 1.4-3.5) remained significant on multivariate analysis. Recent MI was the strongest predictor of an adverse outcome of all the variables studied. More recently, Livhits and colleagues performed an analysis of the Californian Patient Discharge Database for orthopaedic, major abdominal and vascular surgery for the years 1999 to 2004.[68] From the 500,000 patients extracted from the database, 2.9% had suffered an MI within the preceding year. The authors subdivided this group into recent MI; 0 to 30 days prior to surgery (13.7%), 31 to 60 days (13.0%), 61 to 90 days (10.7%), 91 to 180 days (24.8%) and 181 to 365 days (37.8%). The overall PMI rate was 1.4%, but of these 32.8% occurred in

patients with an MI 0-30 days prior to surgery. The PMI rate fell as time from pre-operative MI increased (31-60 days 17.8%, 61-90 days 6.4% and 91-180 days 5.3%, p<0.001). Similarly, the 30 day mortality and 1 year mortality fell as the time from pre-operative MI increased.

Therefore, the American College of Cardioligy and American Heart Association (ACC/AHA) guidelines recommend deferral of elective surgery if an MI is present within 6 weeks of surgery, and caution within the first 6 months.[69]

1.4.1.3 Previous revascularisation

The role of protective coronary revascularisation in patients undergoing NCS is unclear. In an attempt to answer this question, Eagle and colleagues utilised the Coronary Artery Surgery Study (CASS) database, which included 24,959 participants with suspected coronary disease recruited from 1974 to 1979. The cohort included patients who had received a CABG, and patients who were treated medically. They identified those patients who required NCS during the subsequent 10 years. Nearly 2000 patient had subsequent high risk surgery, defined as intra-thoracic, intra-abdominal, head and neck and vascular surgery. Patients with prior CABG had reduced PMI rates (0.8% vs. 2.7%, p=0.002) and fewer postoperative fatalities (1.7% vs. 3.3%, p=0.03), compared with the medically managed group.

Since this trial, there has been an overwhelming trend towards percutaneous coronary intervention (PCI) rather than CABG in patients with unstable CAD.[70] Subsequently, the incidence of patients requiring NCS after coronary stent insertion is rising.[71] Berger and colleagues performed a secondary analysis of a prospectively collected drug eluting stent (DES) registry and found that 4.4% of patients underwent major NCS in the year after stent placement.[72] Similarly, Gandhi and colleagues report their single centre experience of over 800 patients following DES insertion.[73] They found a 7% incidence of NCS at 1 year, 18% at 2 years and 22% at 3 year follow-up.

Subsequently, Hollis and colleagues have published a meta-analysis exploring the outcome of patients with previous coronary stenting undergoing NCS.[74] They examined 28 studies that included patient data regarding previous coronary

stent insertion. Peri-operative MACE rates ranged from 0% to 18% in patients with a stent inserted ≤1 year prior to surgery and 0% to 12% in patients >1 year following stent insertion. They concluded that this offered some further evidence to support deferring non-urgent surgery for more than one year after stent insertion.

1.4.1.4 Other medical co-morbidities

It would be expected that diabetes increases the risk of peri-operative cardiac events due to increased atherosclerosis, enhanced endothelial dysfunction, accentuated systemic inflammatory response and elevated platelet activation.[75] Furthermore, diabetic patients tend to have diffuse, multilevel coronary disease.[76] The ANESCARDIOCAT study found a higher incidence of MACE in type I DM (9.8%) and type II DM (5.1%) than those without diabetes (3.9%, p=0.01).[35] This is in keeping with other studies that have found diabetes to be an independent predictor of MACE.[6,77,78]

Renal impairment has been shown to predict MACE. Lee and colleagues found a raised pre-operative serum creatinine (>2mg/dl) was associated with a higher rate of post-operative MACE in a cohort of nearly three thousand patients (OR 3.0, 95% CI 1.4-6.8).[6] Similarly, Davenport and colleagues found elevated pre-operative creatinine was an independent predictor of post-operative MACE in over 180,000 patients analysed from a large national database.[8]

1.4.1.5 Functional capacity

The use of Metabolic Equivalents (METs) allows an assessment of an individual patient's functional capacity. METs are estimations of the energy cost of a certain activity compared with a reference basal metabolic rate. Hlatky and colleagues introduced the concept of an activity status index in 1989.[79] A subsequent consensus statement from the AHA correlated METs to stages of various exercise tolerance tests[80] and a simplified MET score for routine activities of daily living are now used [Figure 1.3].[69]

Figure 1.3 Estimated energy requirements (metabolic equivalents) for various activities

	Can you....		Can you....
1 MET	Take care of yourself? Eat, dress or use the toilet?	4 METs	Climb a flight of stairs?
↓	Walk indoors around the house?	↓	Run a short distance?
↓	Walk a block on level ground?	↓	Do heavy housework (scrubbing floors moving heavy furniture)?
4 METs	Do light housework (washing dishes or dusting)?	↓	Participate in moderate exercise like golf, bowling or dancing?
		>10 METs	Participate in strenuous activity like swimming tennis or football?

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Abbreviations; MET - metabolic equivalents.

1.4.2 Type of surgery

The type of surgery performed has implications for the rate or peri-operative MACE, with certain procedures carrying a higher risk of an adverse outcome. The ACA / AHA guidelines suggest stratification of operative procedures into low, intermediate and high risk [Table 1.2].[69]

Table 1.2 Risk stratification of non-cardiac surgical procedures

High Risk	Aortic and major peripheral vascular surgery Anticipated prolonged surgical procedure Emergency
Intermediate Risk	Intra-peritoneal and intra-thoracic surgery Carotid endarterectomy Head and neck surgery Prostate surgery
Low Risk	Superficial procedures Breast surgery Cataract surgery Endoscopic procedures

Adapted from Fleisher et al.[69]

1.4.2.1 Expediency of surgery

Patients undergoing elective surgery have an improved post-operative outcome compared with patients having similar surgery performed on a non-elective basis. Several studies have examined the increased risk of MACE and mortality associated with unplanned and emergency surgery. Kumar and colleagues, from an observational study of over 1000 mixed NCS, showed that emergency surgery (defined as within 72 hours of an unplanned admission) was an independent predictor of MACE (OR 2.6, 95% CI 1.2-5.6).[47] Slim and colleagues found that in a prospectively collected multicentre cohort of 1426 colorectal resections, unplanned surgery was the strongest predictor of mortality on multivariate analysis.[81] Likewise, Tekkis and colleagues reported the mortality rates following colonic surgery from the Association of Coloproctology of Great Britain and Ireland national database.[82] Urgent and emergency surgery was an independent predictor of peri-operative mortality in over 8000 patients included.

In high risk populations, urgent surgery increases the risk of adverse events. In over a thousand patients who had previous coronary artery stent insertion undergoing NCS, an urgent procedure was an independent risk factor for peri-operative cardiac complications (OR 3.08, 95% CI 1.74-5.74).[39] Results from a large English intensive care utilisation database show the overall elective mortality following mixed NCS was 0.44%, compared with 5.4% in patients who required an emergency operation.[16]

1.4.3 12-lead electrocardiograph

The use of a resting 12 lead ECG in screening for cardiac disease is controversial. No randomised controlled trial has been performed to investigate the benefit of screening the general population with an ECG to predict subsequent cardiac morbidity and mortality. Chou and colleagues performed a review of the studies investigating the predictive value of an ECG in asymptomatic patients.[83] Sixty-three prospective studies were identified, and the pooled results showed that ST-segment or T-wave abnormalities, left ventricular hypertrophy (LVH), left axis deviation (LAD) or bundle branch block (BBB) were associated with an increased risk of subsequent cardiac morbidity. Recently, a prospective study of an older cohort (aged 70-79 years) was performed.[84] It reported a 23% incidence of major ECG abnormalities (Q-wave abnormalities, LVH, BBB; atrial fibrillation (AF) and major ST-T wave changes) and a 13% incidence of minor abnormalities (minor ST changes). Both major and minor changes were associated with and increased incidence of subsequent MACE in the follow-up period. The authors suggest that a screening ECG in more elderly patients improves risk prediction above traditional risk factors. An accompanying editorial, however, cautions strong conclusions from this study and points out that an adequately powered RCT to investigate the benefits of a screening ECG, even in more elderly patients, would require 30,000 patients and 5 years follow-up.[85]

Nevertheless, the 12-lead ECG remains a commonly performed pre-operative investigation for patients undergoing major surgery. As with the general population, the benefit of routinely performing an ECG has been questioned in the peri-operative patient and the predictive value varies widely in published studies.[86–89] Noordzij and colleagues retrospectively analysed ECGs from over 20,000 patients undergoing non-cardiac surgery.[86] Since this study was performed retrospectively, the only endpoint used was cardiac death. ECG data improved risk prediction when combined with clinical variables in high risk procedures only. The authors conclude that an ECG is not necessary in lower risk procedures.

Van Klei and colleagues performed a retrospective secondary analysis of the post-operative outcome of over 2000 patients enrolled in a cardiac risk study.[87] The end points were PMI and all cause mortality. They found that on univariate

analysis BBB predicted outcome, but was not significant on regression modelling. They concluded that in their study group an ECG did not improve prediction beyond other risk factors identified on a careful history.

Similarly, Lui and colleagues concluded that the preoperative ECG was of limited value in a prospective study of more than 500 elderly patients (aged >70).[88] They found a high prevalence of ECG abnormalities (75.2%) and therefore suggested that the ECG had no discriminatory value. Landesberg et al carried out a prospective study of 405 patients undergoing vascular surgery.[90] They carried out rigorous post-operative screening for cardiac events (daily cardiac enzymes). Despite this, they observed a low post-operative MACE rate (4.7%). However they did find that LVH and ST segment depression was more predictive of poor outcome than standard clinical variables. Correll et al performed a case-control study comparing a cohort of 95 patients with an abnormal pre-operative ECG, matched to 195 patients without an abnormality.[89] They concluded that risk factors obtained from a careful history predicted ECG abnormalities and therefore questioned the value of the routine ECG. Conversely, the ANESCARDIOCAT study found an abnormal ECG, defined as LVH, LBBB or ST-T abnormalities, was an independent risk factor for MACE.[35]

In summary, while the ECG remains a common pre-operative investigation for patients undergoing major NCS, its predictive value for post-operative morbidity and mortality is variable. The incidence of ECG abnormalities in patients in the West of Scotland undergoing major NCS is not known.

1.4.4 Scoring systems

The categorisation of patients into defined risk groups is attractive for both researchers and clinicians alike. The derivation of a convenient, reproducible and validated scoring system that allows accurate prediction of peri-operative risk for individual patients has been attempted by a number of authors.

1.4.4.1 American Society of Anaesthesiologist (ASA) classification

The American Society of Anaesthesiology (ASA) scoring system was devised in 1963 for the standardised reporting of pre-operative functional status. The ASA grade is a simple classification of physical status and is a modification of the classification proposed by Dripps and colleagues [Table 1.3].[91] The ASA grade is universally used in clinical practice. The ASA classification is now widely used as risk stratification tool, although this is not what it was designed for. Despite this, it is often the sole method of medical morbidity stratification in large surgical trials.[92-94] However, it is often criticised due to its over-simplicity and high rate of inter-observer variation.[95-97] The ASA grade uses no information regarding the intended surgical procedure and should not be considered as an accurate tool for risk stratification.

Table 1.3 American Society of Anaesthesiologists (ASA) physical status classification

Grade	Description
I	A normal healthy patient
II	A patient with mild systemic disease
III	A patient with severe systemic disease
IV	Severe systemic disease that is a constant threat to life
V	A moribund patient that is not expected to survive without an operation

1.4.4.2 Multivariate clinical prediction scoring systems

In a landmark study from 1977, Goldman and colleagues examined the predictive value of pre-operative clinical symptoms and signs in 1001 patients undergoing major NCS.[98] From this, they produced what is considered to be the original cardiac risk index. Nine clinical variables were identified from the multivariate analysis and combined to give a 0 to 53 point score [Table 1.4]. The index allowed assignment of patients into one of four risk groups [Table 1.5].

Following the publication of the Goldman's Cardiac Risk Index, Detsky and colleagues investigated 445 consecutive patients that were referred for a cardiology opinion prior to major NCS.[99] They found that the addition of unstable angina and an MI at any time prior to surgery improved the accuracy of cardiac morbidity prediction. Both of these scoring systems are cumbersome and difficult to apply to bedside practice. Also, they proved less accurate out with the derivation population, leading to questions about general applicability of these indices.[46,100]

In 1999, the Cardiac Risk Index was further amended and simplified with Goldman as the senior investigator and presented as the Revised Cardiac Risk Index.[6]

Table 1.4 Components of Goldman's Index

Criteria	Points Weighting
Age >70 years	5
MI within 6 month	10
Signs of Heart Failure*	11
Aortic Stenosis	3
Arrhythmia	7
5 or more PVCs per minute**	7
General Medical Co-morbidity***	3
Emergency Surgery	4
Intraperitoneal, Intrathoracic or Aortic Surgery	3

Definitions;
*Ventricular gallop or raised JVP, ** PVC – Premature Ventricular Complexes, ***Any one of the following; hypoxia, hypercarbia, acidosis, renal impairment, chronic liver disease or bed ridden. Adapted from[98].

Table 1.5 Risk of cardiac complications as predicted by the Goldman Index

Points Score	Risk of Cardiac Complication
0-5	1%
6-12	7%
13-25	14%
26-53	78%

Adapted from[98].

1.4.4.3 Revised Cardiac Risk Index

The Revised Cardiac Risk Index (RCRI) is a commonly used scoring system for assessing cardiac risk in patients undergoing major non-cardiac surgery.[6] The RCRI scores patients according to 6 equally weighted clinical categories [Table 1.6]. The RCRI defines Class 1 as no factors present, Class 2 as 1 factor present, Class 3 as 2 factors present and Class 4 as 3 or more factors present. Results from the validation cohort of the original study suggest that the risk of a major adverse cardiac event (MACE) in Class 1, 2, 3 and 4 was 0.4%, 0.9%, 7% and 11% respectively. The pooled estimated risk of peri-operative MACE is shown in Table 1.7. Risk stratification tools, in particular the RCRI, are now included in clinical guidelines produced by the American College of Cardiology/American Heart Association (ACC/AHA)[69]

Despite the widespread use of the RCRI, few studies have attempted to directly validate the performance of the RCRI in different populations. One study from the Erasmus Centre at Rotterdam analysed the post-operative mortality of 108,593 patients undergoing NCS.[101] Due to the retrospective nature of the study, all-cause mortality and cardiac mortality were the primary endpoints. They found an all-cause mortality rate of 1.7%, and a cardiac mortality rate of 0.5%. The RCRI was predictive of mortality; 0.3% for Class 1, 0.7% for Class 2, 1.7% for Class 3 and 3.6% for Class 4. The authors improved the performance of the scoring system by adding age to the model.

A similar study by Welten and colleagues retrospectively reviewed the outcome of nearly 3000 patients undergoing open vascular surgery.[102] They also found that the predictive value of the RCRI was improved by an adjustment for age.

A recent meta-analysis has examined the uses of the RCRI.[103] The majority of the included studies simply use the RCRI as a stratification tool to display data. Only five high quality, prospectively performed studies were found that specifically aimed to validate the findings of the RCRI. The authors concluded that the RCRI demonstrated moderate performance in differentiating low and high cardiac risk within mixed surgical cohorts. However, a significantly inferior predictive value was found within specific vascular cohorts.

Table 1.6 Components of the Revised Cardiac Risk Index (RCRI)

Ischaemic heart disease*
History of heart failure
History of cerebrovascular disease
Diabetes mellitus requiring insulin therapy
Pre-operative creatinine >2.0mg/dl (176.8umol/l)
High risk surgery**

Definitions; * Presence of previous myocardial infarction, a positive exercise tolerance test, the use of nitrate therapy or the presence of pathological Q-waves on ECG. ** Thoracic, abdominal or supra-inguinal bypass surgery. Adapted from Lee at el.[6]

Table 1.7 Predicted risk of MACE based on the derivation and validation cohorts in the Revised Cardiac Risk Index

Number of Risk Factors	Risk of MACE % (95% CI)
0	0.4 (0.1-0.8)
1	1.0 (0.5-1.4)
2	2.4 (1.3-3.5)
≥3	5.4 (2.8-7.9)

Adapted from Lee et al.[6]

1.4.5 Non-invasive cardiac assessment

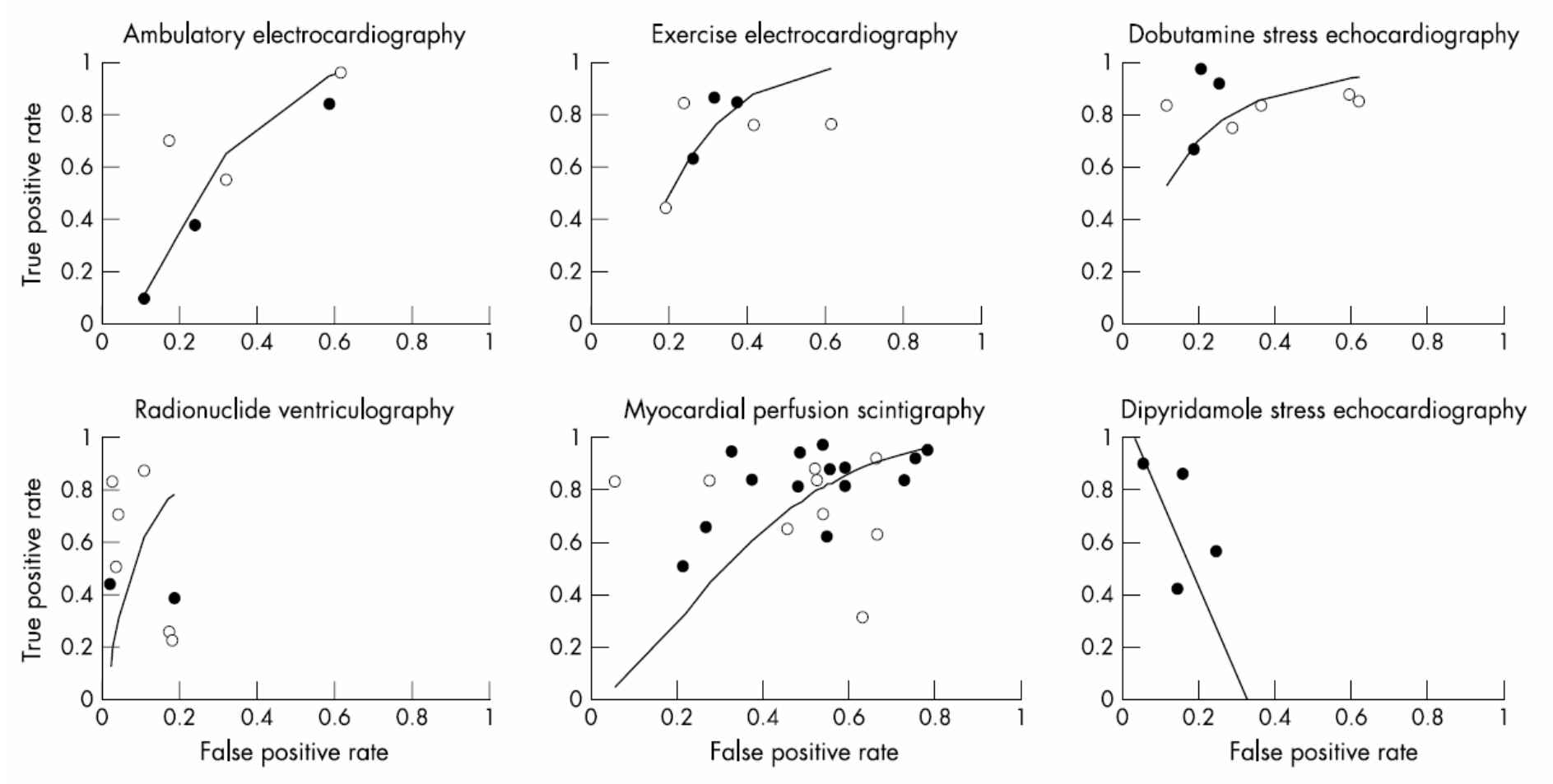
Several tools for non-invasive cardiac assessment have been tested in the pre-operative patient.

- **Transthoracic echocardiography (TTE)** provides information about ventricular function in the resting subject. An ejection fraction (EF) of <50% has been shown to predict PMI in patients undergoing vascular sugery.[104] However, not all studies have shown TTE to be a helpful predictive tool. Halm and colleagues prospectively studied 339 high risk patients undergoing NCS.[105] No echocardiographic variables predicted MACE, although an EF of <40% was predictive of a composite of cardiac death, PMI, heart failure and ventricular tachycardia (OR 2.5, 95% CI 1.2-5.0).

- **Pharmacologic stress echocardiography**, in particular dobutamine stress echocardiography (DSE), allows more accurate assessment of ventricular function and inducible new wall motion abnormalities.[106] Furthermore, it can be performed in patients who are unable to exercise.[107] Boersma and colleagues performed a predefined secondary analysis of 1351 patients recruited in a multicentre Dutch peri-operative cardiac risk trial.[48] A higher MACE rate was seen in patients with new wall motion abnormalities compared with patients without inducible motion abnormalities (13.5% vs. 1.6%, p<0.001). The authors recognize the high negative predictive value (NPV) of DSE as its main strength. More recently, Raux and colleagues examined the negative predictive value (NPV) of DSE for post-operative cTn elevation in over 400 patients undergoing aortic surgery.[108] They expected a higher frequency of elevated cTn due to the use of a more sensitive assay. Patients with a positive DSE proceeded to angiography. Of the patients with a normal DSE, 7% suffered myocardial necrosis (defined as any detectable rise in cTn). The NPV of DSE for necrosis was 92.7%. The authors point out that while the observed NPV is still high, it is lower than any previously reported value.

Several other techniques have been investigated, including radionuclide ventriculography and myocardial perfusion scintigraphy.[109,110] These investigations all have strengths and weaknesses in cardiac risk prediction. Likewise, they have variable availability at the point of care, and many remain research tools. Kertai and colleagues performed a well conducted meta-analysis of 58 studies investigating six diagnostic cardiac tests (ambulatory electrocardiography, exercise electrocardiography, radionuclide ventriculography, myocardial perfusion imaging, DSE and dipyridamole stress echocardiography).[111] They examined the performance of each test using ROC analysis [Figure 1.4] and then compared the respective performance with the other tests. In summary, the only statistically significant superiority was noted when comparing DSE with myocardial perfusion scintigraphy, in favour of DSE (OR 5.5, 95% CI 2.0-14.9). DSE trended towards superiority over all other investigations, although statistical significance was not reached. The authors concluded that DSE appeared to offer the best predictive performance of the imaging modalities studied.

Figure 1.4 Graphs showing ROC curves for non-invasive cardiac imaging



The horizontal axis represents the false positive rate and the vertical axis the true positive rate.[111] Reproduced with permission from publisher.

1.4.6 Cardiopulmonary Exercise Testing (CPET)

Whilst non-invasive cardiac investigations specifically assess cardiac function, cardiopulmonary exercise testing (CPET) allows a more global assessment of an individual patient's cardio-respiratory response to exercise.[112] CPET aims to assess functional capacity through an incremental exercise regimen, during which a breath-by-breath analysis of oxygen uptake and carbon dioxide excretion is performed.[113] The oxygen uptake (VO_2), and in particular the maximum oxygen consumption (VO_{2max}), are calculated. Increasing aerobic work produces a linear response of oxygen consumption and carbon dioxide production. Further increase in work requires additional energy supplementation through the anaerobic system. This leads to the anaerobic threshold when a relative increase in carbon dioxide production compared to oxygen consumption is observed. Other variables such as exercise-induced heart rate, heart rate recovery, arrhythmia, ischaemia and acidosis can be recorded.

Hennis and colleagues have performed a review of the trials that examined the predictive value of CPET in patients undergoing NCS.[114] Twelve studies were identified from a variety of surgical cohorts. The studies were heterogeneous with regard to the CPET derived variables studied and endpoints used. The designs of the studies were also variable, and only 3 studies were prospective. Broadly speaking, all the studies included were able to demonstrate an association between poor performance at CPET and adverse post-operative outcome (mortality or major cardio-respiratory morbidity). However, the optimal CPET-derived variable (VO_{2max} or anaerobic threshold) differed between trials, as did the optimal cut-off value for each variable. Finally, the current availability of CPET to the general clinician is low, limiting its use in pre-operative risk stratification.

In summary, CPET is attractive as a whole body assessment of oxygen uptake, utilisation and aerobic / anaerobic capacity. The test is not a single organ assessment, but a multi-organ response to stress. There are several limitations however; not all patients are able to participate, CPET is not universally available, the methodology is variable and the optimal measurements are unclear.

1.4.7 Institutional operative volume

The outcomes of individual surgeons performing certain types of major surgery have been critically reviewed in recent years following the advent of subspecialisation. This has important implications for the procedures that are performed in lower volume district general hospitals as opposed to larger referral centres.

The relationship between adverse post-operative outcome and operative volume for abdominal aortic aneurysm (AAA) surgery has been investigated by Holt and colleagues.[115] They performed a meta-analysis of 32 studies and English NHS Hospital Episode Statistics (HES) that included over 400,000 patients. The mortality rate fell as institutional operative volume rose. For elective surgery, an OR of 0.66 (95% CI 0.65-0.67) at a threshold of 43 AAA repairs per year was found in favour of higher volume hospitals. For ruptured AAA surgery, an OR of 0.78 (95% CI 0.73-0.82) at a threshold of 15 repairs per year was found in favour of higher volume hospitals. McPhee and colleagues retrospectively scrutinised the US Nationwide Inpatients Sample (NIS) data and found 11 institutions that collected individual surgeon outcomes, as well as institutional data.[116] They found that high individual surgeon activity confers a greater benefit than institutional activity for open AAA surgery. Interestingly, for EVAR, neither individual surgeon nor institutional activity predicted post-operative mortality.

A similar interest in volume related outcomes has been directed towards major oesophago-gastric resections. High volume centres have reduced post-operative complications and improved peri-operative survival.[117] A recently published Cochrane review has examined surgeon and institutional volume in patients undergoing surgery for colorectal cancer. The authors found significantly improved stage adjusted 5 year survival in patients treated at high-volume hospitals with high volume surgeons.[118] This was also true for adverse peri-operative events and post-operative mortality.

There is additional research to support the association between improved outcomes and higher surgeon / institutional volume for the surgical treatment of urological malignancy,[119,120] gynaecological malignancy[121] and oro-pharyngeal malignancy[122]

1.5 Natriuretic peptides

1.5.1 Basic biology

The cardiac neurohormone, B-type natriuretic peptide (BNP), has been identified as a biological marker of cardiac mortality. Pro-BNP is synthesised predominantly within ventricular myocytes in response to cardiac wall stress. Processing of pro-BNP results in the mature BNP molecule and the amino-terminal cleavage fragment of its N-terminal pro-BNP (NT-proBNP), both of which enter the circulation.[123] BNP has an important role in both cardiovascular and renal physiology, reducing sympathetic tone and blood pressure and maintaining circulating volume homeostasis.[123]

1.5.2 The evidence from cardiology

McDonagh and colleagues studied a random sample of asymptomatic patients that were previously enrolled in the Glasgow MONICA coronary risk factor study.[124] In this group of asymptomatic patients, a serum BNP level identified patients with LVSD on echocardiography. They also demonstrated that BNP was a better marker of LVSD than atrial natriuretic peptide. Subsequently, Zaphiriou and colleagues examined the use of BNP as a screening tool for patients' referred from primary care with symptoms suggestive of cardiac failure. This multicentre study, performed in Glasgow and London, found evidence of heart failure (clinical and radiological) in 34% of patients. Patients with heart failure had significantly higher BNP levels (285pg/ml vs. 51 pg/ml, $p<0.001$) than patients without heart failure. They concluded that BNP provided an accurate 'rule-out' test for cardiac failure.

The merits of longer term risk stratification were explored by Wang and colleagues. They recruited 3346 asymptomatic patients who attended for the sixth round of surveillance during the Framingham Offspring Study, an epidemiological study of cardiovascular risk factors.[125] BNP levels were taken, and the patients were followed up for a mean of 5.2 years. High levels of BNP predicted death ($p=0.009$), heart failure ($p<0.001$) and stroke or TIA ($p=0.002$) during the follow-up period, independent of traditional risk factors.

Furthermore, BNP and NT-proBNP can predict the prognosis in patients who already have a diagnosis of cardiac failure. Doust and collegues performed a systematic review of 19 studies assessing the prognostic value of BNP.[126] In nine of these, BNP remained the only significant predictor of mortality on multivariate analysis. More recently, the UK based Heart Protection Study Collaborative has reported the results of a large epidemiological study that followed over 20,000 patients for an average of 5 years.[127] Patients with an elevated NT-proBNP had an increased fully adjusted relative risk of MACE (RR 3.09, $p<0.0001$) and heart failure (RR 9.23, $p<0.0001$)

As demonstrated with the above studies, the predictive value of both BNP and NT-proBNP has been studied. Several trials have included both markers in their analysis.[128] There appears to be little difference in the predictive value of BNP and NT-proBNP, and often local availability dictates the assay used.

1.5.3 BNP in surgical studies

Since BNP can detect subclinical cardiac disease and predict outcome in patients with known cardiac disease, it is no surprise that BNP is attractive for surgical risk stratification.

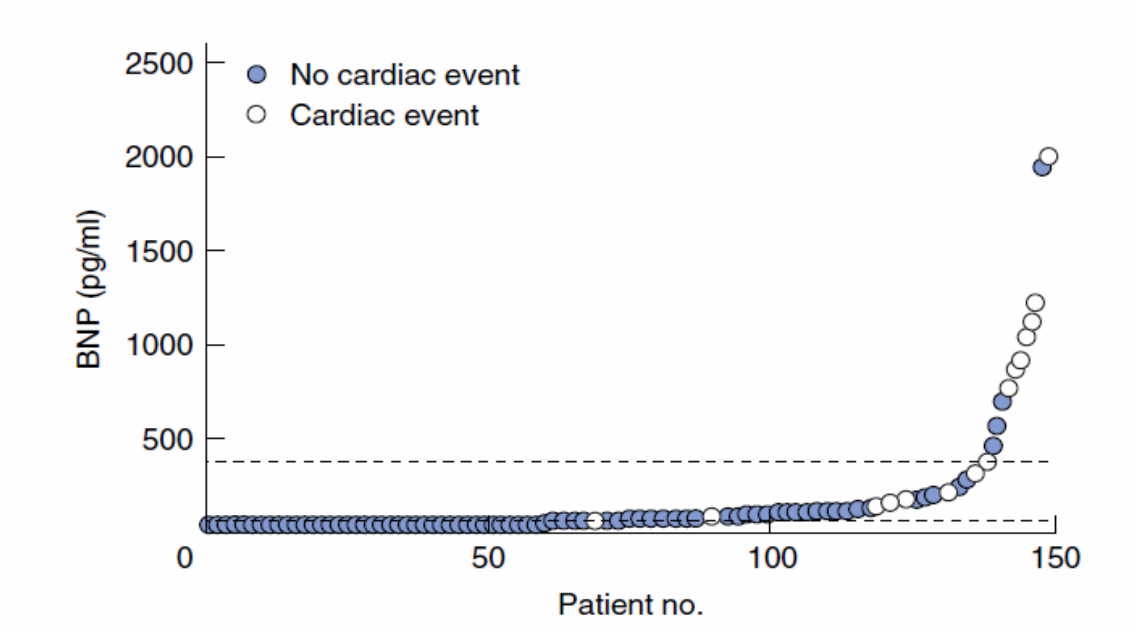
Following the start of the research submitted in this thesis, several studies have been published examining the predictive value of BNP and NT-proBNP in various surgical populations. Yeh and colleagues observed 190 Taiwanese patients undergoing a variety of major NCS procedures.[129] They found a 7.9% MACE rate, with only age and a NT-proBNP >450 pg/l predicting MACE. It is worth noting that this study included congestive cardiac failure (CCF) in the primary endpoint of MACE and CCF contributed to more than half the cases of MACE. The diagnosis of CCF did not require echocardiographical evidence of LVF and could be made with clinical findings alone.

Feringa and colleagues showed that NT-proBNP independently predicted post-operative MACE in a 170 patient cohort undergoing major vascular surgery (AAA or lower limb bypass surgery) at the Erasmus University Medical Centre in Rotterdam.[130] They used a more robust definition for MACE which consisted of non-fatal MI and cardiac death. A MACE rate of 8% was observed with an NT-pro-

BNP level of 533 mg/l providing an area under the curve (AUC) of 0.9 on receiver operator characteristic (ROC) analysis, with a sensitivity of 85% and specificity of 91%. Following this, the Erasmus group showed that the predictive effects of NT-proBNP could be extended beyond the short-term follow-up period of 30 days. At a median follow-up of 14 months, an NT-proBNP of ≥319 pg/l was associated with a HR of 4.0 for all-cause mortality (95% CI 1.8-8.9) and of 10.9 for cardiac events (95% CI 4.1-27.9).

Gibson and colleagues then published our research groups' preliminary findings of the short term predictive value of a pre-operative BNP level.[131] We observed a 13.7% MACE rate (defined as non-fatal MI and cardiac death) in 190 patients undergoing major vascular or abdominal surgery. A small derivation cohort (41 patients) and a larger validation cohort (149 patients) were used during the study. In both the derivation and validation groups, the median BNP was significantly higher in patients who had a peri-operative MACE than those that did not (210 pg/ml vs. 35 pg/ml, p<0.001 and 351pg/ml vs. 31pg/ml, p<0.001). ROC analysis showed that a cut-off of 108.5pg/ml provided the best sensitivity and specificity (87% each). Figure 1.5 shows the relationship between MACE and BNP in this study.

Figure 1.5 Relationship between major adverse cardiac events (MACE) and b-type natriuretic peptide (BNP)



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Cuthbertson and colleagues have published three studies from Aberdeen Royal Infirmary examining the predictive value of BNP.[132-134] Firstly, they showed the median BNP was significantly higher in patients who died or suffered a cardiac event (52.2 vs. 22.2 pg/ml, p=0.001) within the first 3 days after major NCS.[132] They noted a MI rate of 5.8% and a mortality of 0.5% during the 3 day follow-up period. At a median follow-up of 654 days they found a 16% mortality rate.[133] Predictors of mortality were increasing age, post-operative troponin rise and elevated BNP. Cuthbertson and colleagues also examined the predictive value of BNP in the setting of emergency surgery.[134] They studied 40 patients undergoing emergency abdominal or trauma surgery. The primary endpoint was peri-operative MACE, and the secondary endpoint was 6 month all-cause mortality. The MACE rate was high (27.5%) and, as with elective surgery, the median BNP was significantly higher in the MACE group (310 pg/ml vs. 82 pg/ml, p+0.001). More recently, from the same institution, Rajagopalan and colleagues studied the predictive value of NT-proBNP in 136 patients undergoing major vascular surgery.[135] They found that NT-proBNP was an independent predictor of myocardial injury, defined as a post-operative cTn rise. Interestingly, all the cTn elevations were asymptomatic (28 patients) and no patients met the criteria for MI.

Several further studies have confirmed the prognostic use of BNP or NT-proBNP. Lebowitz and colleagues showed that in 44 high risk NCS patients BNP was a significant predictor of MACE.[136] High risk was defined as one of the following; previous congestive cardiac failure (CCF), ejection fraction<40% on echocardiography or severe aortic stenosis. Yun and collegues recruited 279 elderly Korean patients (age >60 years) undergoing a wide variety of operations.[137] They observed a 9.0% cardiovascular complication rate (composite of cardiac death, MI, acute pulmonary oedema and non-fatal stroke). A NT-proBNP >201 pg/ml independently predicted post-operative MACE. Breidthardt and collegues investigated 270 patients undergoing elective orthopaedic surgery.[138] They observed a low (1.5%) post-operative cardiac event rate; however BNP remained a significant predictor of MACE.

Thus, an elevated pre-operative BNP level has been shown to predict post-operative MACE in the following cohorts; major NCS patients, vascular patients, high risk cardiology patients, orthopaedic patients and emergency surgical

patients. It should be noted that these studies have been carried out in a variety of geographical locations.

Furthermore, Mahla and collegues have demonstrated that an elevated post-operative NT-proBNP improves risk stratification in addition to pre-operative levels.[139] They found that a threshold of 280 pg/ml pre-operatively and 860 pg/ml post-operatively predicted for MACE. However on multivariate analysis, adjusting for a number of clinical factors, post-operative BNP elevation was the only significant predictor of post-operative MACE.

Goei and collegues from the Erasmus group have shown that the addition of highly selective CRP (hs-CRP) to NT-proBNP levels further improves risk prediction.[140] They observed a large cohort of patient (n=592) undergoing major vascular surgery (carotid, aortic and infra-inguinal bypass surgery). The authors defined a raised hs-CRP as >6.5mg/l and a raised NT-proBNP as >350pg/ml. They found that hs-CRP (OR 2.54, 95% CI 1.50-4.30) and BNP (OR 4.78, 95% CI 2.71-8.42) independently predicted MACE on multivariate analysis. Furthermore, combining both variables improved risk prediction (OR 6.63, 95% CI 3.01-13.25).

The predictive values of BNP and NT-proBNP have been examined in three meta-analyses. Rodseth and colleagues investigated the utility of BNP and NT-proBNP in patients undergoing vascular surgery.[141] A search of trials published up to January 2008 was performed and seven suitable studies were included. The authors found that an elevated BNP and NT-proBNP were predictive of cardiac death (OR 7.6, 95% CI 1.3-43.3, p=0.02), non-fatal MI (OR 6.2, 95% CI 1.8-21.4, p=0.004) and MACE (OR 17.4, 95% CI3.3-91.2, p<0.001). The analysis was performed at the discriminatory threshold as identified in each individual study. The authors concluded that these biomarkers were useful prognostic tests, however they were unable to ascertain which marker was preferable and what was the optimal cut-off threshold.

Karthikeyan and colleagues included nine prospective studies investigating the short term predictive value of BNP (4 studies) and NT-proBNP (5 studies) in patients undergoing a variety of non-cardiac surgical procedures.[7] There was an overlap of 4 studies examined in the Rodseth analysis.[141] Similarly, they conclude that both BNP and NT-proBNP are good independent predictors of post-

operative cardiac events. However, due to the small number of studies included, they were unable to suggest a threshold value for optimal predictive utility.

Ryding and colleagues included 15 studies in their analysis (8 relating to BNP, 7 to NT-proBNP).[142] Similarly, they found that patients with elevated BNP (or NT-proBNP) had a significantly higher MACE rate than those without. A pooled odds ratios for MACE of 19.77 (95% CI 13.18-29.65, $p<0.0001$) was found in patients with elevated BNP compared with those that did not. No study to date has directly compared BNP with NT-proBNP in a surgical cohort; however all the meta-analyses concluded that BNP and NT-proBNP are powerful predictors of post-operative cardiac events. In summary, the predictive value of BNP is evident but the best cut-off point is not.

1.6 Modification of risk

The benefit to individual patients of accurate pre-operative risk assessment and stratification relies on the availability of therapeutic options that allow modification of risk. Several areas of pre- and peri-operative optimisation have been examined.

1.6.1 Beta-blockers

The use of peri-operative ß-blockers gained popularity in the 1990s following the publication of two landmark RCTs. Firstly, Mangano and colleagues randomised 200 patients with, or at high risk of, CAD to either orally administered atenolol peri-operatively or placebo.[143] They showed a significant reduction in mortality and cardiac morbidity in the atenolol group during the 2 year follow-up period. A Dutch group of researchers (Poldermans and colleagues) then reported the results of the DECREASE-I study.[144] High risk patients undergoing vascular surgery were identified pre-operatively and underwent dobutamine stress echocardiography. One hundred and twelve patients with stress-induced ischaemia were randomised to peri-operative bisoprolol and standard care versus standard care alone. Patients in the ß-blocker arm of the study had a significantly lower rate of cardiac death (3.4% vs. 17%, $p=0.02$) and non-fatal MI (17% vs. 0%, $p<0.001$). The differences were not explained by patient characteristics, echocardiography results or type of surgery and the authors concluded that beta-blockage should be considered routine in high risk patients.

However, the combined size of these studies (only 312 patients) was small; and both studies have been criticised for methodological errors. The DECREASE-I study was unblinded in the setting of a high proportion of silent MIs. The Mangano study did not follow an intention to treat protocol. With these concerns in mind, the PeriOperative ISchemic Evaluation (POISE) trial was performed.[5] This was a large multicentre RCT that recruited over 8000 patients undergoing non-cardiac surgery from nearly 200 institutions. Patients were recruited if the they had a history of atherosclerotic disease (CAD, CVD, PVD) or if they had one or more risk factor (major intra-abdominal or intra-thoracic surgery, diabetes, renal impairment, age >70 years or emergency surgery). Patients received pre-operative extended release metoprolol or placebo, given

2-4 hours prior to surgery and continued for 30 days. The authors found a statistically significant reduction in the composite end-point of cardiovascular death, non-fatal MI and non fatal cardiac arrest in the treatment group (5.8% vs. 6.9%, p=0.0399). However, these results were offset by a higher overall mortality (3.1% vs. 2.3%, p=0.0317) and higher stroke rate (1.0% vs. 0.5%, p=0.0053) in the metoprolol group. This study used a relatively unselected population compared with the DECREASE-I trial, and performed no pre-operative cardiac imaging. Beta-blockade in patients with subclinical LVSD can induce bradycardic hypotension, which may explain the higher rate of stroke in the treatment arm. Critics of the POISE study suggest that the study protocol resulted in aggressive dosing of metoprolol in patients who had not previously been exposed to beta-blockers, just hours before major surgery.

The smaller UK based Peri-Operative B-Blocker (POBBLE) trial was recruiting in parallel to the POISE study.[42] One hundred and three patients undergoing infra-renal vascular surgery were randomised to oral metoprolol from admission to day 7 post surgery or placebo. Exclusion criteria included previous MI or positive DSE. Hence a lower risk population was selected. Despite this, a non-fatal MI rate of 8% and unstable angina rate of 9% was noted. Patients had 72 hour Holter monitoring starting at induction of anaesthesia. A composite end point of MI, unstable angina, ventricular tachycardia and stroke was used. No difference in cardiovascular complications was seen between the treatment and placebo groups (32% vs. 34%), although median time to discharge was shorter in the treatment group (10 days vs. 12 days, p<0.02)

The Dutch group have subsequently reported the results of the DECREASE-IV study.[44] They performed a four-armed RCT, with patients assigned bisoprolol, fluvastatin, combination therapy or placebo. Patients considered to be at intermediate risk of peri-operative cardiac events were included. Patients were started on the study protocol prior to admission for surgery (median 34 days prior to surgery) and the dose was tailored to resting heart rate targets. Patients who received bisoprolol had a lower cardiac event rate (2.1% vs. 6.0%, p=0.002). No difference in stroke rate was seen. The authors claim that peri-operative beta-blockage is safe, if administered with a careful protocol of dose titration to aim for a heart rate of 50-70 beats per minute, and reduces adverse cardiac outcomes.

In summary, there are conflicting results from the studies examining the benefits of peri-operative beta-blockade. The largest study (POISE) demonstrated a significant adverse event rate in the treatment arm. Smaller studies, with a more careful dose-response protocol, have showed benefit with less adverse events. The optimal agent and the timing of beta-blocker commencement prior to surgery remain contentious.

1.6.2 Antiplatelet agents

Antiplatelet agents (APA) are the cornerstone of best medical therapy in patients with, or at high risk of, cardiovascular disease.[145] Aspirin and clopidogrel inhibit platelet aggregation and therefore prevent thrombosis.[146] Despite the benefits of APA therapy, concerns about peri-operative bleeding complications often lead to cessation of anti-platelet therapy prior to surgery. This common practice is not based on current evidence for most types of surgical procedure. Furthermore, there is now a recognised acute rebound effect after withdrawal of aspirin therapy that leads to a pro-thrombotic state as a result of increased thromboxane levels and impaired fibrinolysis.[147] This, in combination with the pro-thrombotic state produced by the stress of surgical trauma itself, leads to a heightened risk of ischaemic events.[148] Lastly, with the advent of drug eluting stents, withholding APAs peri-operatively may have adverse outcomes such as delayed stent occlusion.[149] Collet and colleagues investigated the use of antiplatelet agents in patients admitted with ACS.[150] A small group of patients were identified who had recently (<30 days) stopped APA therapy. Two thirds of these patients had the APA stopped for elective surgery. These patient had a higher mortality (21.9% versus 12.4%, P=0.04) than those who did not interrupt APA or those who were never on APA therapy.

Oscarsson and colleagues have performed the only RCT to date examining the safety of continuation or discontinuation of aspirin during the peri-operative period.[45] Patients with high or intermediate risk factors for peri-operative MACE, who were already taking aspirin, were randomised to continuation of aspirin or placebo. The study was stopped early, prior to interim analysis due to changes in national guidelines regarding the management of high risk cardiovascular patients, and increasing evidence that antiplatelet cessation was harmful. The study recruited 220 of an intended 540 patients. Despite this

limitation, the authors were able to demonstrate a significantly improved MACE rate in the treatment arm (1.8% vs. 9.0%, p=0.02) and no difference in bleeding complications were seen. Subsequently, Albaladejo and collegues have published the results of the RECO study, a large multicentre observational study of patients with coronary stents undergoing elective NCS.[39] APA was continued in 72% of patients, stopped for <5 days in 14% and stopped for ≥5 days in 14%. A significantly higher MACE rate was seen in the group without APA for 5≥days. Overall mortality in the MACE group was 14.5%

A recent meta-analysis has examined 28 studies that recruited patients with a history of coronary stents undergoing NCS.[74] As previously discussed, a reduced MACE rate in patients undergoing NCS greater than one year after stent insertion was noted, compared with patients who had a stent placed less than 1 year before surgery. However they also found no improvement in MACE rates in patients continued on dual APA therapy compared with those on aspirin only. In particular the authors highlighted the results of a study performed at the Erasmus Centre, Rotterdam that investigated the outcomes of 550 patients undergoing NCS after stent insertion.[151] Of the patients who experienced MACE, 45% were on single APA, compared with 55% in the dual APA group (p=0.92). Significant bleeding complications were higher in the dual APA group compared with the single APA group (21% vs. 4%, p<0.001).

Finally, we await the results of the on-going POISE-II trial which is currently randomising APA naïve patients to aspirin, clonidine (α-2 agonist) or placebo.

In summary, there is a growing body of evidence to support the continuation of APAs during the peri-operative period in all but a few select circumstances. However, there remains a lack of evidence regarding the safety of dual APA in patients undergoing NCS.

1.6.3 Lipid-lowering therapy

The beneficial effects of statins in patients with cardiovascular disease are evident. For example, the MRC/BHF Heart Protection Study randomised over 20,000 U.K. patients with risk factors for cardiovascular disease to 40mg simvastatin or placebo. There was a significant reduction in the 5 year mortality in the treatment group (12.9% vs. 14.7%, p<0.001), predominantly due to a reduction in cardiac death (5.7% vs. 6.9%, p<0.0001).[152] Similar reductions in non-fatal MI and stroke were observed. Aside from lipid-lowering, statins also demonstrate other desirable effects such as plaque stabilisation and reduced vascular inflammation, independent of changes in serum cholesterol.[153,154]

Accordingly, several studies have demonstrated improved peri-operative outcomes with statin therapy. O'Neil-Callaghan and colleagues retrospectively examined the outcome of patients undergoing major vascular surgery over a 2 year period (1999-2000) in a single centre.[78] An adverse outcome was defined as death, MI, CCF and ventricular arrhythmia. Patients receiving a statin had a lower adverse event rate than those not on a statin (9.9% vs. 16.5%, p<0.001). After adjustment for other significant predictors, statin therapy remains a significant protective factor (OR 0.52, 95% CI 0.35-0.77). Similarly, Lindenauer and colleagues presented analysis of a large national US database of discharge information and pharmacy prescription from 329 institutions.[155] Over 780,000 patients undergoing mixed major NCS were included. Unadjusted crude mortality was lower in patients prescribed statins (2.13% vs. 3.05%, p<0.001). After adjustment for confounding factors, the authors reported a preserved protective effect (OR 0.62, 95% CI 0.58-0.67). Subsequent to these retrospective database analyses, Le Manach and colleagues prospectively studied the post-operative outcome of 1,674 patients undergoing aortic surgery.[156] Half the patients (52.6%) were receiving chronic statin therapy at the time of surgery. Patients treated with statins had a significantly reduced peri-operative mortality (OR 0.40; 95% CI 0.28-0.59) and reduced PMI (OR 0.52; 95% CI 0.38-0.71); similar reductions in peri-operative stoke and acute kidney injury were observed.

More recently, Chopra and colleagues have performed a meta-analysis of 15 RCTs examining the influence of peri-operative treatment with statins.[157] Patients included had not previously received statin therapy. The majority of

trials were in patients undergoing cardiac surgery (11 of 15). Statin therapy was associated with a significantly reduced risk of PMI (RR 0.53; 95% CI 0.38-0.74). However, no reduction in peri-operative mortality was observed. Therefore, current evidence supports continuation or commencement of statins prior to NCS.

1.6.4 Myocardial revascularisation

The management of patients who are found to have significant CAD is not clear. Pre-operative revascularisation, by way of coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), adds to the patients' morbidity and mortality and may delay the intended surgical procedure. However, as previously discussed, Eagle and colleagues demonstrated a significantly improved peri-operative MACE rate and mortality in patients with CAD treated with previous CABG compared with those patients treated medically.[158]

McFalls and colleagues reported the results of the Coronary Artery Revascularization Prophylaxis (CARP) study, in which they randomised 510 patients to revascularisation or standard care prior to AAA or PVD surgery.[40] In the treatment arm, PCI was performed in 59% of patients and CABG in 41%. The primary endpoint, long term mortality, was similar in the revascularisation group compared with placebo (22% vs. 23%, p=0.92). The secondary outcome of peri-operative MI was also similar (12% vs. 14%, p=0.37).

Poldermans and colleagues performed a multicentre RCT, the DECREASE-V trial, in which they recruited high risk patients prior to AAA or PVD surgery.[41] DSE was performed to identify those patients with extensive stress-induced ischaemia. One hundred and one patients were randomised to revascularisation (n=49) or no revascularisation (n=52). There was no difference between the revascularisation group and the no-revascularisation group for all-cause mortality (22.5% vs. 11.5%, p=0.14) and a composite of mortality and non-fatal MI (42.9% vs. 32.7%, p=0.30). Alarmingly, 2 patients in the treatment arm died due to a ruptured AAA following successful PCI, but prior to vascular surgery. Also, one patient suffered a post-PCI MI that precluded proceeding to vascular intervention. Further evidence against the routine use of myocardial revascularisation came following the publication of the long-term follow-up results. At a median of 2.8 years following randomisation to the DECREASE-V trial, patients in the revascularisation group had a similar survival rate than those in the non-treatment arm (61% vs. 64%, p=0.61).[159] There was also no difference when considering a composite endpoint of mortality, non-fatal MI and coronary

revascularisation. Only 2 of 52 patients in the no revascularisation arm required coronary intervention during the follow-up period.

Garcia and colleagues performed a subgroup analysis of the long term follow-up of the CARP trial, focussing on patients with significant left main coronary artery stenosis (>50%).[160] Log-rank analysis within this group demonstrated an improved survival in the revascularisation group compared with standard care (0.84 vs 0.52, p <0.01). This benefit was not seen in patients with 2 or 3 vessel disease without left main coronary stenosis.

Finally, it is noteworthy that deferral of surgery for cardiac investigation and intervention is not without risk, as illustrated by the interval AAA rupture rate seen in the DECREASE V trial. Krupski and colleagues observed 42 patients in whom further cardiology assessment was considered necessary prior to vascular surgery. They found a 38% complication rate following cardiac intervention (percutaneous or open), including graft infection, pseudoaneurysm formation and renal failure. A median delay to vascular surgery of nearly a month was encountered during the study. Furthermore, 2 patients with reconstructable PVD required amputation during the workup period.

In summary, routine pre-operative revascularisation in patients with CAD does not improve post-operative morbidity and mortality and exposes patients to the risks and delays of an additional procedure. However, high risk patients with significant left main coronary disease may benefit from intervention.

1.6.5 Ventricular assist devices

The use of left ventricular assist devices (LVAD) is increasing for patients with end-stage heart failure (ESHF), and is now considered an alternative to transplantation.[161] Some authors have described a >50% survival at 2 years following LVAD inserion.[162] Studies investigating patients with LVAD undergoing NCS are limited to case series. Morgan and colleagues reported on 20 patients with ESHF requiring LVAD who underwent elective NCS.[163] No mortality, thromboembolic complications or device failures were seen and the main complications were bleeding related to anticoagulation. While no studies have examined the pre-operative management of ESHF with or without LVAD, the anticipated rise in the number of patient with such devices makes them noteworthy in this thesis.

1.6.6 Enhanced Recover after Surgery (ERAS)

Enhanced recovery after surgery (ERAS) or 'fast track surgery' is a concept first described by Henrik Kehlet in the early 1990's.[164] The approach employs a multimodal peri-operative care pathway with the aim of attenuating the stress response to surgery and accelerating recovery.[165] Implementation of enhanced recovery protocols has led to improved outcomes across a range of different specialties including reductions in surgical morbidity and hospital stay. [166-168] The primary end-points in most studies examining ERAS versus conventional care, particularly in intestinal surgery, are time to discharge, return to normal gut function and surgical morbidity.[169,170] However, there are certain components that are of particular interest from a cardiac morbidity perspective.

1.6.6.1 Goal directed fluid administration

Targeted fluid administration during and after surgery, guided by non-invasive cardiac output monitoring, is increasingly used within the ERAS pathway.[165] Intra-operative use of Oesophageal Doppler (OD) monitoring aims to reduce intra-operative hypotension and allow fluid administration tailored to the patient's cardiac output.[171] A meta-analysis of five RCTs studying the use of OD-monitored fluid administration recruited 420 patients undergoing major NCS.[172] The authors showed a reduced overall complication rate, reduced post-operative stay and improved peri-operative cardiac output in the OD group compared with the standard care arm.

How these measures affect high risk patients is unclear. The ongoing optimisation of peri-operative cardiovascular management to improve surgical outcome trial (OPTIMISE) may clarify this. The trial is currently recruiting high risk patients undergoing intestinal surgery, with one or more of the following inclusion criteria required; emergency surgery, acute or chronic renal impairment, DM, age >65 or the presence of a risk factor for cardiac or respiratory disease. Patients are randomised to a goal-directed fluid regime, guided by OD, with a fixed dose intra-venous infusion of dopexamine, or standard care.

1.6.6.2 Minimally invasive surgery

Many surgical procedures are now performed in a minimally invasive fashion. In the early stages of interest in laparoscopic colorectal surgery, several large RCTs were performed to compare outcomes against standard open surgery. The COLOR trial was a European multicentre RCT, comparing laparoscopic with open colonic resection.[92] Over 500 patients were recruited to each arm. Disappointingly, there was no improvement in overall, respiratory or cardiac complications in either group. Similarly, the multicentre UK-based MRC CLASSIC trial randomised 794 patients to laparoscopic or open colorectal surgery.[93] No difference in overall complications or cardio-respiratory complications was observed. The US multicentre COST trial randomised 872 patients to laparoscopic or open colorectal surgery.[173] Again, no improvement in peri-operative morbidity or mortality was seen. These finding may be explained by the relative inexperience of the operators for laparoscopic surgery compared with conventional open surgery. For example, in the COST trial, participating surgeons were only required to have performed 20 laparoscopic colectomies before they were able to recruit for the study. More recently, Feroci and colleagues reported a single centre experience of laparoscopic colorectal surgery for high risk patients (defined as the presence of respiratory, cardiac or renal co-morbidity).[174] Cardio-respiratory complications were lower in the laparoscopic group compared with the open group (5.8% vs. 15.8%, p=0.003) as was mortality less (1.5% vs. 7.5%, p=0.038).

Endovascular AAA repair (EVAR) is now feasible for certain patients with anatomically appropriate aneurysms.[175] Brown and colleagues investigated the incidence of cardiac morbidity in the year following randomisation to the EVAR 1 trial.[176] This study compared open AAA repair versus EVAR in patients suitable for both procedures. They found a reduced rate of cardiovascular morbidity (composite of MI and stroke) in the EVAR group (2.6%) compared with the open group (3.2%), although this difference was non-significant (p=0.164). No differences were seen in one year mortality (3.8% vs. 3.6% respectively, p=0.674).

1.6.7 Post-operative monitoring

The level of care a patient receives after major NCS has implications for the risk of adverse events. To illustrate this, Pearse and colleagues examined data extracted from the Intensive Care National Audit and Research Centre Database (ICNARC) from nearly 100 English Institutions over a five year period.[16] The study included data from over four million operations. A high risk procedure was defined as an operation with an expected mortality of 5% or more. High risk patients comprised only 12.5% over the total cohort, yet 83.8% of the overall mortality. Focused analysis on the high risk group showed that the highest elective surgical mortality was in patients that were initially cared for at a standard ward level, before escalation to a critical care bed (36.4%) compared with patients who were planned admissions to a critical care area immediately post-operatively (10.1%). A limitation of this study was the incomplete participation of some institutions. Therefore, Jhanji and colleagues used the ICNARC and HES database to examine this further in a single NHS trust over a 3 year period.[17] They claimed improved data capture, and a more accurate reflection of post-operative practice. The same operative codes to define high risk patients were used as in the national trial. They found that only 35.3% of high risk patients were admitted to a critical care bed at any stage post-operatively. Only 49.0% of high risk patients that died were admitted to critical care areas, and only 25.6% died in a critical care area. Carlise and colleagues identified unplanned critical care bed admission following elective colorectal resection as an independent predictor of peri-operative and long term mortality.[177] Thus, increasing evidence is available to support the elective post-operative admission of high risk patients to a critical care area. However, this will raise inevitable problems about healthcare resources, particularly in the UK.

1.7 Therapeutic intervention for post-operative myocardial infarction

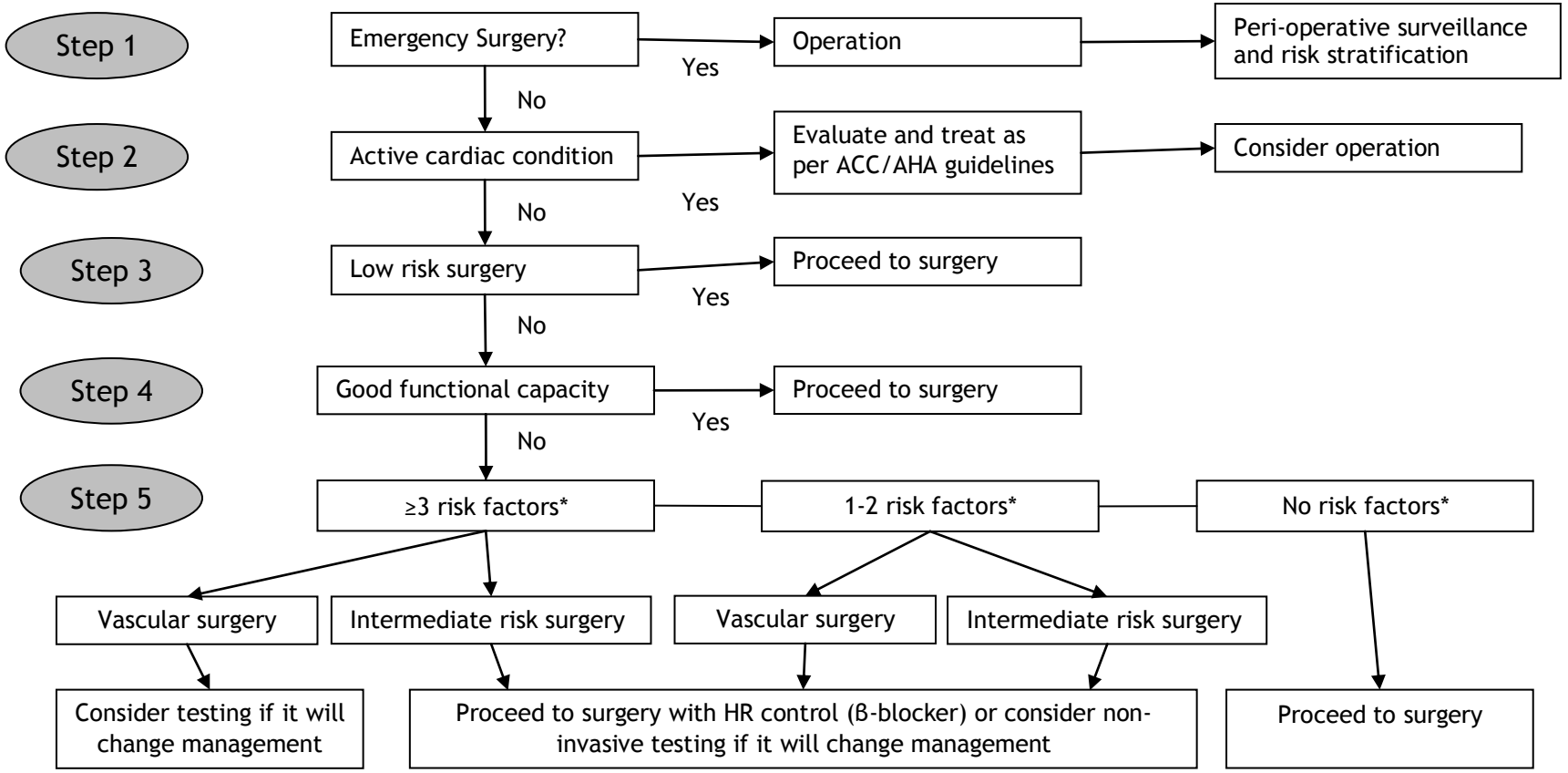
Finally, it is worth noting that there are no randomised trials assessing the efficacy of any interventions on patients suffering a PMI. This is surprising in view of the large number of studies in primary (non-operative) infarction, the high incidence of PMI in certain populations, and the uncertainty regarding the use of many cardiac medications in the immediate post-operative period. Overwhelming evidence from therapeutic trials in the non-operative population suggests intervention following MI is superior to medical therapy and that the timing of intervention is crucial.[70] No such information is available in the post-operative setting.

1.8 Current guidelines for the assessment and management of cardiac risk in patients undergoing non-cardiac surgery (NCS)

The first well recognised consensus report regarding the assessment and management of cardiac risk in NCS was produced jointly by the American College of Cardiology (ACC) and the American Heart Association (AHA) in 1996.[178] These guidelines were updated in 2002[179] and then most recently amended in 2007[69]. A framework for the evaluation of patients prior to NCS is presented in Figure 1.6. Guidance is also offered for the management of specific peri-operative circumstances. For example, advice about the management of recent PCI is provided [Figure 1.7]. Recommendations about the use of beta-blockers, statins, pre-operative revascularisation and intra-operative considerations (anaesthetic agents, glycaemic control, monitoring) are made.

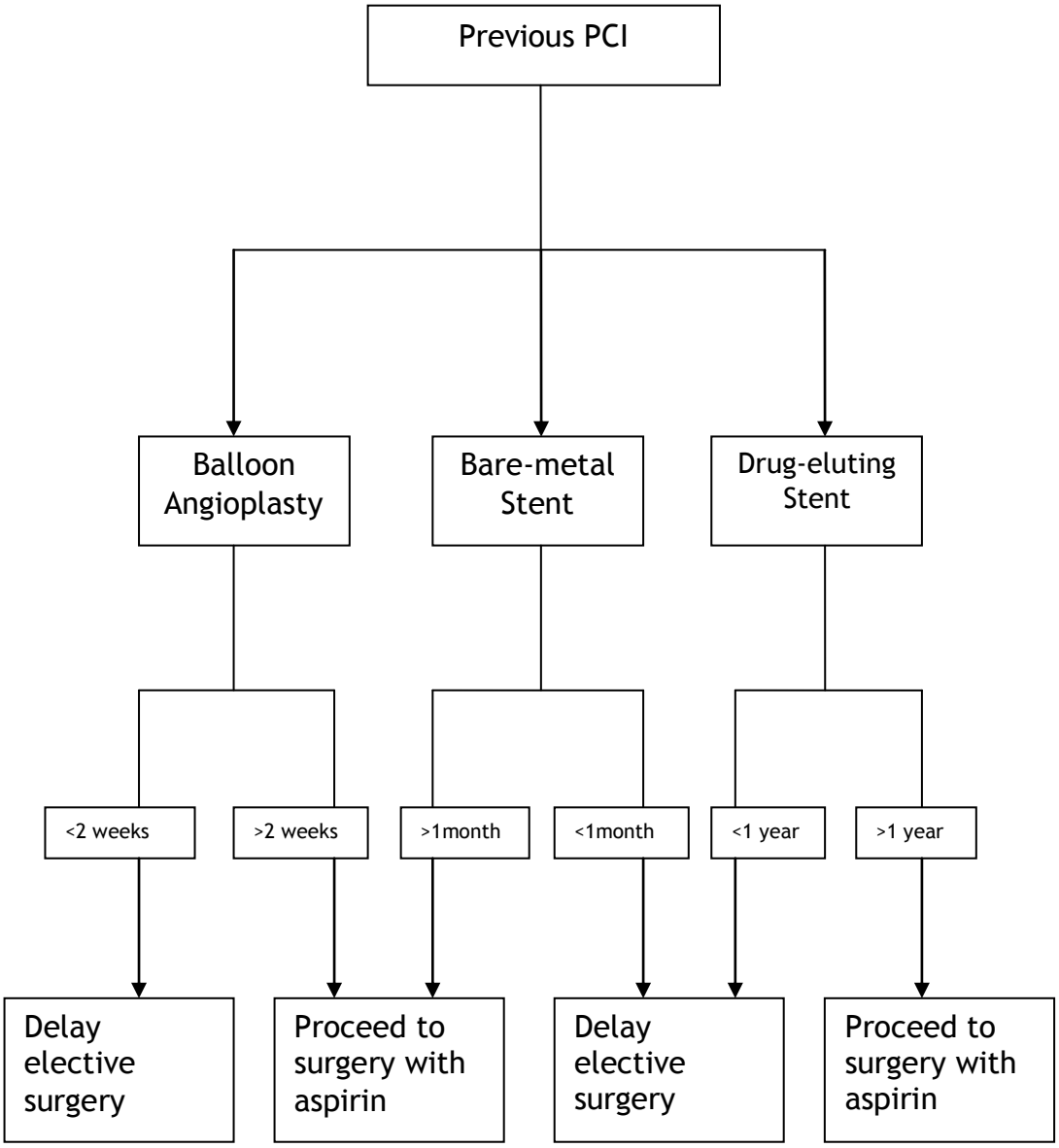
More recently, guidelines from the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology have been produced.[180] Broadly speaking, these guidelines follow a similar format to the ACC/AHA guidelines. However some variation is present. Additional interest is focused on optimal methods of non-invasive cardiac imaging. Reliance on the currently available risk stratification scoring systems is questioned and a different strategy for pre-operative beta-blockade is suggested.

Figure 1.6 AHA/ACA Algorithm for cardiac evaluation prior to non-cardiac surgery



*Clinical risk factors include ischaemic heart disease, prior heart failure, diabetes mellitus, renal insufficiency and cerebrovascular disease. Reproduced with publisher's permission.[63]

Figure 1.7 Suggested approach to management of patients with previous percutaneous coronary intervention (PCI)



Reproduced with publisher's permission.[69]

1.9 Scientific misconduct and peri-operative research

The spectre of research fraud has over-shadowed peri-operative medicine in recent years, with two noteworthy examples. Joachim Bolt was a German anaesthetist and academic practicing in Rhineland-Pfalz and had published over 200 peer reviewed studies. He was considered a leading expert in the field of peri-operative intravenous fluid management and his department had produced a strong body of research to support the use of colloid for resuscitation during surgery, particularly hydroxyethyl starch solution (HeS).[181,182] In December 2009, a RCT was published in Anaesthesia and Analgaesia by Joachim Boldt studying the benefits of colloid versus albumin when used as a pump-priming solution during CABG.[183] Anaesthesia and Analgaesia's editor-in-chief, Steven Shafar, received correspondence shortly after questioning the study's amazingly perfect results despite a small study size. Then followed a period of investigation by Dr Shafar, culmination in the shocking findings that this study had not received ethical approval, no written consent was obtained, no randomisation was performed and no follow-up was carried out. All these omitted steps were described by Boldt in the methods section of the paper. Anaesthesia and Analgaesia subsequently published a notice of retraction, which also questioned the validity of Boldt's other work.[184] Boldt's research empire slowly crumbled over the following months, and the veracity of his studies were rigorously investigated. This culminated in the publication of a joint statement signed by 16 editors of anaesthetic journals that had previously published Boldt's papers.[185] The editors were unable to find research board and ethical approval for 88 of the 102 article investigated and these articles were all retracted. Boldt was fired and stripped of his professorship and a criminal investigation is ongoing. Finally, a revised meta-analysis has been published since the scandal, which examines the outcomes following the use of HeS compared with other fluids for intravenous resucitation.[186] They analysed trials with and without Boldt's research included. Alarmingly, when Boldt's data was excluded, HeS resuscitation was associated with a higher rate of mortality and renal failure than other solutions. This association was not previously observed when Boldt's data was included.

More directly related to this literature review, though currently less scandalous, is the question of ethical misconduct raised against Don Poldermans. Formerly,

Poldermans was head of the department of anaesthetics and peri-operative medicine at the Erasmus Medical Centre in Rotterdam. Poldermans led a well respected research group that produced over 500 publications in the field of peri-operative medicine, including several seemingly well designed RCTs. In November 2011, a press release from Erasmus MC stated the Poldermans had been dismissed for 'violation of academic integrity'.[187] A committee investigation found evidence of irregularities of data collection, use of patient data without consent and fictitious data use, particularly in relation to the DECREASE II, III, IV and V studies.[188]

To date, no publications that Poldermans has contributed to have been retracted, however some journals have published notices of concern.[189,190] Due to the large number of studies over many years, investigation of the integrity of all Poldermans research contributions is probably impractical. The investigating committee published a follow-up report in 2012, highlighting evidence of research irregularities and negligence in several studies.[191] Furthermore, the report states that the lack of record keeping in various databases meant that further investigation would be time consuming and likely unsuccessful.

Poldermans was head of the ESC/ESA guidelines committee for pre-operative cardiac risk assessment and peri-operative cardiac management in non-cardiac surgery and there are calls for these guidelines to be revised in his abscence.[180] Likewise, his research strongly influenced approaches to non-invasive cardiac assessment and peri-operative beta-blockade. In light of his dismissal, all Poldermans studies will now come under suspicion.

1.10 Aims of the thesis

The incidence of peri-operative MACE and mortality is variable. Furthermore, numerous methods of risk stratification are available, with variable performance in different observed populations. As demonstrated in this chapter, several peri-operative interventions are available to modify an individual's risk before, during and after major surgery. Therefore, the aims of this thesis are as follows;

i. To review current literature regarding cardiac risk stratification and modification prior to major non-cardiac surgery

ii. To identify the incidence and clinical predictors of peri-operative MACE and mortality in a prospectively collected cohort of patients undergoing major non-cardiac surgery in a West of Scotland setting.

iii. To assess the utility of B-type natriuretc peptide (BNP) in cardiac risk prediction.

iv. To determine whether plasma BNP concentration can predict the long-term survival of patients following major NCS.

v. To assess the utility of a pre-operative 12-lead ECG in prediction of post-operative adverse events and mortality.

vi. To determine the efficacy of a commonly used risk stratification scoring system (RCRI) in our prospectively collected cohort.

2 Methods

2.1 Patient selection

A prospective single centre observational cohort study was performed. Consecutive patients undergoing major non-cardiac surgery at Gartnavel General Hospital between 2003 and 2006 were selected for inclusion in the study. Gartnavel General Hospital is a large teaching hospital with vascular, intestinal and urological surgery services. Four groups of patient were included in the study;

1. Aortic surgery. Both open repair and endovascular aortic aneurysm repair (EVAR) procedures were included.

2. Peripheral vascular disease requiring re-vascularisation surgery. This included femoral artery surgery, femoro-popliteal and femoro-distal bypass surgery and extra-anatomical bypass surgery such as axillo-bifemoral surgery.

3. Peripheral vascular disease unsuitable for vascularisation requiring lower limb amputation. Both below-knee and above knee amputation were included.

4. Laparotomy for gastro-intestinal or urological pathologies

2.1.1 Urgency of procedure

The urgency of surgical intervention was defined as;

- Elective – following planned admission for surgery

- Urgent – following un-planned emergency admission requiring same admission intervention

Patients requiring emergency surgery, defined as surgery within 24 hours of an un-planned admission, were excluded.

2.2 Ethical approval

Ethical approval for this study (REC reference number 04/193(1)) was provided by the West of Scotland Research Ethics Committee. Participating patients were given a patient information sheet and signed a study consent form prior to inclusion. This study involved no additional intervention other than an extra blood test, which was taken at the time of the routine pre-operative blood tests.

2.3 Pre-operative clinical assessment

The presence of risk factors such as diabetes, hyperlipidaemia, previous myocardial infarction (MI) and chronic obstructive pulmonary disease (COPD) were obtained from the patient's history and medical records. Ischaemic heart disease was defined as a previous myocardial infarction, a positive exercise tolerance test, the use of nitrate therapy or the presence of pathological Q-waves on ECG. Left ventricular failure (LVF) was considered present if the patient had a prior hospital admission with heart failure or left ventricular impairment on previous echocardiography. Cerebrovascular disease was defined as a previous cerebrovascular accident or transient ischaemic attack. The glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease (MDRD) equation.[192] Renal impairment was considered present if the estimated GFR was <60mls/min. A patient was considered a smoker if they were smoking at the time of admission for surgery. Hypertension was considered present if the patient had a previous medical documentation of hypertension and was currently taking antihypertensive medication. The current medication was also recorded, in particular the prescription of anti-platelet agents, statins and beta-blockers.

All patients had standard pre-operative assessment including a 12-lead ECG the day before surgery. Further cardio-respiratory assessment was carried out at the discretion of the operating team.

2.4 Laboratory investigations

2.4.1 Haematology

A 5ml venous blood sample was taken in an ethylenediaminetetraacetic acid (EDTA) tube and sent to the haematology laboratory for an analysis of full blood count. Another 5ml sample was collected in a citrate tube for a coagulation screen.

2.4.2 Biochemistry

A 5ml venous blood sample was taken in a lithium-heparin tube and sent to the biochemistry laboratory for measurement of serum urea and electrolytes, liver function tests, C-reactive protein, non-fasting total cholesterol, triglycerides and high-density lipoprotein fraction of cholesterol.

Serum cardiac troponin-I (cTnI) was measured using the ADVIA Centaur® immunoassay (Bayer Diagnostics), which has a sensitivity and assay range of 0.02-50 ng/ml.

2.4.3 BNP analysis

An additional venous blood sample was taken for plasma BNP the evening prior to surgery. This was collected in chilled EDTA and aprotinin (Trasylol; 50 IU/ml), immediately centrifuged and stored at –25° Celsius. BNP concentrations were measured using a direct radioimmunoassay (Shionoria BNP kit, Shinogi & Co, Osaka, Japan).[193] The minimum detectable quantity of BNP is 2pg/ml. The within-assay and between assay co-efficients of variation are 5.3% and 5.9%, respectively. Batch sample analysis was performed during the study by a biochemist blinded to clinical details. The longest sample storage period was 6 months.

2.5 Post-operative monitoring

The patients were managed post-operatively in the intensive care unit, the high dependency unit or the ward. Requirement for critical care after surgery was determined by the anaesthetic and surgical teams. Routine laboratory investigations (haematology and biochemistry) were performed daily for the first 3 post-operative days, as per local policy.

2.5.1 Serial cardiac screening

Post-operative screening for cardiac events was performed. This consisted of daily clinical assessment and serial ECGs and troponin I measurement on day 2 and day 5 post-operation. Patients that were discharged were seen at a clinic appointment at 6 weeks. ECGs and troponin I measurement were repeated at this point.

2.6 12-Lead electrocardiography

All electrocardiographs (ECGs) were batch analysed at the end of the study by two investigators (general surgeon and cardiologist), blinded to the clinical outcomes. The ECG results were then double checked by a second cardiologist and disagreements were resolved by consensus. ECGs were examined for the presence of the following abnormalities;

- *Left ventricular hypertrophy*: Sokolow-Lyon voltage criteria (S wave in V1 and R wave in V5 or V6 > 35mm, or R wave in aVL > 11 mm).[194]

- *Bundle branch block*: The standard morphological appearance of left or right bundle branch block, with a QRS duration of >120 ms.

- *Atrial fibrillation*: presence or absence.

- *Axis deviation*: Using standard QRS axis electrical criteria, left axis deviation > -30°, right axis deviation > +90°.

- *Q-waves*: Present of a negative deflection preceding the R wave in two contiguous leads with duration of >40ms and amplitude greater than 25% of corresponding R wave.

- *Ventricular strain pattern*: Planar ST segment depression ≥ 1mm or T wave inversion in V5/V6.

- *Premature ventricular contraction (PVC)*: presence or absence of broad complex ectopic beats.

An ECG was considered abnormal if one or more of the above characteristics were present. Cumulative abnormalities on individual ECGs were also recorded.

ECG findings: heart rate (HR), QRS duration and QTc were recorded directly from the automated data display on the ECG. Tachycardia was defined as HR >100, broad QRS complex as >130ms and prolonged QTc as >440ms.

2.7 Short term endpoints

2.7.1 Non-fatal myocardial infarction (MI)

The definition of a non-fatal MI was that used by The Joint European Society of Cardiology/American College of Cardiology Committee:[34] a typical rise and gradual fall of cardiac troponin with at least one of the following: ischaemic symptoms, development of pathological Q waves on the ECG, ECG changes indicative of ischaemia (ST segment elevation or depression) or coronary artery intervention.

2.7.2 Cardiac Death

Cardiac death was defined as death secondary to myocardial infarction, cardiogenic shock or intractable dysrhythmia.

2.8 Long term follow-up

Patient status was monitored by scrutiny of administrative and inpatient databases to identify those patients who had died during the follow-up period. The final census point was carried out in the autumn of 2009. A patient was considered alive if they were under active outpatient follow-up or had an inpatient admission within the preceding month. In those patients who had not had contact with secondary care, the GP was contacted for current status. Where information from the GP was unsatisfactory, the patient was contacted directly. All patients were followed-up for a minimum of 1 year.

Mortality during the follow-up period was either inpatient or out-of-hospital. Medical records were reviewed to confirm death in the case of in-patient mortality. Out-of-hospital death was identified from administrative databases and confirmed by direct contact with the GP.

2.9 Statistical analysis

2.9.1 Data handling

All patient data was entered into a Microsoft Access database. All patients were assigned an individual anonymous patient number, and all patient data was stored on a password encrypted file with no identifiable patient factors. On completion of the data collection period, the database was exported into SPSS (Version 15) (SPSS, Chicago, IL, USA) for statistical analysis.

2.9.2 Comparisons of categorical and continuous data

Categorical data were compared using the X^2 test or Fisher's exact tests where applicable. Normally distributed continuous data was described as mean (+/- standard deviation) and comparison was performed using an independent samples t-test. Non-parametric data was described as median (interquartile range) and comparison was performed using the Mann-Whitney test and Kruskal-Wallis test as appropriate. A p value reflects the probability of an event having taken place by chance. For the purposes of this thesis, a p-value of less than 0.05 was considered significant.

The performance of individual variables for predicting post-operative outcomes was further analysed using receiver operating characteristics (ROC) and the area under the curve (AUC) was calculated.

2.9.3 Univariate and multivariate analysis

Univariate survival analysis was performed using Kaplan-Meier curves and comparisons made using the log rank statistic. Variables with a p-value of less than 0.10 were further evaluated with a multivariate Cox analysis using a backward stepwise selection.

3 Determinants of an elevated b-type natriuretic peptide in patients undergoing major non-cardiac surgery

3.1 Introduction

B-type Natriuretic peptide (BNP) is a cardiac neurohormone released from cardiac myocytes in response to ventricular wall stress.[195] BNP has a significant role in both cardiovascular and renal physiology. BNP reduces sympathetic tone, blood pressure and circulating volume homeostasis.[123] The presence of raised plasma BNP is strongly associated with left ventricular systolic dysfunction in the general population[196,197], and with a poorer prognosis in patients with cardiac disease.[126] With an aging population, the incidence of heart disease and heart failure is rising.[198] The European Society of Cardiology estimates that more than 15 million patients in Europe have symptomatic heart failure, with a similar number having asymptomatic or sub-clinical ventricular dysfunction.[199] This report suggests that the prevalence of heart failure rises to between 10 and 20% in patients over the age of 70.

Biomarkers of heart failure, in particular BNP, are now widely used in the diagnosis of heart failure, as well as prognostic indicators of outcome in cardiology patients.[200] Inevitably, this has generated interest in BNP as a point of care marker for patients undergoing surgical intervention. Early reports of the prognostic utility of BNP in the peri-operative period were promising[201]; however the factors associated with a raised BNP are not clear. Therefore, the aim of this study is to identify the incidence and determinants of raised pre-operative serum BNP in a West of Scotland cohort undergoing major non-cardiac surgery.

3.2 Methods

A prospective single centre observational cohort study was performed. Consecutive patients undergoing major non-cardiac surgery were selected for inclusion in the study. Operative groups included were aortic surgery, bypass surgery for peripheral vascular disease, lower limb amputation and laparotomy. The study was approved by the Central Ethics Committee and local Research and Development Committee. Patients were given a patient information sheet and signed a study consent form prior to inclusion. The definitions of the clinical variables used are described in full in Chapter 2.

3.2.1 B-type natriuretic peptide analysis

A venous blood sample was taken for plasma BNP the evening prior to surgery. This was collected in chilled EDTA and aprotinin (Trasylol; 50 IU/ml), immediately centrifuged and stored at –25° Celsius. BNP concentrations were measured using a direct radioimmunoassay (Shionoria BNP kit, Shinogi & Co, Osaka, Japan).[193] The minimum detectable quantity of BNP is 2pg/ml. The within-assay and between assay co-efficients of variation are 5.3% and 5.9%, respectively. Batch sample analysis was performed during the study by a biochemist blinded to clinical detail. The longest sample storage period was 6 months.

3.2.2 Statistical analysis

Statistical analysis was performed using SPSS version 15 (SPSS, Chicago, IL, USA). BNP values are presented as median and interquartile range (IQR). Comparison of the non-parametric data was performed using the Mann-Whitney tests and Kruskal-Wallis test as appropriate.

3.3 Results

Three hundred and forty-five patients were included in the study. The mean age was 68.4 years. Eighty-seven (25.2%) patients underwent lower limb amputation, 100 (29.0%) bypass surgery for peripheral vascular disease, 89 (25.8%) aortic surgery and 69 (20.0%) underwent laparotomy.

3.3.1 Determinants of a raised b-type natriuretic peptide

Across the whole group, the median BNP (IQR) was 38 (16-106) pg/ml, and the range was 1 to 2009 pg/ml. The distribution of pre-operative BNP is demonstrated in Figure 3.1. The median BNP (IQR) was higher in patients undergoing lower limb amputation (84 (38-214) pg/ml), than those having bypass surgery (38 (16-96) pg/ml), aortic surgery (31 (13-84) pg/ml) and laparotomy (28 (10-78) pg/ml), $p<0.001$ [Figure 3.2].

Pre-operative BNP (IQR) was higher in patients aged ≥70 years compared with those aged <70 years (82 (32-186) pg/ml vs. 26 (11-61) pg/ml, $p<0.001$) [Table 3.1]. Similarly, BNP was higher in patients with diabetes ($p=0.030$), hypertension ($p<0.001$), renal impairment (eGFR <60ml/min) ($p<0.001$), previous MI ($p=0.001$), ischaemic heart disease ($p<0.001$) and a history of left ventricular failure ($p=0.007$). Patients who were receiving beta-blockers, antiplatelet therapy and a statin had a higher pre-operative BNP ($p<0.001$, $p=0.004$, $p=0.007$ respectively).

Figure 3.1 Distribution of pre-operative b-type natriuretic peptide (BNP) in patients undergoing major non-cardiac surgery

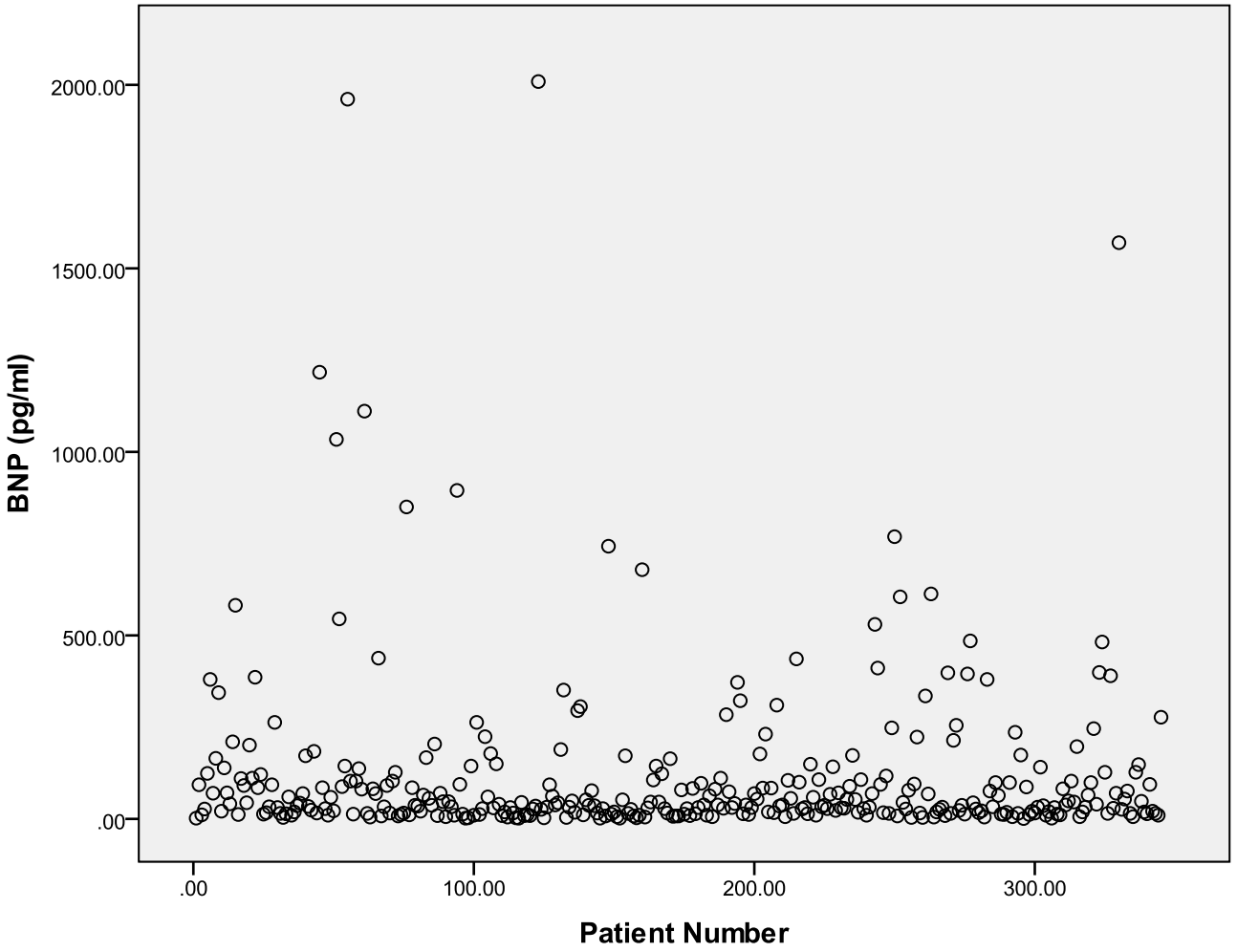


Figure 3.2 B-type natriuretic peptide concentration (BNP) by operation type

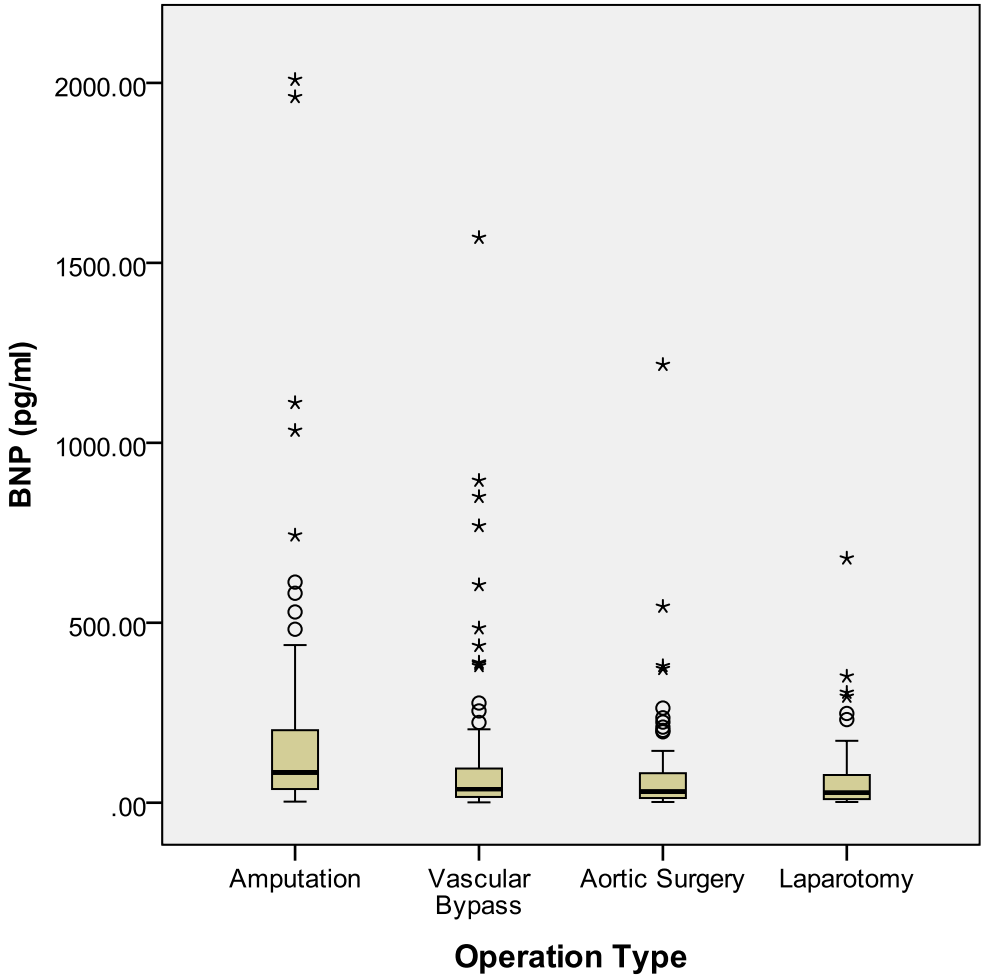


Table 3.1 Clinical variables and b-type natriuretic peptide (BNP) concentration

		n	BNP (IQR)	p*
Age	≥70 years	165	82 (32-186)	<0.001
	<70 years	180	26 (11-61)	
Sex	Male	217	35 (15-99)	0.070
	Female	128	55 (18-127)	
Smoker	Yes	145	40 (16-96)	0.716
	No	200	37 (15-126)	
Diabetes	Yes	69	69 (20-161)	0.030
	No	276	36 (15-99)	
Hypertension	Yes	196	60 (19-149)	<0.001
	No	149	31 (13-73)	
Renal Impairment †	Yes	142	70 (28-172)	<0.001
	No	203	31 (13-81)	
Hyperlipidaemia	Yes	110	39 (16-105)	0.871
	No	235	38 (15-106)	
Previous MI	Yes	64	76 (32-174)	0.001
	No	281	35 (15-99)	
Ischaemic Heart Disease	Yes	104	69 (29-167)	<0.001
	No	241	32 (14-95)	
History of Left Ventricular Failure	Yes	64	76 (22-205)	0.007
	No	281	36 (15-99)	
Cerebrovascular Disease	Yes	43	54 (22-184)	0.078
	No	302	38 (15-103)	
COPD	Yes	49	35 (15-94)	0.661
	No	296	39 (16-109)	

ß-Blocker	Yes	86	82 (28-180)	<0.001
	No	259	33 (15-91)	
APA	Yes	179	46 (22-137)	0.004
	No	166	33 (13-89)	
Statin	Yes	175	49 (19-127)	0.007
	No	170	32 (14-89)	
Operation type	Amputation	87	84 (38-214)	<0.001**
	Bypass	100	38 (16-96)	
	Aortic	89	31 (13-84)	
	Laparotomy	69	28 (10-78)	

* Mann-Whitney U-test, unless otherwise stated, ** Kruskal-Wallis Test.
† Defined as eGFR <60mls/min.
Abbreviations: MI - Myocardial Infarction, COPD - Chronic Obstructive Airways Disease, APA - Anti-Platelet Agent.

3.4 Discussion

An elevated BNP is strongly linked to left ventricular systolic dysfunction (LVSD). McDonagh and colleagues studied 1252 West of Scotland patients, randomly selected from the general population.[124] All patients had full clinical assessment, natriuretic peptide sampling and trans-thoracic echocardiography. LVSD was defined as an ejection fraction of ≤30%. The median concentration BNP (IQR) was significantly higher in patients with LVSD than those with normal ventricular function (24(18-33) pg/ml vs. 8(3-13) pg/ml). Subsequently, Zaphiriou and colleagues reported the results of the UK Natriuretic peptide study.[128] This study was performed between Glasgow and London and investigated the diagnostic utility of BNP in patients referred to an open access clinic with dyspnoea suspicious of cardiac failure. Plasma BNP concentrations were significantly higher in patients with LVSD, and a BNP of >30pg/ml provided a useful 'rule-out' test with a NPV of 0.93. Knudsen and colleagues performed a subgroup analysis of patients enrolled into a large multicentre heart failure study.[202] They studied patients with an elevated BNP, but no evidence of current acute heart failure, to identify other determinants of a raised BNP. Unsurprisingly, previous CCF predicted a raised BNP. On multivariate analysis, increasing age, atrial fibrillation, cardiomegaly on chest x-ray and anaemia predicted a raised BNP.

The reported incidence of raised pre-operative BNP in research published after the start of the present study is variable, depending on which patient group was selected for investigation. For example, Cuthbertson and colleagues studied a cohort of over 200 mixed NCS patients from a Scottish centre.[132] The median BNP (IQR) was 27 (12-50) pg/ml. Another study from the same institution showed the median BNP (IQR) rose to 100 (62-205) pg/ml in patients undergoing emergency surgery.[134] Bredthardt and collegues recruited 270 patients undergoing major orthopaedic procedures.[138] They found and median (IQR) BNP of 36 (17-82) pg/ml. Biccard and colleagues found similar results in a vascular cohort.[203]

This study shows that in a cohort of patients undergoing major NCS, an elevated pre-operative BNP is associated with increasing age, several cardiac co-morbidities (hypertension, IHD, previous MI and previous LVF), renal impairment

and diabetes. Also, patients with severe PVD requiring amputation had a higher BNP. Interestingly, there was no association with a history of cerebrovascular disease.

Unfortunately, most of the subsequently published studies examining the prognostic utility of natriuretic peptides in patients undergoing surgical procedures do not report the associations between clinical variables and a raised BNP. Bolliger and colleagues examined the predictors of a raised BNP in 133 clinically stable patients undergoing major vascular surgery.[204] Using a cut-off point of 50 pg/ml, the authors demonstrated that the group with a high BNP (>50 pg/ml) were older and had a higher rate of IHD, previous MI, previous cardiac failure and hypertension. However, the presence of diabetes was not associated with a raised BNP. Feringa and colleagues studied 144 Dutch patients undergoing major vascular surgery. They measured NT-proBNP, the cleavage fragment from BNP pro-hormone. They found an elevated NT-proBNP was associated with increasing age, IHD, previous MI, previous cardiac failure, diabetes and renal impairment. These results support the present study's findings.

This study has shown that a raised pre-operative plasma BNP may act as a surrogate marker for a number of medical co-morbidities. The efficacy with which BNP can predict post-operative morbidity and mortality, in particular cardiac morbidity, requires a prospective observational study.

4 Prediction of peri-operative cardiac morbidity and mortality

4.1 Introduction

Post-operative major adverse cardiac events (MACE) occur with varying incidence, depending on which patient population is studied. In cohorts of mixed non-cardiac surgery (NCS) operations, including intermediate as well as major procedures, MACE rates are less than 3%.[6,8,51] However, when cohorts are confined to major surgery or high risk patients then observed MACE rates are greater than 10%.[39,47,68] Post-operative cardiac morbidity has significant implications for patients. Patients suffering a PMI have a higher rate of subsequent cardiac events and increased short-term mortality.[36,37]

Currently, there is no 'gold-standard' method for prediction of risk of cardiac morbidity following surgery. Risk scoring systems may be accurate within certain patient groups, but they have limited predictive value when applied to cohorts out with their derivation population.[103] Non-invasive cardiac imaging techniques, such as stress echocardiography, are sensitive predictors of MACE, but have limited availability to the general clinician.[111]

Scotland, and in particular the West of Scotland, has a high incidence of coronary artery disease and a high incidence of asymptomatic heart disease.[205] The use of cardiac biomarkers, in particular BNP, is helpful in the detection of subclinical ventricular dysfunction in non-surgical patients.[124] The incidence of subclinical heart disease in patients attending for surgical procedures, and the rate of post-operative MACE in the West of Scotland is not known.

This study aims to document the incidence of post-operative cardiac morbidity and mortality. Secondly, we aim to identify the prognostic utility of pre- and peri-operative clinical variables in the prediction of adverse post-operative outcomes, in particular cardiac morbidity and mortality. Furthermore, we have previously shown (Chapter 3) that a single pre-operative serum BNP appears to be a surrogate marker for a number of medical co-morbidities. We aim to examine the prognostic utility of BNP for the occurrence of peri-operative adverse events.

4.2 Methods

4.2.1 Participants

A prospective single centre observational cohort study of consecutive patients undergoing major non-cardiac surgery was performed. Emergency patients (operated within 24 hours of an unplanned admission) were not included. This left 345 patients that were included in this study.

All patients had standard pre-operative assessment including clinical history, laboratory blood tests and a 12 lead ECG. Co-morbidities were based on medical history and self reporting. Ischaemic heart disease was defined as a previous myocardial infarction, a positive exercise tolerance test, the use of nitrate therapy or the presence of pathological Q-waves on ECG.[6] Left ventricular failure (LVF) was considered present if the patient had a prior hospital admission with heart failure or left ventricular impairment on previous echocardiography. Cerebrovascular disease was defined as a previous cerebrovascular accident or transient ischaemic attack. The glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease (MDRD) equation.[192] Renal impairment was considered present if the estimated GFR was <60mls/min. A patient was considered a smoker if they were smoking at the time of admission for surgery. Hypertension was considered present if the patient had a previous medical documentation of hypertension and was currently taking antihypertensive medication. The presence of hyperlipidaemia and chronic obstructive pulmonary disease (COPD) was extracted from the patient's primary care records and past medical history. The current medication was also recorded, in particular the prescription of anti-platelet agents, a statin and beta-blockers.

An additional venous blood sample was taken for plasma BNP the evening prior to surgery. This was collected in chilled EDTA and aprotinin (Trasylol; 50 IU/ml), immediately centrifuged and stored at –25° Celsius. BNP concentrations were measured using a direct immunoradiometric assay (Shionoria BNP kit, Shinogi & Co, Osaka, Japan).[193] The minimum detectable quantity of BNP is 2pg/ml. The within-assay and between assay co-efficients of variation are 5.3% and 5.9%, respectively. Batch sample analysis was performed during the study by a

biochemist blinded to clinical detail. The longest sample storage period was 6 months.

Post-operative screening for cardiac events was performed. This consisted of daily clinical assessment and serial ECGs and troponin I measurement on day 2, day 5 and 6 weeks following surgery. The primary outcomes were death within the post-operative period (6 weeks) and all cause mortality during the follow-up period. Regional ethics committee approval was obtained and all patients gave written consent to the study following a verbal explanation and written information.

4.2.2 Statistical analysis

Statistical analysis was performed using SPSS (Version 15) statistical software package (SPSS, Chicago, Illinois, USA). A p-value of less than 0.05 was considered significant. Comparison of interval data was performed using independent samples t-test, Mann-Whitney test and Kruskal-Wallis test as appropriate. Categorical data was compared using the X^2 test. Performance of continuous variables was analysed used receiver operating characteristics (ROC) and the area under the curve (AUC) was calculated. Variables with a p-value of less than 0.10 on univariate analysis were selected for multivariate analysis and were entered into a logistic regression model.

4.3 Results

4.3.1 Incidence and clinical predictors of peri-operative major adverse cardiac event (MACE)

MACE occurred in 46 (13.3%) patients during the post-operative period (within 6 weeks). The peri-operative MACE rate was higher in patients with hypertension (18.4% vs. 6.7%, p=0.002) and patients aged >70 years (19.4% vs. 7.8%, p=0.002) [Table 4.1]. Similarly, patients with pre-operative anaemia had a higher MACE rate those who were not anaemic (22.2% vs. 7.0%, p<0.001) [Table 4.2]. A higher MACE rate was observed following an urgent surgical procedure compared with an elective one (20.9% vs. 6.6%, p<0.001). The presence of cardiac variables such as IHD, a previous MI, a previous CVA and a history of CCF did not predict MACE. Patients undergoing lower limb amputation had a higher MACE rate (21.8%), compared with patients undergoing lower limb bypass (11.0%), aortic surgery (12.4%) and laparotomy (7.2%) (p=0.042) [Table 4.3].

Table 4.1 Pre-operative clinical variables and peri-operative major adverse cardiac event (MACE)

		n = 345	MACE n= 46	p*
Sex	Male	217	30 (13.8%)	0.727
	Female	128	16 (12.5%)	
Age > 70 years	Yes	165	32 (19.4%)	0.002
	No	180	14 (7.8%)	
Smoker	Yes	145	20 (13.8%)	0.831
	No	200	26 (13.0%)	
Diabetes	Yes	69	12 (17.4%)	0.268
	No	276	34 (12.3%)	
Hypertension	Yes	196	36 (18.4%)	0.002
	No	149	10 (6.7%)	
Renal Impairment (eGFR <60)	Yes	142	25 (17.6%)	0.051
	No	203	21 (10.3%)	
Hyperlipideamia	Yes	110	14 (12.7%)	0.821
	No	235	32 (13.6%)	
Previous MI	Yes	64	11 (17.2%)	0.315
	No	281	35 (12.5%)	
Ischaemic Heart Disease	Yes	104	16 (15.4%)	0.462
	No	241	30 (12.4%)	
History of Left Ventricular Failure	Yes	64	11 (17.2%)	0.315
	No	281	35 (12.5%)	
Cerebrovascular Disease	Yes	43	9 (20.9%)	0.147
	No	302	37 (12.3%)	
COPD	Yes	49	4 (8.2%)	0.363
	No	296	42 (14.2%)	

* X^2 test

Abbreviations: MACE - Major Adverse Cardiac Event, eGFR - estimated glomerular filtration rate, MI - myocardial infarction, COPD - chronic obstructive pulmonary disease.

Table 4.2 Other clinical variables and major adverse cardiac event (MACE)

		n = 345	MACE n= 46	p*
ß-Blocker	Yes	86	14 (16.3%)	0.354
	No	259	32 12.4%)	
APA	Yes	179	26 (14.5%)	0.499
	No	166	20 (12.0%)	
Statin	Yes	175	27 (15.4%)	0.245
	No	170	19 (11.2%)	
Anaemia†	Yes	144	32 (22.2%)	<0.001
	No	201	14 (7.0%)	
Blood Loss >500mls	Yes	36	7 (19.4%)	0.296
	No	309	39 (12.6%)	
Intra-operative hypotension	Yes	61	11 (18.0%)	0.234
	No	284	35 (12.3%)	
Urgent Surgery	Yes	163	34 (20.9%)	<0.001
	No	182	12 (6.6%)	

* Chi-Square Test,
†Anaemia defined as haemoglobin <13 g/dl in males and <11g/dl in females.

Abbreviations: MACE - Major Adverse Cardiac Event, APA – Antiplatelet agent

Table 4.3 Major adverse cardiac event (MACE) by procedure type

	n	MACE n=46	p*
Aortic Surgery	89	11 (12.4%)	0.042
Bypass Surgery	100	11 (11.0%)	
Amputation	87	19 (21.8%)	
Laparotomy	64	5 (7.2%)	

* X^2 test.

Abbreviations: MACE - Major Adverse Cardiac Event

4.3.2 Incidence and clinical predictors of peri-operative mortality

Twenty-seven (7.8%) patients died during the immediate peri-operative period. The peri-operative mortality was higher in diabetics (15.9% vs. 5.8%, p=0.005) and in patients with renal impairment (11.3% vs. 5.4%, p=0.047) [Table 4.4]. Similarly, the mortality rate was higher in anaemic patients compared with patients that were not anaemic (12.5% vs. 4.5%, p=0.006), and in patients undergoing urgent rather than elective surgery (12.3% vs. 3.8%, p=0.004) [Table 4.5]. There was no significant difference in mortality rates between the operative subgroups [Table 4.6]. As with peri-operative MACE, the presence of cardiac variables such as IHD, previous MI, previous LVF or cerebrovascular disease did not predict peri-operative mortality.

Table 4.4 Pre-operative clinical variables and peri-operative mortality

		n = 345	Mortality n=27	p*
Sex	Male	217	19 (8.8%)	0.403
	Female	128	8 (6.3%)	
Age > 70 years	Yes	165	17 (10.3%)	0.101
	No	180	10 (5.6%)	
Smoker	Yes	145	10 (6.9%)	0.584
	No	200	17 (8.5%)	
Diabetes	Yes	69	11 (15.9%)	0.005
	No	276	16 (5.8%)	
Hypertension	Yes	196	20 (10.2%)	0.059
	No	149	7 (4.7%)	
Renal Impairment (GFR <60)	Yes	142	16 (11.3%)	0.047
	No	203	11 (5.4%)	
Hyperlipideamia	Yes	110	10 (9.1%)	0.550
	No	235	17 (7.2%)	
Previous MI	Yes	64	6 (9.4%)	0.609
	No	281	21 (7.5%)	
Ischaemic Heart Disease	Yes	104	8 (7.7%)	0.942
	No	241	19 (7.9%)	
History of Left Ventricular Failure	Yes	64	2 (3.1%)	0.121
	No	281	25 (8.9%)	
Cerebrovascular Disease	Yes	43	4 (9.3%)	0.760
	No	302	25 (8.9%)	
COPD	Yes	49	7 (14.3%)	0.083
	No	296	20 (6.8%)	

* Chi-Square Test

Abbreviations: eGFR - estimated glomerular filtration rate, MI - myocardial infarction, COPD - chronic obstructive pulmonary disease.

Table 4.5 Other clinical variables and peri-operative mortality

		n = 345	Mortality n=27	p*
ß-Blocker	Yes	86	8 (9.3%)	0.556
	No	259	19 (7.3%)	
APA	Yes	179	11 (6.1%)	0.227
	No	166	16 (9.6%)	
Statin	Yes	175	13 (7.4%)	0.780
	No	170	14 (8.2%)	
Anaemia†	Yes	144	18 (12.5%)	0.006
	No	201	9 (4.5%)	
Blood Loss >500mls	Yes	36	2 (5.6%)	1.000
	No	309	25 (8.1%)	
Intra-operative hypotension	Yes	61	2 (3.3%)	0.192
	No	284	25 (8.8%)	
Urgent Surgery	Yes	163	20 (12.3%)	0.004
	No	182	7 (3.8%)	

* Chi-Square Test,
†Anaemia defined as haemoglobin <13 g/dl in males and <11 g/dl in females.

Abbreviations: APA – Antiplatelet agent

Table 4.6 Mortality by procedure type

	n	Mortality n= 27	p*
Aortic Surgery	89	3 (3.4%)	0.101
Bypass Surgery	100	6 (6.0%)	
Amputation	87	11 (12.6%)	
Laparotomy	64	7 (10.1%)	

* X^2 test

4.3.3 Predictive utility of b-type natriuretic peptide in patients undergoing major non-cardiac surgery

The median BNP (IQR) of the 345 patients enrolled in the study was 38 pg/ml (16-106 pg/ml). The determinants of a pre-operatively raised BNP have been discussed in Chapter 3. The median BNP was significantly higher in patients who suffered a peri-operative MACE, a peri-operative death and a peri-operative non-fatal MI [Table 4.7]). Figure 4.1 demonstrates the distribution of BNP in patients with and without a post-operative MACE. Figure 4.2 demonstrates the distribution of BNP in patients with and without post-operative mortality.

Table 4.7 Median b-type natriuretic peptide (BNP) of patients who suffered a peri-operative major adverse cardiac event (MACE), a peri-operative death and a peri-operative non-fatal myocardial infarction (MI)

		n	BNP (IQR)	p*
Peri-operative MACE	Yes	46	199 (102-430)	<0.001
	No	299	33 (15-85)	
Peri-operative Mortality	Yes	27	165 (36-380)	<0.001
	No	318	37 (15-95)	
Peri-operative Non-fatal MI	Yes	33	144 (51-379)	<0.001
	No	299†	33 (15-85)	

* Mann-Whitney U Test
† Fatal cardiac event patients removed from denominator

Abbreviations: MACE - Major Adverse Cardiac Event, BNP - B-type natriuretic peptide, MI - myocardial infarction.

Figure 4.1 Box plot of b-type natriuretic peptide (BNP) concentration and peri-operative major adverse cardiac event (MACE)

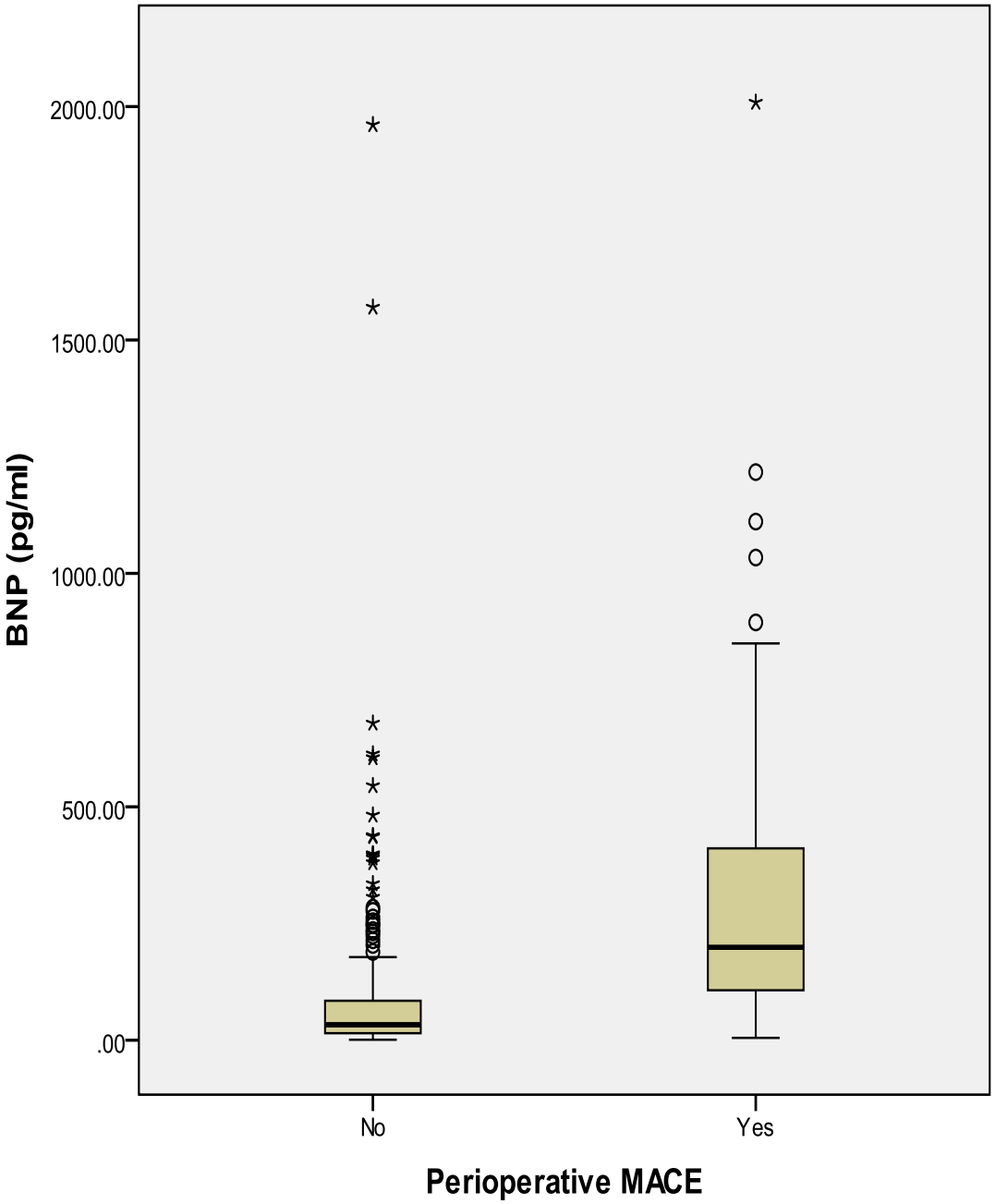
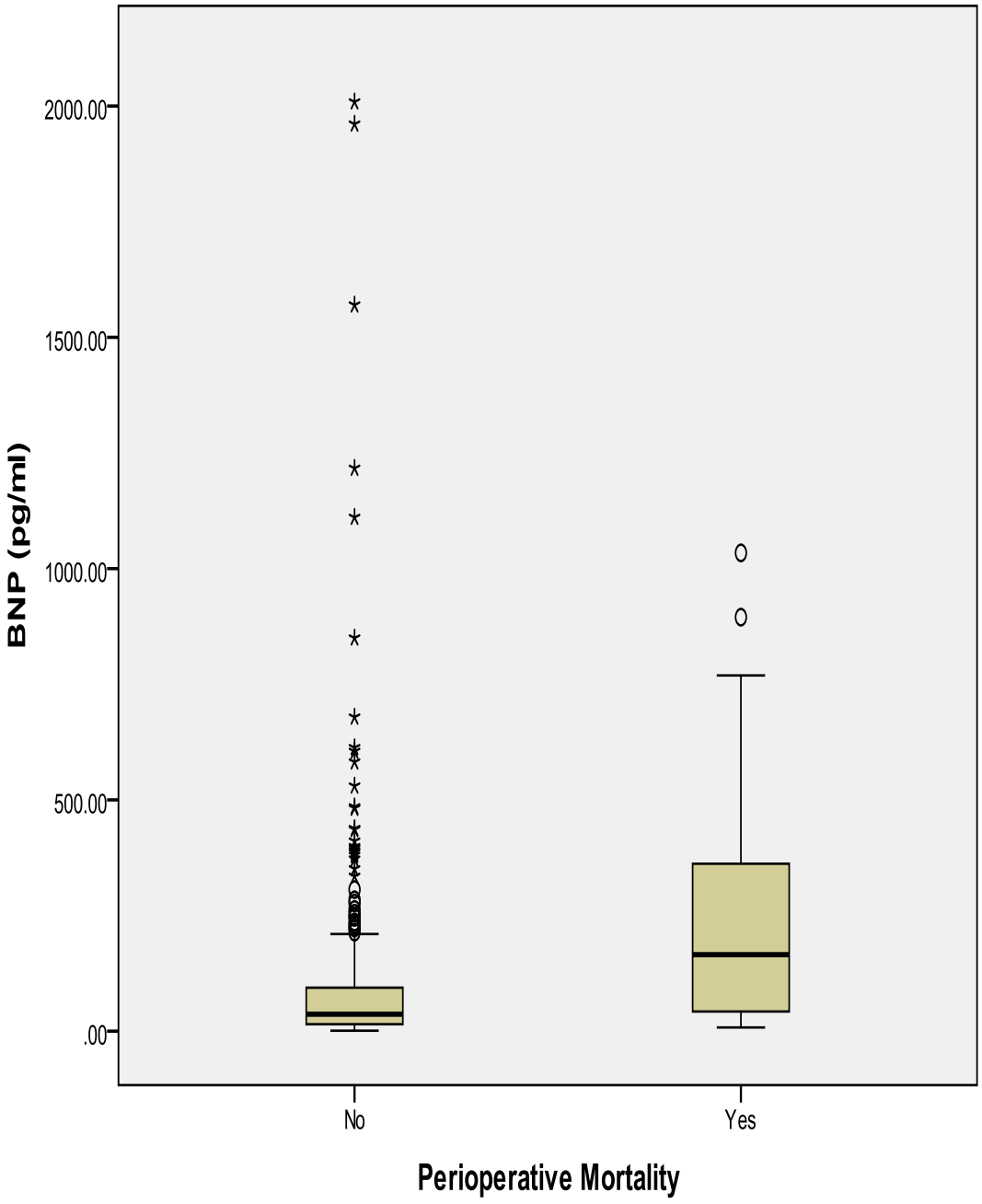


Figure 4.2 Box plot of b-type natriuretic peptide (BNP) concentration and peri-operative mortality



4.3.4 Best b-type natriuretic peptide (BNP) cut-off point for prediction of major adverse cardiac events (MACE)

The optimal cut-off point for prediction of post-operative MACE was examined using ROC curve analysis. A pre-operative BNP concentration of 107pg/ml had the best combined sensitivity (76.1%) and specificity (83.3%), and an AUC of 0.821 (SE 0.036, 95% CI; 0.751-0.890, p<0.001) [Figure 4.3]. Using this cut-off point, the positive predictive value was 41.2% and the negative predictive value was 95.8%.

Using the threshold level of 107 pg/ml, as identified from ROC curve analyses, BNP predicted outcome independently of all preoperative risk factors that were significant from univariate analysis [Table 4.8].

Figure 4.3 ROC curve analysis: BNP concentration and major adverse cardiac event (MACE)

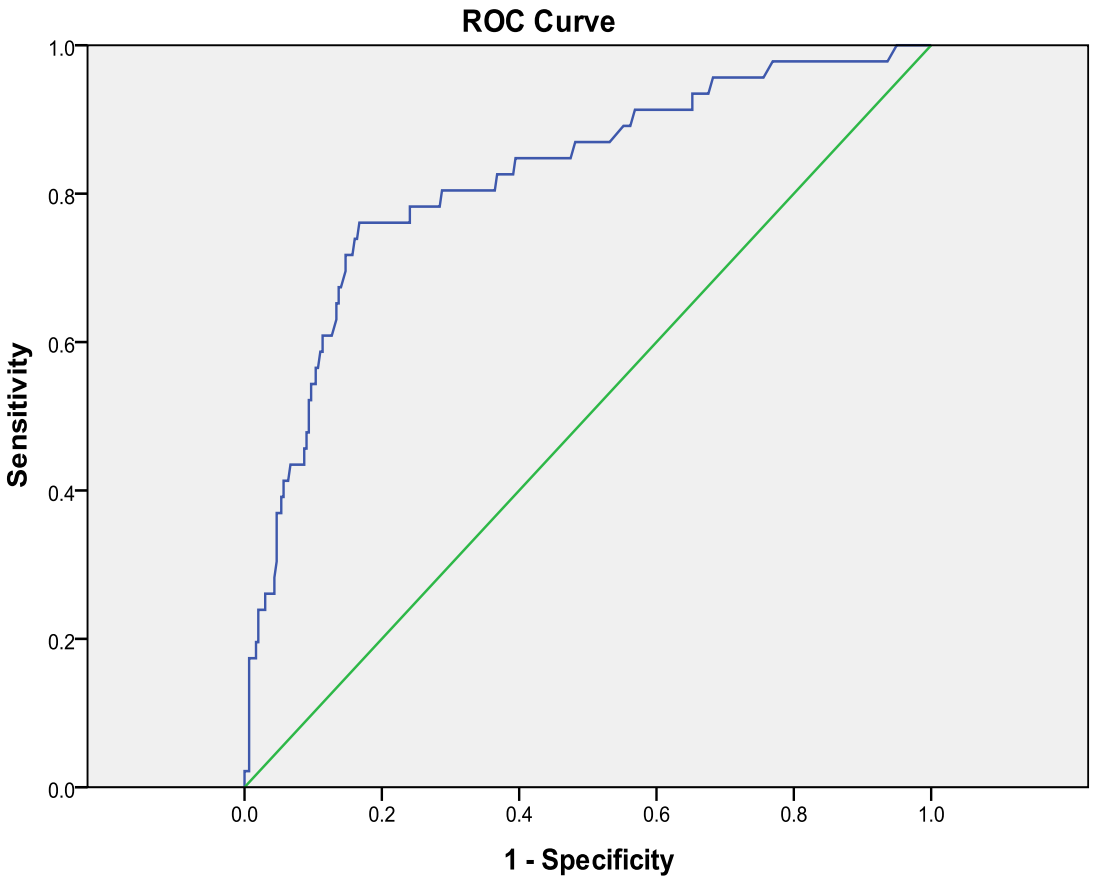


Table 4.8 Major adverse cardiac events (MACE) by a b-type natriuretic peptide (BNP) cut-off point of 107pg/ml and by other risk factors

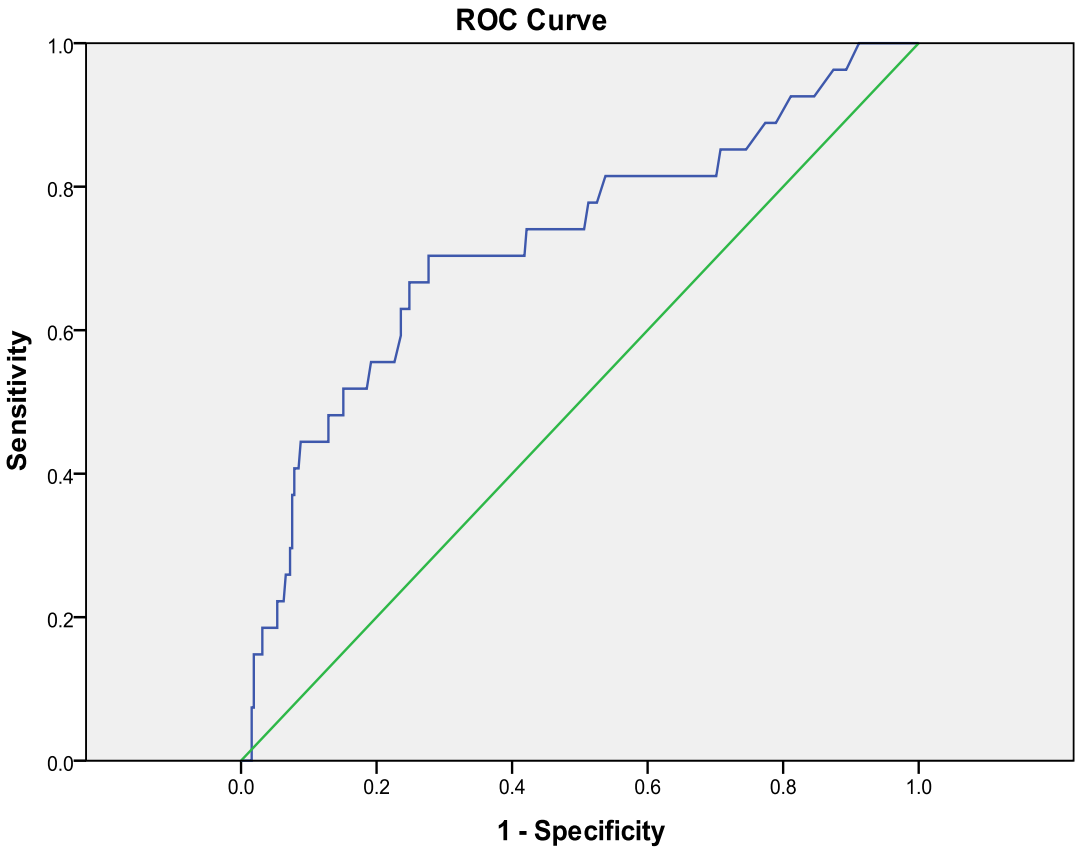
Characteristic		BNP level (pg/ml)	MACE	p*
Age	>70	<107	8/103 (7.8%)	<0.001
		≥107	24/62 (38.7%)	
	<70	<107	3/157 (1.9%)	<0.001†
		≥107	11/23 (47.8%)	
Hypertension	Yes	<107	6/131 (4.6%)	<0.001
		≥107	30/65 (46.2%)	
	No	<107	5/129 (3.9%)	0.004†
		≥107	5/20 (25.0%)	
Anaemia	Yes	<107	5/92 (5.4%)	<0.001
		≥107	27/52 (51.9%)	
	No	<107	6/168 (3.6%)	<0.001
		≥107	8/33 (24.2%)	
Urgent Surgery	Yes	<107	7/100 (7.0%)	<0.001
		≥107	27/63 (42.9%)	
	No	<107	4/160 (2.5%)	<0.001†
		≥107	8/22 (36.4%)	

* X^2 test unless otherwise stated. † Fisher's Exact Test
Abbreviations: MACE - Major Adverse Cardiac Event, BNP - B-type natriuretic peptide.

4.3.5 Best b-type natriuretic peptide (BNP) cut-off point for prediction of post-operative mortality

The optimal cut-off point for prediction of post-operative mortality (within 6 weeks) was examined using ROC curve analysis. A pre-operative BNP concentration of 88pg/ml had the best combined sensitivity (70.4%) and specificity (72.3%), and an AUC of 0.720 (SE 0.057, 95% CI; 0.609-0.832, p<0.001) [Figure 4.4]. Using this cut-off point, the positive predictive value was 17.7% and the negative predictive value was 96.6%.

Figure 4.4 ROC curve analysis: BNP concentration and post-operative mortality



4.3.6 Performance of b-type natriuretic peptide (BNP) in prediction of major adverse cardiac events (MACE) and mortality within operation type subgroup analysis

The predictive value of a pre-operative BNP concentration was analysed within the 4 main subgroups (aortic surgery, lower limb bypass surgery, amputation and laparotomy) and by urgency of procedure (elective or urgent). The median BNP was significantly higher in patients who had a MACE compared with those that did not, across all subgroups examined [Table 4.9]. Likewise, the median BNP was significantly higher in patients who had a MACE compared with those that did not following elective and urgent surgery.

Table 4.9 Median BNP and peri-operative major adverse cardiac event (MACE) by operative subgroup

Operative Group	MACE	n	BNP (IQR)	p*
Aortic	Yes	11	144 (31-210)	0.003
	No	78	29 (11-65)	
Bypass	Yes	11	380 (107-769)	<0.001
	No	89	33 (15-80)	
Amputation	Yes	19	263 (124-582)	0.001
	No	68	70 (33-150)	
Laparotomy	Yes	5	127 (83-323)	0.004
	No	64	27 (9-60)	
Urgent	Yes	34	242 (110-622)	<0.001
	No	129	59 (26-124)	
Elective	Yes	12	170 (32-274)	<0.001
	No	170	27 (11-55)	

*Mann-Whitney U test

Abbreviations: MACE - Major Adverse Cardiac Event

4.3.7 Multivariate analysis of predictors of peri-operative major adverse cardiac events (MACE) and mortality

The clinical variables with a p value of <0.10 from univariate analysis of peri-operative MACE were entered into a logistic regression model. All four clinical factors (age > 70 years, hypertension, urgent surgery and anaemia) that were significant on univariate remained significant on multivariate analysis [Table 4.10]. However, when BNP, at the cut-off point of 107 pg/ml, was added to the model, only BNP (OR 9.836, 95% CI 4.443-21.824, p<0.001) and anaemia (OR 2.357, 95% CI 1.107-5.017, p<0.001) remained significant predictors of MACE [Table 4.11].

Similarly, the clinical variables with a p value of <0.10 from univariate analysis of peri-operative mortality were entered into a logistic regression model. On multivariate analysis, no clinical variable was a significant predictor of peri-operative mortality [Table 4.12]. When BNP, at a cut-off of 88pg/ml, was added to the model, BNP (OR 4.129, 95% CI 1.596-10.683, p=0.003) remained a strong predictor of mortality [Table 4.13].

Table 4.10 Logistic regression model for prediction of peri-operative major adverse cardiac event (MACE) by pre-operative clinical variables

	Univariate		Multivariate	
Factor	OR (95% CI)	p	OR (95% CI)	p
Anaemia	3.816 (1.952-7.460)	<0.001	2.693 (1.330-5.450)	0.006
Urgent Surgery	3.734 (1.860-7.495)	<0.001	2.433 (1.165-5.081)	0.018
Hypertension	3.127 (1.497-6.532)	0.002	2.556 (1.190-5.493)	0.016
Age >70 years	2.853 (1.462-5.565)	0.002	2.252 (1.117-4.539)	0.023

Table 4.11 Logistic regression model for prediction of peri-operative major adverse cardiac event (MACE) by b-type natriuretic peptide (BNP) and pre-operative clinical variables

	Univariate		Multivariate	
Factor	OR (95% CI)	p	OR (95% CI)	p
BNP >107pg/ml	15.845 (7.542-33.293)	<0.001	9.836 (4.433-21.824)	<0.001
Anaemia	3.816 (1.952-7.460)	<0.001	2.357 (1.107-5.017)	0.026
Urgent Surgery	3.734 (1.860-7.495)	<0.001	1.593 (0.715-3.548)	0.255
Hypertension	3.127 (1.497-6.532)	0.002	1.692 (0.737-3.884)	0.215
Age >70 years	2.853 (1.462-5.565)	0.002	1.468 (0.673-3.198)	0.355

Table 4.12 Logistic regression model for prediction of peri-operative mortality by pre-operative clinical variables

	Univariate		Multivariate	
Factor	OR (95% CI)	p	OR (95% CI)	p
Urgent Surgery	3.497 (1.438-8.503)	0.006	2.462 (0.963-6.296)	0.060
Diabetes	3.082 (1.359-6.989)	0.007	1.823 (0.749-4.441)	0.186
Anaemia	3.048 (1.327-6.997)	0.009	2.004 (0.826-4.865)	0.124
eGFR <60	2.216 (0.996-4.932)	0.051	2.029 (0.870-4.733)	0.101
COPD	2.300 (0.917-5.771)	0.076	2.343 (0.877-6.260)	0.089

Abbreviations: eGFR - estimated glomerular filtration rate (mls/min), COPD - chronic obstructive airways disease.

Table 4.13 Logistic regression model for prediction of peri-operative mortality by b-type natriuretic peptide (BNP) and pre-operative clinical variables

	Univariate		Multivariate	
Factor	OR (95% CI)	p	OR (95% CI)	p
BNP >88pg/ml	6.207 (2.622-14.696)	<0.001	4.129 (1.596-10.683)	0.003
Urgent Surgery	3.497 (1.438-8.503)	0.006	1.879 (0.714-4.947)	0.201
Diabetes	3.082 (1.359-6.989)	0.007	1.935 (0.763-4.906)	0.164
Anaemia	3.048 (1.327-6.997)	0.009	1.681 (0.678-4.170)	0.262
eGFR <60	2.216 (0.996-4.932)	0.051	1.477 (0.606-3.601)	0.391
COPD	2.300 (0.917-5.771)	0.076	2.371 (0.862-6.523)	0.094

Abbreviations: eGFR - estimated glomerular filtration rate (mls/min), COPD - chronic obstructive airways disease.

4.3.8 Relationship between previous history of cardiac disease, medication and MACE

The rates of prescription of best medical therapy (BMT) for cardiac disease (anti-platelet agent (APA), a statin and a beta-blocker) were investigated. Overall, prescription rates for APAs were 51.9%, statins 50.7% and beta-blockers 24.9%. Prescription rates were significantly higher in patients with IHD for APAs (68.3% vs. 44.8%, $p<0.001$), statins (66.3 vs. 44.0%, $p<0.001$) and beta-blockers (42.3% vs. 17.4%, $p<0.001$), compared with patients without IHD [Table 4.14]. Similarly, prescription rates were higher for all three medications groups in patients with a previous MI [Table 4.15].

The relationship between BMT, presence of IHD or previous MI and peri-operative MACE was then investigated. There was no association between MACE rate in patients with IHD with or without prescription of APAs (15.5% vs. 15.2%, 0.964), statins (15.9% vs. 14.3%, $p=0.825$) or beta-blockers (11.4% vs. 18.3%, $p=0.330$) [Table 4.16]. Similarly, there was no association between MACE rate in patients with a previous MI for all three medication groups [Table 4.17].

Table 4.14 Rate of prescription of anti-platelet agents (APA), statin and beta-blockers by presence or absence of ischaemic heart disease (IHD)

IHD	Medication		p*
Yes	APA	71/104 (68.3%)	<0.001
No		108/241 (44.8%)	
Yes	Statin	69/104 (66.3%)	<0.001
No		106/241 (44.0%)	
Yes	Beta Blocker	44/104 (42.3%)	<0.001
No		42/241 (17.4%)	

*Chi-squared test.
Abbreviations: IHD - ischaemic heart disease, MI - myocardial infarction, APA - anti-platelet agent.

Table 4.15 Rate of prescription of anti-platelet agents (APA), statin and beta-blockers by presence or absence of previous myocardial infarction (MI)

Previous MI	Medication		p*
Yes	APA	45/64 (70.3%)	<0.001
No		134/281 (47.7%)	
Yes	Statin	49/64 (76.6%)	<0.001
No		126/281 (44.8%)	
Yes	Beta Blocker	27/64 (42.2%)	<0.001
No		59/281 (21.0%)	

*Chi-squared test.
Abbreviations: IHD - ischaemic heart disease, MI - myocardial infarction, APA - anti-platelet agent.

Table 4.16 Incidence of major adverse cardiac event (MACE) by presence or absence of ischaemic heart disease (IHD) and by prescription of anti-platelet agents (APA), statin and beta-blockers

IHD	Medication		MACE	p*
Yes	APA	Yes	11/71 (15.5%)	0.964
		No	5/33 (15.2%)	
No	APA	Yes	15/108 (13.9%)	0.542
		No	15/133 (11.3%)	
Yes	Statin	Yes	11/69 (15.9%)	0.825
		No	5/35 (14.3%)	
No	Statin	Yes	16/106 (15.1%)	0.270
		No	14/135 (10.4%)	
Yes	Beta-blocker	Yes	5/44 (11.4%)	0.330
		No	11/60 (18.3%)	
No	Beta-blocker	Yes	9/42 (21.1%)	0.052
		No	21/199 (10.6%)	

* Chi-squared test.
Abbreviations: MACE - major adverse cardiac event, IHD - ischaemic heart disease, APA - anti-platelet agent.

Table 4.17 Incidence of major adverse cardiac event (MACE) by presence or absence of a history of previous myocardial infarction (MI) and by prescription of anti-platelet agents (APA), statin and beta-blockers

Previous MI	Medication		MACE	p*
Yes	APA	Yes	11/64 (17.2%)	0.594
		No	7/45 (15.6%)	
No	APA	Yes	19/134 (14.2%)	0.404
		No	16/147 (10.9%	
Yes	Statin	Yes	7/49 (14.3%)	0.266
		No	4/15 (26.7%)	
No	Statin	Yes	20/126 (15.9%)	0.118
		No	15/155 (9.7%)	
Yes	Beta-blocker	Yes	3/27 (11.1)	0.331†
		No	8/37 (21.6)	
No	Beta-blocker	Yes	11/59 (18.6%)	0.105
		No	24/222 (10.8%)	

* Chi-squared test unless otherwise stated. † Fisher's Exact Test
Abbreviations: MACE - major adverse cardiac event, MI - myocardial infarction, APA - anti-platelet agent.

4.4 Discussion

This study has three important findings. Firstly, commonly recorded markers of cardiac disease, such as previous MI and IHD, do not predict cardiac morbidity or mortality. Secondly, a number of non-cardiac related variables predict morbidity and mortality. Thirdly, a single pre-operative BNP measurement strongly predicts both MACE and mortality.

4.4.1 Poor performance of cardiac clinical variables

With the exception of a history of hypertension, none of the recorded cardiac variables predicted an adverse post-operative outcome. There are several possible reasons for this.

The first reason may be the influence of best medical therapy prescription in patients with a past cardiac history. The use of APAs and statins are at the heart of primary and secondary prevention of cardiovascular events.[145] The use of APAs and statins reduces the risk of MI and death in patients with or at high risk of cardiovascular disease.[206,207] Continuation of APA therapy through the peri-operative period appears safe and is likely to be beneficial in most circumstances.[45,74,151] The prescription of statins is associated with reduced peri-operative MACE and mortality in patients undergoing major NCS.[78,155] Peri-operative administration of beta-blockers have reduced peri-operative cardiac morbidity in large RCTs.[143,144] The beneficial effects of beta-blockers are not a universal finding. The POISE trial identified a higher stroke and mortality rate in patients receiving peri-operative metoprolol.[5] Our study demonstrated a higher prescription rate for APAs, statins and beta-blockers in patients with IHD or a previous MI. However, we were not able to show an association between improved MACE rate and these medications.

Secondly, the presence of subclinical heart disease may explain the lack of difference of MACE rate between patients with cardiac risk factors and those without. A high rate of asymptomatic LVSD has previously been demonstrated in the general population in the West of Scotland.[205] Therefore, some patients in our cohort will present for surgery with 'latent' CAD or LVSD. Also, a proportion of our cohort was undergoing vascular surgical procedures. This group has a

notoriously high prevalence of CAD, of which a subgroup will have asymptomatic disease.[10] Patients with short distance claudication or critical limb ischaemia may be unable to perform adequate activity in their daily living to elicit symptoms of cardiac disease.[208]

Finally, we were, in part, relying on the documentation of cardiac disease in patient's case records and the patients self-reporting of cardiac disease. Both sources of data collection represent a source of error. We were not able to independently corroborate all positive histories of cardiac disease, particularly if the diagnosis originated from primary care or historical records. Nevertheless, this limitation reflects the day-to-day experience of assessing patients prior to surgery.

4.4.2 Non-cardiac predictors of MACE and mortality

We found several clinical variables predicted poor post-operative outcomes.

4.4.2.1 Patient Age

We found that elderly patients (defined as age >70 years) had a higher rate of MACE than those aged less than 70 years. Numerous studies have demonstrated a similar association with increasing age and a poorer outcome following surgery.[8,51,61,62] Whilst increasing age is a non-modifiable risk factor for adverse post-operative outcome, it is an important factor to consider when stratifying a patients risk during and after surgery.

4.4.2.2 Urgent surgery

Urgent surgery, defined as surgery performed during an unplanned admission, was associated with MACE and mortality on univariate analysis, and remained significant on multivariate analysis of clinical variables for MACE. This finding is confirmed by other studies of peri-operative outcomes.[39,47] For example, urgent surgery was the strongest predictor of mortality on multivariate analysis of a prospectively collected multicentre cohort of patient undergoing colorectal resection.[81] Likewise, urgent and emergency surgery was an independent predictor of peri-operative mortality following colonic surgery in over 8000

patients analysed from the Association of Coloproctology of Great Britain and Ireland national database.[82]

4.4.2.3 Anaemia

Pre-operative anaemia was associated with MACE and mortality on univariate analysis, and remained significant on multivariate analysis for MACE. Since this was not anticipated as a major finding of this study, we did not include a more detailed assessment of anaemia in our data set, and we have no information about chronicity of anaemia, categorisation of anaemia (i.e. haematinic assessment) or previous investigations for anaemia. Therefore, we are unable to suggest causes for anaemia in this discussion. Nevertheless, anaemia appears to be a strong marker of poor outcome. Anaemia limits myocardial oxygenation and is poorly tolerated in patients with CAD or LVF.[209,210] Analysis of a Canadian cohort of >12,000 patients with first presentation LVF identified a 17% incidence of anaemia, of which more than half the patients had anaemia of chronic disease.[211] The group with anaemia and LVF had a higher mortality (HR 1.34, 95% CI 1.24-1.46) during the follow-up period.

Anaemia prior to surgery has been recognised as a predictor of adverse outcome. Beattie and colleagues studied their single centre experience of patients undergoing NCS.[212] Nearly eight thousand patients were included, and the prevalence of pre-operative anaemia was 39.8%. Anaemia was associated with increased post-operative mortality after multivariate analysis (OR 2.36, 95% CI 1.57-3.41, $p<0.001$). Interestingly, this association was independent of requirement for blood transfusion. Subsequently, Musallam and colleagues used NSQIP data for over 200,000 patients undergoing surgery.[213] Nearly one third (30.4%) were found to be anaemic, and this group had higher 30-day mortality (adjusted HR 1.42, 95% CI 1.31-1.54).

Wu and colleagues performed a larger retrospective analysis of NSQIP data, including over 300,000 patients.[214] The authors defined anaemia as a pre-operative haematocrit value of less than 39%. They examined the association with post-operative death and included a secondary endpoint of major cardiac events (cardiac arrest or Q-wave MI). They demonstrated that a fall in pre-operative haematocrit was associated with increased mortality and cardiac

morbidity. These large database analyses confirm the association between anaemia and increased peri-operative mortality, and the present study demonstrates an independent association between anaemia and MACE. However, the limitations of retrospective database analyses and the limited data we prospectively collected regarding the aetiology of anaemia means that it remains unclear if anaemia represents a modifiable variable or simply acts as an indicator of other chronic diseases. Therefore, this is a potentially important area for future research.

4.4.3 BNP predicts MACE and mortality

Serum BNP is a strong predictor of poor outcomes in cardiac patients.[126,215] Our group published interim results of the predictive utility of BNP for MACE in the peri-operative period (6 weeks following NCS).[131] Analysis of the initial 149 patients showed a peri-operative MACE rate of 10.1%, and the median BNP (IQR) was higher than in patients who did not have a MACE (351 (127-1034) pg/ml vs. 31 (11-80) pg/ml, $p<0.001$). The final analysis of the entire cohort of 345 patients confirms that a single pre-operative serum BNP measurement is independently associated with increased MACE and increased mortality in patients undergoing MACE. Patients with an elevated BNP had a 10-fold increase in peri-operative MACE and a 6-fold increase in peri-operative mortality.

Following the start of our study, other researchers have reported similar associations with raised BNP (or NT-proBNP) and adverse post-operative outcomes. Table 4.18 lists publications examining the prognostic utility of BNP (or NT-proBNP) in NCS. All the published studies have demonstrated a significant association between raised post-operative BNP (or NT-proBNP) and poor post-operative outcome. The methodology of these studies has been variable, as discussed in Chapter 1.

The predictive values of BNP and NT-proBNP have been examined in several meta-analyses.[7,141,142,216] In 2008, Rodseth and colleagues investigated the utility of BNP and NT-proBNP from seven studies of patients undergoing vascular surgery.[141] Karthikeyan and colleagues included nine prospective studies investigating the short term predictive value of BNP (4 studies) and NT-proBNP (5 studies) in patients undergoing a variety of non-cardiac surgical procedures.[7]

Both studies concluded that both BNP and NT-proBNP are good independent predictors of post-operative cardiac events. However, due to the small number of studies included, they were unable to suggest a threshold value for optimal predictive utility. Ryding and colleagues included 15 studies in their analysis, published in 2009.[142] Similarly, they found that patients with elevated BNP (or NT-proBNP) had a significantly higher MACE rate than those without. A pooled odds ratios for MACE of 19.77 (95% CI 13.18-29.65, p<0.0001) was found in patients with elevated BNP compared with those that did not.

More recently, Lurati Buse and colleagues reported their meta-analysis of 23 studies (published in 2011). They included cardiac surgery trials and only half the number of studies included concerned NCS. No additional conclusions were drawn from this repeat analysis. Therefore, despite several prospective trials and four meta-analyses, several questions remain unanswered. Firstly, since no study to date has directly compared BNP with NT-proBNP in a surgical cohort, which marker is superior? However, evidence suggests (from medical and surgical cohorts) that both are similarly powerful predictors of MACE then individual institutional availability or personal preference may dictate which marker is used.

Secondly, what is the optimal cut-off point? In our analysis, BNP performed most strongly as a 'rule-out' test. At a cut-off of 88pg/ml, the NPV for MACE was 95.8% and at a cut-off of 107pg/ml, the NPV for mortality was 96.6%. This is similar to the pooled analysis from the Lurati Buse paper; they found a NPV for all-cause mortality of 99%. In simple terms, a 'normal' BNP is highly suggestive of an event-free post-operative course, whereas a raised BNP stratifies patients into a high risk group requiring further attention. Deciding what is 'normal' and 'abnormal' is more challenging, and there is no consensus from the surgical literature. Our data suggest a cut-off point at 100 pg/ml would be appropriate. This is supported by research from screening studies in non-surgical cohorts where a BNP <100pg/ml is considered highly unlikely to be associated with heart disease.[217,218]

In summary, an elevated pre-operative BNP level predicts post-operative MACE in a variety of settings. However, the optimal cut-off point is not clear.

Table 4.18 Prognostic utility of BNP and NT-proBNP for peri-operative major adverse cardiac event (MACE) in non-cardiac surgery

Studies using BNP							
Author	Year of Reporting	Cohort Size	Study Population and Country	Screened for MI?	MACE rate	BNP Theshold	Comments
Current Study	-	*345*	*Mixed NCS, UK*	*Yes*	*13.3%*	*88*	-
Gibson[131]	2007	149	Mixed NCS, UK	Yes	10.1%	109	-
Cuthbertson[132]	2007	204	Mixed NCS, UK	Yes	6.0%	40	Follow-up limited to 72 hours.
Cuthbertson[134]	2007	40	Emergency NCS, UK	Yes	27.5%	170	58% of cohort had hip fracture surgery.
Leibowitz[136]	2008	44	NCS, High cardiac risk, Israel	No	34.1%	165	High risk - LVF or Aortic stenosis.
Bolliger[204]	2009	133	Elective Vascular, Switzerland	Yes	4.5%	50	Theshold taken from 1 year MACE rate. Secondary analysis.
Breidthart[138]	2010	270	Orthopaedic, Switzerland	No	1.5%	174	Low MACE rate. No screening.
Biccard[203]	2012	788	Elective vascular, South Africa	No	17.3%	39	Only half the cohort had BNP measured.

Studies using NT-proBNP							
Author	Year of Reporting	Cohort Size	Study Population and Country	Screened for MI?	MACE rate	NT-proBNP Theshold	Comments
Yeh[129]	2005	190	Mixed NCS, Taiwan	No	7.9%	450	CCF included in MACE definition (comprised 73% of events).
Feringa[130]	2006	170	Elective vascular, Holland	Yes	7.6%	533	Erasmus study.
Rajagopalan[135]	2008	136	Elective vascular, UK	Yes	20.6%	308	Asymptomatic cTn rise included within endpoint.
Yun[137]	2008	279	NCS, age >60 years, Korea	Yes	9.0%	201	Post-op screening only performed for 1 day.
Goei[140]	2009	592	Elective vascular, Holland	No	14.0%	350	Erasmus study. Endpoint included asymptomatic cTn rise.
Chong[219]	2010	89	Emergency orthopaedic, Australia	Yes	25.8%	842	MACE included CCF and AF.

5 BNP as predictor of long-term mortality after major non-cardiac surgery

5.1 Introduction

Cardiac death following major non-cardiac surgery is the commonest cause of surgical mortality in the Western world.[1] Whilst various methods can stratify risk on a population basis, accurate individual assessment of cardiac risk following major surgery is difficult. Clinical assessment and ECG analysis are simple, low cost and routinely available, but have little predictive value[87] and cardiac scoring systems are notoriously inaccurate.[46] Other more specialised tests of cardiac structure and function which show promise, such as stress echocardiography, may not be widely available and have low positive predictive values.[111]

Recently, the cardiac neurohormone, B-type natriuretic peptide (BNP), has emerged as a biological marker (biomarker) of cardiac mortality. BNP is synthesised predominately within ventricular myocytes in response to cardiac wall stress. BNP is a sensitive marker of left ventricular systolic dysfunction (LVSD) [124] and is a useful tool in the investigation of patients with suspected heart failure.[128,197] Furthermore, BNP can predict major adverse cardiac events (MACE), defined as cardiac death and myocardial infarction, in acute coronary syndrome patients[215] and in heart failure.[126]

We have previously shown that BNP is an independent predictor of peri-operative cardiac events in patients undergoing major non-cardiac surgery,[131] and this observation has been confirmed by other groups.[132,134,136,220] In order to test the long term significance of pre-operative BNP, we aimed to determine if plasma BNP concentration also predicted long term survival in patients undergoing major non-cardiac surgery.

5.2 Methods

5.2.1 Participants

A prospective single centre observational cohort study of consecutive patients undergoing major non-cardiac surgery between Jan 2004 and August 2006 was performed. Emergency patients (operated within 24 hours of an unplanned admission) were not included. This left 345 patients that were included in this study.

All patients had standard pre-operative assessment including clinical history, laboratory blood tests and a 12 lead ECG. Further cardio-respiratory investigations were carried out at the discretion of the operating team. Ischaemic heart disease (IHD) was defined as a previous myocardial infarction, a positive exercise tolerance test, the use of nitrate therapy or the presence of pathological Q-waves on ECG.[6] Left ventricular failure (LVF) was considered present if the patient had a prior hospital admission with heart failure or left ventricular impairment on previous echocardiography. Cerebrovascular disease was defined as a previous cerebrovascular accident or transient ischaemic attack. The glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease (MDRD) equation.[192] Renal impairment was considered present if the estimated GFR was <60mls/min. A patient was considered a smoker if they were smoking at the time of admission for surgery. Hypertension was considered present if the patient had a previous medical documentation of hypertension and was currently taking antihypertensive medication. The presence of hyperlipidaemia and chronic obstructive pulmonary disease (COPD) was extracted from the patient's primary care records and past medical history. The current medication was also recorded, in particular the prescription of anti-platelet agents, a statin and ß-blockers.

An additional venous blood sample was taken for plasma BNP the evening prior to surgery. This was collected in chilled EDTA and aprotinin (Trasylol; 50 IU/ml), immediately centrifuged and stored at –25° Celsius. BNP concentrations were measured using a direct immunoradiometric assay (Shionoria BNP kit, Shinogi & Co, Osaka, Japan).[193] The minimum detectable quantity of BNP is 2pg/ml. The within-assay and between assay co-efficients of variation are 5.3% and 5.9%,

respectively. Batch sample analysis was performed during the study by a biochemist blinded to clinical detail. The longest sample storage period was 6 months.

Patient follow-up was carried out until the end of 2009. All patients were followed-up for a minimum of 1 year, either at outpatient follow-up, with the general practitioner or by direct patient contact. The primary outcomes were death within the post-operative period (6 weeks) and all cause mortality during the follow-up period. Regional ethics committee approval was obtained and all patients gave written consent to the study following a verbal explanation and written information.

5.2.2 Statistical Analysis

Statistical analysis was performed using SPSS (Version 15) statistical software package (SPSS, Chicago, Illinois, USA). A p-value of less than 0.05 was considered significant. Comparison of interval data was performed using independent samples t-test, Mann-Whitney test and Kruskal-Wallis test as appropriate. Categorical data was compared using the x^2 test. Performance of continuous variables was analysed used receiver operating characteristics (ROC) and the area under the curve (AUC) was calculated. Survival analysis was performed using Kaplan-Meier curves and comparisons made using the log rank statistic. Univariate analysis was performed using Cox regression analysis. Variables with a p-value of less than 0.10 were further evaluated with a multivariate Cox analysis using a backward stepwise selection.

5.3 Results

5.3.1 Predictors of survival at one year following major non-cardiac surgery

All patients recruited to the trial were followed for a minimum 1 year. Of the 345 patients recruited for the study, 276 (80.0%) patients underwent a vascular procedure (aortic surgery 25.8%, lower limb bypass 29.8% and amputation 25.2%) and 69 (20.0%) patients underwent a laparotomy. This reflected the work load of the operating unit and to prevent selection bias the results are presented for the entire cohort.

Twenty-seven patients died during the immediate post-operative period (6 weeks) and a further 39 patients died in the 1 year follow-up period. In total, 66 patients (19.1%) died by 1 year post-surgery.

The following clinical variables are associated with higher 1-year mortality rates; age >70 years ($p<0.021$), diabetes ($p=0.008$), hypertension ($p=0.004$), renal impairment ($p=0.029$), previous MI ($p=0.043$), previous LVF ($p=0.043$), cerebrovascular disease ($p=0.048$), anaemia ($p<0.001$) and urgent surgery ($p<0.001$) [Table 5.1 and Table 5.2].

Table 5.1 Clinical variables and 1-year mortality

		n = 345	Mortality n= 66	p*
Sex	Male	217	42 (19.4%)	0.890
	Female	128	24 (18.84%)	
Age > 70 years	Yes	125	40 (24.2%)	0.021
	No	180	26 (14.4%)	
Smoker	Yes	145	31 (21.4%)	0.366
	No	200	35 (17.5%)	
Diabetes	Yes	69	21 (30.4%)	0.008
	No	276	45 (16.3%)	
Hypertension	Yes	196	48 (24.5%)	0.004
	No	149	18 (12.1%)	
Renal Impairment (GFR <60)	Yes	142	35 (24.6%)	0.029
	No	203	31 (15.3%)	
Hyperlipideamia	Yes	110	23 (20.9%)	0.566
	No	235	43 (18.3%)	
Previous MI	Yes	64	18 (28.1%)	0.043
	No	281	48 (17.1%)	
Ischaemic Heart Disease	Yes	104	24 (23.1%)	0.221
	No	241	42 (17.4%)	
History of Left Ventricular Failure	Yes	64	18 (28.1%)	0.043
	No	281	48 (17.1%)	
Cerebrovascular Disease	Yes	43	13 (30.2%)	0.048
	No	302	53 (17.5%)	
COPD	Yes	49	12 (24.5%)	0.303
	No	296	54 (18.2%)	

* Chi-Square Test
Abbreviations: eGFR - estimated glomerular filtration rate, MI - myocardial infarction, COPD - chronic obstructive pulmonary disease.

Table 5.2 Other selected clinical variables and peri-operative mortality

		n = 345	Mortality n=	p*
ß-Blocker	Yes	86	21 (24.4%)	0.150
	No	259	45 (17.4%)	
APA	Yes	179	35 (19.6%)	0.836
	No	166	31 (18.7%)	
Statin	Yes	175	38 (21.7%)	0.216
	No	170	28 (16.5%)	
Anaemia†	Yes	144	46 (31.9%)	<0.001
	No	201	20 (10.0%)	
Urgent Surgery	Yes	163	53 (32.5%)	<0.001
	No	182	13 (7.1%)	

* Chi-Square Test,
†Anaemia defined as haemoglobin <13 g/dl in males and <11 g/dl in females.

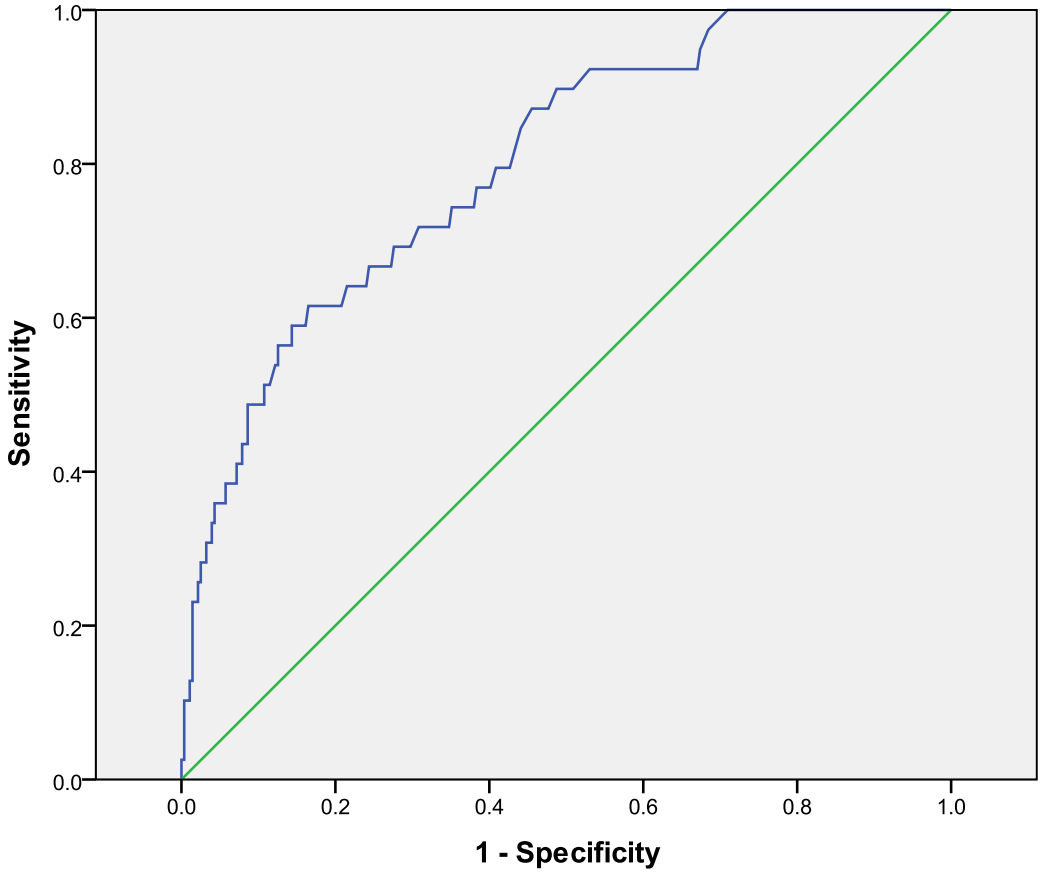
Abbreviations: APA – Antiplatelet agent

5.3.2 Predictive value of BNP for 1-year mortality

The median (IQR) of BNP in patients that died during the first year following surgery was significantly higher than those patients that survived (158(46-400) pg/ml vs. 32 (14-82) pg/ml, p<0.001)

Receiver operating characteristic (ROC) curve analysis was performed to identify the BNP concentration that best predicted mortality at 1 year [Figure 5.1]. In all patients, a BNP concentration of 87.5 pg/ml had the best combined sensitivity (65.7%) and specificity (78.6%), and the area under the ROC curve (AUC) was 0.781 (95% C 0.717-0.845, p<0.001). The AUC for patients undergoing a vascular procedure (n=276) was 0.792 (95% CI 0.724-0.861, p<0.001), with the same BNP concentration providing the best sensitivity and specificity in this group (67.8% and 76.8% respectively). The one-year mortality rate for patients with a BNP >87.5 pg/ml compared with a BNP <87.5 pg/ml was 38.4% vs. 8.5%, p<0.001.

Figure 5.1 ROC curve analysis: BNP concentration and all-cause mortality



5.3.3 Pre-operative clinical variables and the prediction of long term survival

From the study group of 345 patients, there were 27 (7.8%) peri-operative deaths (within 6 weeks) and 84 (24.3%) deaths within the subsequent follow-up period. The median follow-up period was 953 days (IQR 661-1216 days).

Survival curve analysis showed that mean survival was shorter in association with the following variables; age >70 years (991 days vs. 1229 days, p<0.001), diabetes (925 days vs. 1163 days, p=0.002), hypertension (1036 days vs. 1214 days, p=0.006), renal impairment (1028 days vs. 1173 days, p=0.045), a history of LVF (914 days vs. 1152 days, p=0.020), anaemia (883 days vs. 1266 days, p<0.001) and urgent surgery (885 days vs. 1298 days, p<0.001) [Table 5.3].

In order to examine the predictive value of variables in the longer term only and to remove any bias attributed directly to surgical mortality, the survival curve analysis was repeated after exclusion of patients who died during the peri-operative period (within 6 weeks). The only associations that became non-significant following this analysis were diabetes and renal impairment [Table 5.4]. Therefore, age>70 years, hypertension, a history of LVF, anaemia and urgent surgery were associated with a higher long term mortality.

Table 5.3 Kaplan-Meier survival analysis for clinical variables and long-term follow-up

		n=345	Mean Survival (days) (95% CI)	p
Sex	Male	217	1099 (1018-1179)	0.838
	Female	128	1120 (1014-1226)	
Age > 70 years	Yes	165	991 (894-1088)	<0.001
	No	180	1229 (1148-1311)	
Smoker	Yes	145	1136 (1033-1238)	0.587
	No	200	1103 (1020-1186)	
Diabetes	Yes	69	925 (771-1079)	0.002
	No	276	1163 (1092-1234)	
Hypertension	Yes	196	1036 (946-1126)	0.006
	No	149	1214 (1128-1299)	
Renal Impairment (eGFR <60)	Yes	142	1028 (925-1131)	0.045
	No	203	1173 (1091-1254)	
Hyperlipdidaemia	Yes	110	1095 (978-1212)	0.589
	No	235	1122 (1045-1199)	
Previous MI	Yes	64	986 (840-1132)	0.171
	No	281	1136 (1065-1207)	
Ischaemic Heart Disease	Yes	103	1071 (950-1192)	0.450
	No	242	1130 (1054-1205)	
History of Left Ventricular Failure	Yes	64	914 (766-1061)	0.020
	No	281	1152 (1082-1221)	
Cerebrovascular Disease	Yes	43	926 (751-1100)	0.102
	No	302	1139 (1070 -1207)	
COPD	Yes	49	955 (794-1115)	0.125
	No	296	1137 (1068-1206)	
Anaemia[†]	Yes	144	883 (781-984)	<0.001
	No	170	1266 (1192-1339)	
Urgent Surgery	Yes	163	885 (782-999)	<0.001
	No	182	1298 (1226-1369)	

*Log-rank test, [†]Anaemia defined as haemoglobin <13 g/dl in males and <11 g/dl in females.
Abbreviations: eGFR - estimated glomerular filtration rate, MI - myocardial infarction, COPD - chronic obstructive pulmonary disease.

Table 5.4 Kaplan-Meier survival analysis for clinical variables and long-term follow-up, after exclusion of patients who died in the peri-operative period

		n=345	Mean Survival (days) (95% CI)	p
Sex	Male	198	1202 (1129-1275)	0.800
	Female	120	1192 (1092-1292)	
Age > 70 years	Yes	148	1103 (1011-1195)	0.002
	No	170	1300 (1226-1374)	
Smoker	Yes	135	1218 (1122-1314)	0.747
	No	183	1203 (1128-1279)	
Diabetes	Yes	58	1097 (952-1243)	0.069
	No	260	1233 (1167-1299)	
Hypertension	Yes	176	1151 (1066-1236)	0.038
	No	142	1271 (1194-1349)	
Renal Impairment (eGFR <60)	Yes	126	1156 (1062-1251)	0.255
	No	192	1240 (1162-1314)	
Hyperlipdidaemia	Yes	100	1202 (1093-1310)	0.761
	No	218	1208 (1137-1280)	
Previous MI	Yes	58	1085 (948-1223)	0.196
	No	260	1226 (1160-1291)	
Ischaemic Heart Disease	Yes	96	1164 (1050-1277)	0.421
	No	222	1223 (1153-1292)	
History of Left Ventricular Failure	Yes	62	943 (796-1089)	<0.001
	No	256	1262 (1200-1324)	
Cerebrovascular Disease	Yes	39	1018 (850-1186)	0.094
	No	279	1231 (1168-1293)	
COPD	Yes	42	1110 (971-1250)	0.472
	No	276	1217 (1153-1283)	
Anaemia[†]	Yes	126	1007 (908-1105)	<0.001
	No	192	1323 (1257-1390)	
Urgent Surgery	Yes	143	1007 (904-1110)	<0.001
	No	175	1347 (1284-1412)	

*Log-rank test, [†]Anaemia defined as haemoglobin <13 g/dl in males and <11 g/dl in females.
Abbreviations: eGFR - estimated glomerular filtration rate, MI - myocardial infarction, COPD - chronic obstructive pulmonary disease.

5.3.4 Predictive utility of BNP for long term mortality after major non-cardiac surgery

For the entire cohort, the median (IQR) pre-operative BNP concentration was higher in patients who died during follow-up than in those who did not (95 pg/ml (37-310) vs. 29 pg/ml (13-75), p<0.001). Furthermore, analysis of the 318 patients who survived beyond the peri-operative period showed that BNP was higher in those patients who died compared with those who survived (147 pg/ml (44-407) vs. 32 pg/ml (14-83), p<0.001).

The BNP cut-off point identified at ROC curve analysis for prediction of 1 year mortality was used for long-term analysis. The mean survival of patients with a BNP >87.5 pg/ml compared with a BNP <87.5 pg/ml was 732 days (95% CI 613.6-850.2) vs. 1285 days (95% CI 1219.3-1350.0), p <0.001 [Figure 5.2]. When survival analyses are restricted to patients who survived the post-operative period (6 weeks), patients with an elevated BNP (>87.5 pg/ml) had a reduced survival (887 days (95% CI 764.9-1008.2) vs. 1328 days (95% CI 1267.7-1388.3), p<0.001 [Figure 5.3].

Subgroup analysis by type of procedure showed that the mean survival of patients with an elevated BNP (>87.5 pg/ml) was significantly lower in all groups (aortic surgery (800 days vs. 1461 days, p<0.001), lower limb bypass (860 days vs. 1180 days, p=0.021), amputation (506 days vs. 1086 days, p<0.001) and laparotomy (877 days vs. 1212 days, p=0.009).

Similarly, when stratified for the presence of IHD, patients with an elevated BNP (>87.5pg/ml) had a lower mean survival in the group with IHD (769 days vs. 1269 days, p<0.001) and the group without IHD (700 days vs. 1289 days, p<0.001).

Figure 5.2 Kaplan-Meier survival curve according to BNP level

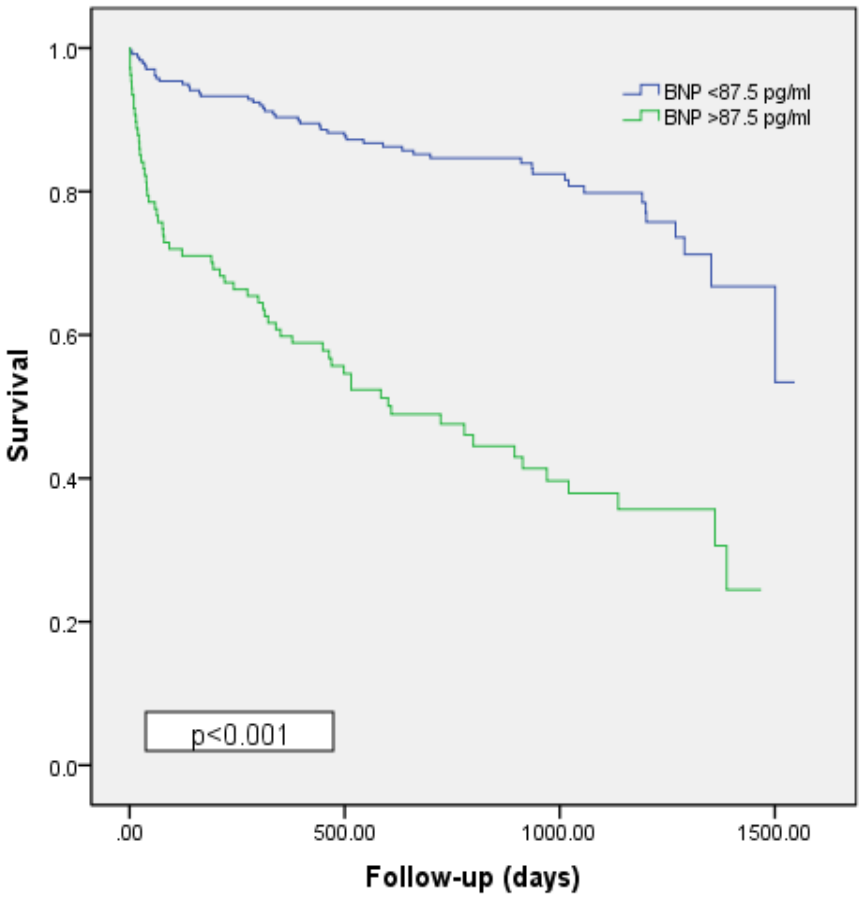
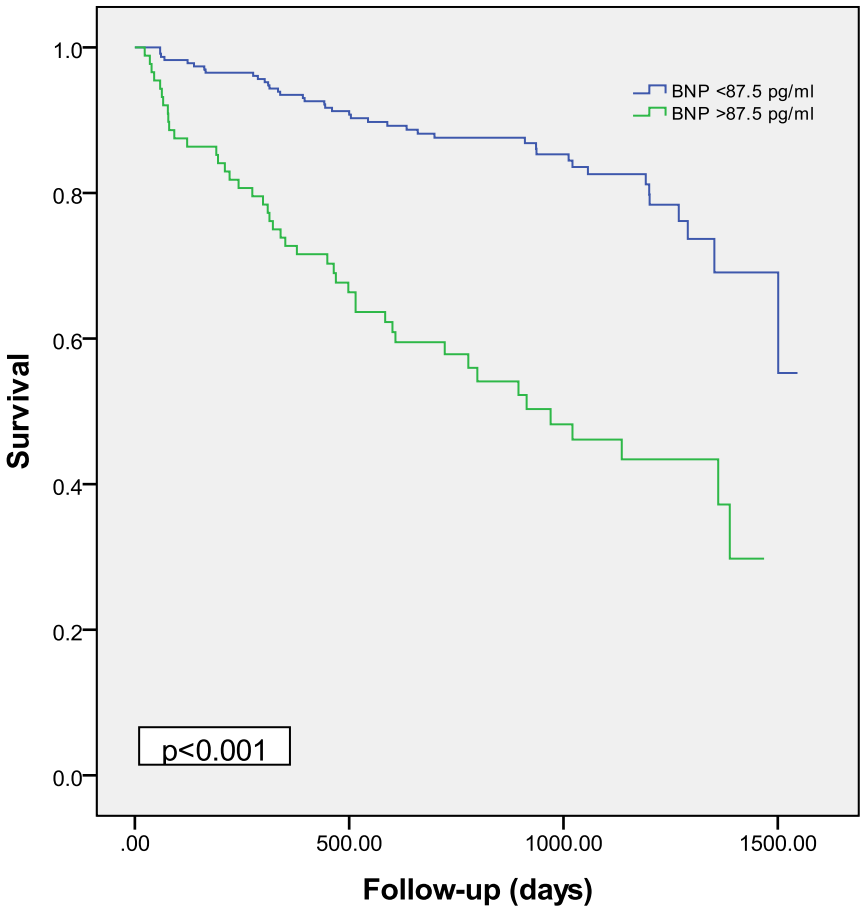


Figure 5.3 Kaplan-Meier survival curve according to BNP level in patients who survived the peri-operative period



5.3.5 Multivariate analysis of clinical variables and long-term survival

Cox regression analysis was performed to examine the value of the clinical variables for the prediction of long-term survival. For the entire cohort, urgent surgery (p<0.001), anaemia (p<0.001), age >70 years (p=0.001), diabetes (p=0.003), hypertension (p=0.007), a history of LVF (p=0.021) and renal impairment (p=0.047) were associated with increased mortality on univariate analysis [Table 5.5]. Only urgent surgery (HR 2.485, 95% CI 1.631-3.785, p<0.001) and anaemia (HR 2.106, 95% CI 1.406-3.156, p<0.001) were associated with increased mortality on multivariate analysis.

The analysis was repeated excluding the patients that died within the peri-operative period (6 weeks). Urgent surgery (p<0.001), anaemia (p<0.001), a history of LVF (p<0.001), age >70 years (p=0.003) and hypertension (p=0.040) were associated with increased mortality on univariate analysis [Table 5.6]. Only urgent surgery (2.573, 95% CI 1.604-4.127, p<0.001), a history of LVF (HR 2.360, 95% CI 1.451-3.535) and anaemia (HR 2.240, 95% CI 1.419-3.535, p=0.001) were associated with increased mortality on multivariate analysis.

Since urgent surgery is such a strong predictor of mortality, the analysis was repeated for patients undergoing elective surgery only. Only anaemia (p<0.001) and age > 70 years (p=0.038) were significant on univariate analysis. Both factors remained significant on multivariate analysis [Table 5.7]. Interestingly, diabetes became significant on multivariate analysis (HR 2.948, 95% CI 1.256-6.916, p=0.013).

Table 5.5 Cox regression analysis of clinical variables for all cause mortality during long term follow-up

	Univariate		Multivariate	
Factor	HR (95% CI)	p	HR (95% CI)	p
Urgent Surgery	3.348 (2.236-5.012)	<0.001	2.485 (1.631-3.785)	<0.001
Anaemia	2.848 (1.936-4.189)	<0.001	2.106 (1.406-3.156)	<0.001
Age >70 years	1.945 (1.329-2.847)	0.001		
Diabetes	1.870 (1.239-2.821)	0.003		
Hypertension	1.732 (1.163-2.580)	0.007		
History of LVF	1.687 (1.081-2.630)	0.021		
Renal Impairment*	1.459 (1.005-2.118)	0.047		

* defined as eGFR <60mls/min

Abbreviations; LVF - left ventricular failure.

Table 5.6 Cox regression analysis of clinical variables for all cause mortality during long term follow-up in peri-operative survivors only

	Univariate		Multivariate	
Factor	HR (95% CI)	p	HR (95% CI)	p
Urgent Surgery	3.336 (2.112-5.268)	<0.001	2.573 (1.604-4.127)	<0.001
Anaemia	2.813 (1.810-4.370)	<0.001	2.240 (1.419-3.535)	0.001
History of LVF	2.421 (1.495-3.920)	<0.001	2.360 (1.451-3.535)	0.001
Age >70 years	1.949 (1.260-3.017)	0.003		
Hypertension	1.604 (1.021-2.520)	0.040		
Diabetes	1.576 (0.961-2.584)	0.071		
Cerebrovascular disease	1.626 (0.915-2.890)	0.097		

Abbreviations; LVF - left ventricular failure

Table 5.7 Cox regression analysis of clinical variables for all cause mortality during long term follow-up for patients undergoing elective surgery only

	Univariate		Multivariate	
Factor	HR (95% CI)	p	HR (95% CI)	p
Anaemia	5.081 (2.552-10.117)	<0.001	5.228 (2.594-10.540)	<0.001
Age >70 years	2.006 (1.040-3.867)	0.038	2.313 (1.137-4.706)	0.021
Diabetes	1.901 (0.862-4.192)	0.092	2.948 (1.256-6.916)	0.013
Hypertension	1.808 (0.912-3.584)	0.090		

5.3.6 Mutlivariate analysis of clinical variables, BNP and long term survival

When BNP was added to the model, BNP >87.5 pg/ml was predictive of long term mortality (HR 4.196, 95% CI 2.870-6.136, p<0.001), and remained significant on multivariate analysis (HR 3.173, 95% CI 2.145-4.693, p<0.001) [Table 5.8]. Other variables that remained significant in this multivariate model were urgent surgery (HR 2.148 , 95% CI 1.408-3.275, p<0.001) and anaemia (HR 1.990, 95% CI 1.336-2.966, p=0.001). No 'traditional' risk factors for cardiac disease (IHD, previous MI, a history of LVF or cerebrovascular disease) demonstrated any independent efficacy in the prediction of long term survival.

The findings were similar when considering only the patients that survived the peri-operative period (6 weeks). Multivariate analysis identified BNP >87.5 pg/ml (HR 2.658, 95% CI 1.697-4.163, p<0.001), urgent surgery (HR 2.200, 95% CI 1.368-3.538, p=0.001) and anaemia (HR 2.095, 95% CI 1.329-3.302, p=0.001) as independent predictors of long-term mortality. In addition, a history of LVF was significant in this model (HR 1.989, 95% CI 1.219-3.246, p=0.006).

Table 5.8 Cox regression analysis of clinical variables and BNP for all cause mortality during long term follow-up

	Univariate		Multivariate	
Factor	HR (95% CI)	p	HR (95% CI)	p
BNP >87.5pg/ml	4.196 (2.870-6.136)	<0.001	3.173 (2.145-4.693)	<0.001
Urgent Surgery	3.348 (2.236-5.012)	<0.001	2.148 (1.408-3.275)	<0.001
Anaemia	2.848 (1.936-4.189)	<0.001	1.990 (1.336-2.966)	0.001
Age >70 years	1.945 (1.329-2.847)	0.001		
Diabetes	1.870 (1.239-2.821)	0.003		
Hypertension	1.732 (1.163-2.580)	0.007		
History of LVF	1.687 (1.081-2.630)	0.021		
Renal Impairment*	1.459 (1.005-2.118)	0.047		

Abbreviations: HR - Hazard Ratio, BNP – B-type Natriuretic Peptide, LVF – Left Ventricular Failure, eGFR – Estimated Glomerular Filtration Rate, CVD – Cerebrovascular Disease, COPD – Chronic Obstructive Pulmonary Disease, IHD – Ischaemic Heart Disease.

5.3.7 Long term implications of non-fatal cardiac event / cardiac injury

From the group of patients that survived the peri-operative period, 33 patients had a non-fatal PMI. A further 23 patients had an elevated troponin, but did not meet the criteria for MI. Therefore, 56 patients in total had a peri-operative troponin rise. A raised troponin was associated with poorer 1 year mortality (25.0% vs. 9.5%, p=0.001) [Table 5.9]. Similarly, patients who suffered a non fatal MI had a poorer 1 year mortality rate than patients who did not suffer an MI (30.3% vs. 10.2%, p=0.001). Interestingly, an asymptomatically raised troponin without meeting the criteria for MI was not associated with a lower 1 year survival.

Mean (95% CI) survival was shorter in patients who suffered a non-fatal MI (920 days, 95% CI 706-1132 days) and an asymptomatic troponin rise (931 days, 95% CI 754-1112 days) than patients with no post-operative cardiac morbidity (1251 days, 95% CI 1189-1314 days, p=0.002) [Figure 5.4].

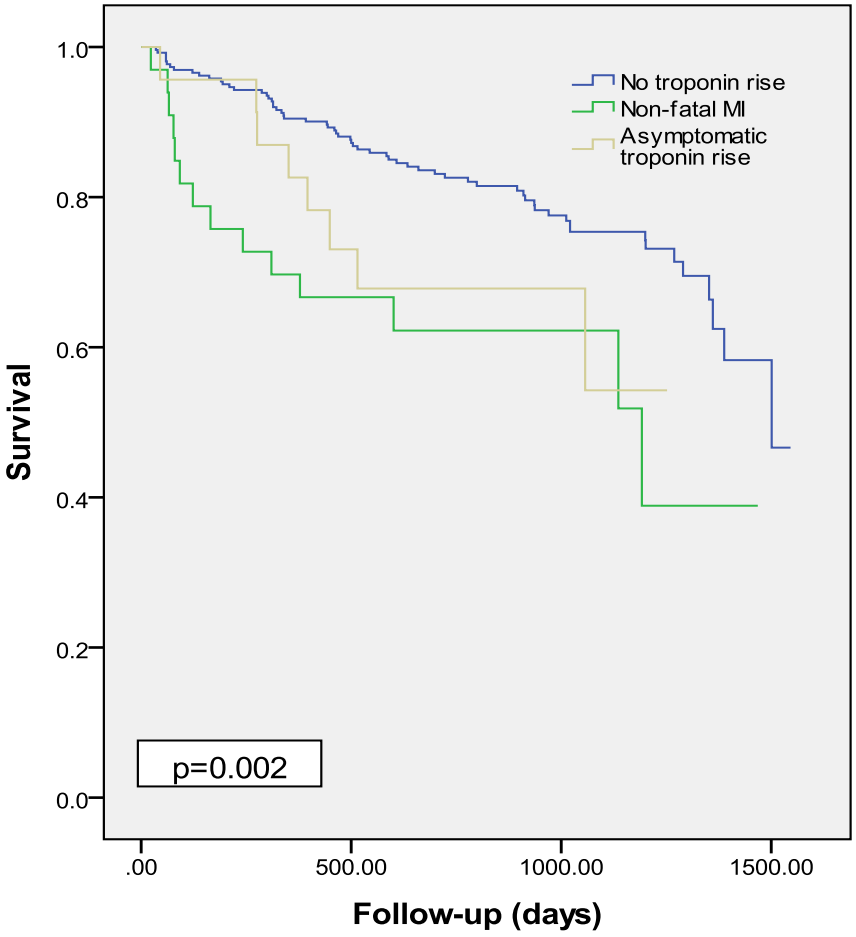
Table 5.9 Post-operative cardiac morbidity and 1 year survival after surgery

		n=318	1 year mortality	p
All raised troponins	Yes	56	14/56 (25.0%)	0.001
	No	262	25/262 (9.5%)	
Non-fatal PMI	Yes	33	10/33 (30.3%)	0.001
	No	285	29/285 (10.2%	
Raised troponin, no PMI	Yes	23	4/23 (17.4%)	0.206
	No*	262	25/262 (9.2%)	

*Non-fatal MI patients excluded from denominator

Abbreviations: PMI - post-operative myocardial infarction

Figure 5.4 Kaplan-Meier survival curve according to post-operative myocardial infarction or troponin rise



5.4 Discussion

This study shows, for the first time, that preoperative BNP predicts long term survival following major non-cardiac surgery, independent of other prognostic characteristics. Secondly, we found that the prognostic value of BNP was similar in both vascular and non-vascular surgical cohorts, and in the presence and absence of ischaemic heart disease. Thirdly, we extend the findings of other smaller cohort studies in this subject, which had shorter follow up periods.

For the past 20 years, much effort has been spent in devising stratification systems to identify patients at higher risk of post-operative mortality. A point-of-care test that is easy to perform, cheap and reliably informative has proved elusive. Recent interest in the predictive value of a pre-operative BNP has been fuelled by a number of studies published in recent years that have shown BNP to predict long term outcomes in non-surgical patients with both stable cardiac disease and cardiac failure.[124,128,215] BNP has also been shown to predict post-operative MACE and therefore post-operative mortality.[11 12]

Few studies have analysed the long term efficacy of natriuretic peptides in the prediction of post-operative outcome. Cuthbertson and colleagues studied the medium term follow-up (median 654 days) of 204 patients undergoing major non-cardiac surgery at Aberdeen Royal Infirmary and found pre-operative BNP to be a significant independent predictor of mortality.[133] From the same institution, Rajagopalan and colleagues performed medium term follow-up on a cohort of 136 patients undergoing major vascular surgery.[221] Patients with an elevated NT-proBNP had a significantly reduced 2-year survival compared with patients who had a non-elevated NT-proBNP (68% vs. 93%, $p<0.001$). Likewise, Feringa and colleagues pre-operatively measured N-terminal pro-BNP (NT-proBNP), the inactive precursor of BNP, and found it to predict long term mortality in 335 patients undergoing major vascular surgery.[222]

This study shows that an elevated pre-operative BNP is associated with a reduced long term survival, independent of other factors. These results appear, in this study, to be consistent in both vascular patients in addition to other patients groups undergoing major surgery. BNP was a more accurate predictor

of long term survival in vascular patients, which reflects the high incidence of cardiovascular disease in these patients.

Since consecutive patients were included in our study, there is considerable heterogeneity in patient characteristics. Thus, our patients had a broad range of concomitant health problems and the surgical problems involved acute illness and critical chronic disease, such as due to chronic progressive limb ischaemia. While the prognostic value of BNP may be greater in particular subgroups (and future studies could address this question), we suggest that the heterogeneity in our population may in fact make our results more transferable to ordinary clinical practice. Our follow-up data were obtained in 3 ways: by hospital clinicians, by GP contact and by direct patient contact, however since the end-point was all-cause mortality there is not a risk of bias in the assessment of outcomes.

We found that a BNP level of 87.5 pg/ml provided the best sensitivity and specificity for all cause mortality. Previous studies have identified variable levels of BNP that provided the best combined sensitivity and specificity for perioperative MACE; Cuthbertson and colleagues concluded that 40 pg/ml offered the best 'cut-off' point for elective surgery, and 170 pg/ml for emergency surgery.[12 13] Gibson and colleagues found that a level 108.5 pg/ml best predicted the likelihood of perioperative MACE[131], and Dernellis and colleagues found a level of 189 pg/ml.[220] Breidthardt and colleagues investigated 270 patients undergoing orthopaedic surgery.[223] They observed a low (1.5%) post-operative cardiac event rate. ROC curve analysis showed that 174 pg/ml provided the optimal predictive accuracy. In all the studies, the predictive value of BNP is evident but the best cut-off point is not.

The predictive value of BNP and NT-proBNP, have been examined in two recent meta-analyses. Karthikeyan et al include nine prospective studies investigating the short term peridictive value of BNP (4 studies) and NT-proBNP (5 studies).[7] They conclude that both BNP and NT-proBNP are good independent predictors of post-operative cardiac events. However, due to the small number of studies included, they were unable to suggest a threshold value for optimal predictive value. Ryding et al included 15 studies in their analysis (8 relating to BNP, 7 to NT-proBNP).[142] Similarly, they found that patients with elevated BNP (or NT-

proBNP) had a significantly higher MACE rate than those without. A pooled odds ratios for MACE of 19.77 (95% CI 13.18-29.65, p<0.0001) was found in patients with elevated BNP compared with those that did not. No study to date has directly compared BNP with NT-proBNP in a surgical cohort; however both meta-analyses concluded that BNP and NT-proBNP are powerful predictors of post-operative cardiac events.

This study also identified pre-operative anaemia and urgent surgery as predictors of long term mortality and extends the finding that these factors were associated with increased peri-operative morbidity and mortality. The significance of these variables are considered in the discussion in Chapter 5 (5.4.2.2-5.4.2.3)

Pre-operative risk stratification has become more important in recent years as the range of surgical options has increased, and older patients with greater comorbidty are being considered for surgical intervention. Alternatives to traditional surgery, such as minimally invasive surgery, endovascular intervention and endoscopic procedures, have become commonplace, with a corresponding risk reduction in the surgical procedure. Furthermore improvements in intra-operative anaesthetic techniques and post-operative critical care in the high dependency setting may also contribute to reduced overall risk. These improvements have several beneficial consequences. Firstly, since procedure related risk is reduced overall clinical outcomes are improved. Secondly, a broader range of higher-risk patients (e.g. increased co-morbidity) may be considered for surgery when previously surgery would not have been performed. Thirdly, in patients who are identified to be at high risk of procedure-related complications, implementation of selected contemporary surgical and anaesthetic techniques, could lead to individualised risk reduction. Most importantly, since BNP predicts long term prognosis, this information may be used to guide surgical management.

6 The predictive value of the 12 lead ECG for peri-operative outcomes

6.1 Introduction

A history of heart disease is associated with a higher rate of peri-operative major adverse cardiac events (MACE),[224] and peri-operative mortality.[4] The prevalence of coronary heart disease in 2006/2007 was 4.1% for the West of Scotland, compared with a UK mainland prevalence of 3.7%.[225] Previous studies have shown that the West of Scotland has a high rate of asymptomatic cardiac disease.[205] In the absence of any clinical symptoms to identify patients with ischaemic heart disease (IHD), pre-operative assessment is crucial.

Cardiac risk assessment is multifactorial.[226] Clinical characteristics and procedure type have predictive value for post-operative adverse cardiac events, especially when combined as risk scoring systems.[6] Non-invasive cardiac tests, such as stress echocardiography, are fairly sensitive methods for prediction of cardiac risk.[111] Such tests, however, are not routinely available. The pre-operative use of cardiac biomarkers, such as B-type natriuretic peptide, provides additional risk stratification in patients with known ischaemic heart disease and in the general population.[131] Again, these tests have limited availability in the National Health Service and further afield.

A 12-lead ECG is part of the standard pre-operative assessment for patients undergoing major surgery. However, new diagnostic technologies (e.g. echocardiography) have, arguably, diminished the importance applied to a pre-operative ECG, which is universally cheap and easily acquired. Furthermore, automated analysis is now standard in ECG machines such that an interpretation of the ECG is usually provided. The benefit of routinely performing an ECG has been questioned,[86–89] and the pre-operative ECG is often not examined properly prior to surgery.[227]

Therefore, we aimed to assess the predictive value of a pre-operative 12-lead ECG in patients undergoing major surgery in a population with a high prevalence of cardiovascular disease.

6.2 Methods

6.2.1 Patient Selection

A prospective single centre observational cohort study was performed. Consecutive patients undergoing major vascular surgery (aortic surgery, bypass, amputation) or laparotomy were selected for inclusion in the study. All patients had standard pre-operative assessment including a 12-lead ECG the day before surgery. Further cardiac assessment was carried out at the discretion of the operating team. The presence of risk factors such as smoking, diabetes, hyperlipidaemia, previous myocardial infarction (MI) and chronic obstructive airways disease (COPD) were obtained from the patient's history and medical records. A history of ischaemic heart disease was defined as a previous myocardial infarction, a report from a cardiologist describing ischaemia on an exercise tolerance test, use of nitrate therapy for angina or the presence of pathological Q-waves on ECG.[6] Left ventricular failure (LVF) was considered present if the patient had a prior hospital admission with heart failure or left ventricular impairment on previous echocardiography. Cerebrovascular disease was defined as a previous cerebrovascular accident or transient ischaemic attack. The glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease (MDRD) equation.[192] Renal impairment was considered present if the estimated GFR was <60mls/min. A patient was considered a smoker if they were smoking at the time of admission for surgery. Hypertension was considered present if the patient had a previous medical documentation of hypertension and was currently taking antihypertensive medication. The current medication was also recorded, in particular the prescription of antiplatelet agents, a statin and beta-blockers.

Post-operative screening for cardiac events was performed. This consisted of daily clinical assessment and serial ECGs and troponin I measurement on days 2 and 5 and 6 weeks following surgery. The primary outcomes were MACE (non-fatal MI and cardiac mortality) and all-cause mortality within the post-operative period (6 weeks). The definition of a non-fatal MI was that used by The Joint European Society of Cardiology/American College of Cardiology Committee:[34] a typical rise and gradual fall of cTnI with at least one of the following: ischaemic symptoms, development of pathological Q waves on the ECG, ECG changes

indicative of ischaemia (ST segment elevation or depression) or coronary artery intervention. Cardiac death was defined as death secondary to MI, cardiogenic shock or intractable arrhythmia. Regional ethics committee approval was obtained and all patients gave written consent to the study following a verbal explanation and written information.

ECG Analysis

All electrocardiographs (ECGs) were batch analysed at the end of the study by two investigators (general surgeon and cardiologist), blinded to the clinical outcomes. The ECG results were then double checked by a second cardiologist and disagreements were resolved by consensus. ECGs were examined for the presence of the following abnormalities;

- *Left ventricular hypertrophy*: Sokolow-Lyon voltage criteria (S wave in V1 and R wave in V5 or V6 > 35mm, or R wave in aVL > 11 mm).[194]

- *Bundle branch block*: The standard morphological appearance of left or right bundle branch block, with a QRS duration of >120 ms.

- *Atrial fibrillation*: presence or absence.

- *Axis deviation*: Using standard QRS axis electrical criteria, left axis deviation > -30°, right axis deviation > +90°.

- *Q-waves*: Present of a negative deflection preceding the R wave in two contiguous leads with duration of >40ms and amplitude greater than 25% of corresponding R wave.

- *Ventricular strain pattern*: Planar ST segment depression ≥ 1mm or T wave inversion in V5/V6.

- *Premature ventricular contraction (PVC)*: presence or absence of broad complex ectopic beats.

An ECG was considered abnormal if one or more of the above characteristics were present. Cumulative abnormalities on individual ECGs were also recorded.

ECG findings: heart rate (HR), QRS duration and QTc were recorded directly from the automated data display on the ECG. Tachycardia was defined as HR >100, broad QRS complex as >130ms and prolonged QTc as >440ms.

6.2.2 Statistical Analysis

Statistical analysis was performed using SPSS (Version 15) statistical software package (SPSS, Chicago, Illinois, USA). A p-value of less than 0.05 was considered significant. Categorical data were compared using the x^2 test or Fisher's exact tests were applicable. Univariate analyses were performed using logistic regression methods. Only variables with a p-value of less than 0.10 were further evaluated with a multivariate logistic regression analysis using a backward stepwise selection.

6.3 Results

6.3.1 Patient characteristics

345 patients were included in the study. Two hundred and seventy six (80.0%) patients underwent a vascular procedure (aortic surgery 25.8%, lower limb bypass 29.0% and amputation 25.2%) and 69 (20.0%) patients underwent laparotomy. The ECGs were obtained on average 1 day (range 0 – 8 days) prior to surgery.

6.3.2 Post-operative outcomes: frequency and associations

MACE occurred in 46 (13.3%) patients, and 27 (7.8%) patients died in the post-operative period (within 6 weeks). The peri-operative MACE rate was higher in patients with hypertension (18.4% vs. 6.7%, p=0.002) and those aged ≥ 70 years (19.4% vs. 7.8%, p=0.002) [Table 6.1]. Patients with diabetes and renal impairment had a higher peri-operative mortality rate than patients without these co-morbidities (15.9% vs. 5.8%, p=0.005, and 11.3% vs. 5.4%, p=0.047 respectively) [Table 6.2].

An abnormal ECG was present in 141 (40.9%) patients. The commonest abnormalities were prolonged QTc (19.7%), left ventricular strain (12.5%), tachycardia (11.6%), an abnormal axis (10.7%) and LVH (10.1%).

Patients with an abnormal ECG had a higher incidence of MACE (21.6% vs. 8.3%, p<0.001) [Table 6.3]. The individual ECG abnormalities that were associated with post-operative MACE were ventricular strain (p<0.001), AF (p=0.016) and prolonged QTc (p<0.001). Patients who died were also more likely to have an abnormal ECG than those who survived (63.0% vs. 39.0%, p=0.015) [Table 6.4].

Table 6.1 Pre-operative clinical variables and perioperative major adverse cardiac event (MACE)

		n=345	MACE n =46 (%)	p*
Sex	Male	217	30 (13.8%)	0.727
	Female	128	16 (12.5%)	
Age	≥ 70 years	165	32 (19.4%)	0.002
	<70 years	180	14 (7.7%)	
Smoker	Yes	145	20 (13.8%)	0.831
	No	200	26 (12.0%)	
Diabetes	Yes	69	12 (17.4%)	0.268
	No	276	34 (12.3%)	
HTN	Yes	196	36 (18.4%)	0.002
	No	149	10 (6.7%)	
GFR <60	Yes	142	25 (17.6%)	0.051
	No	203	21(10.3%)	
Hyperlipideamia	Yes	110	14 (12.7%)	0.821
	No	235	32 (13.6%)	
Previous MI	Yes	64	11 (17.2%)	0.315
	No	281	35 (12.5%)	
IHD	Yes	104	16 (15.4%)	0.462
	No	241	30 (12.4%)	
LVF	Yes	64	11 (17.2%)	0.315
	No	281	35 (12.5%)	
Cerebrovascular	Yes	43	9 (20.9%)	0.117
	No	302	37 (12.3%)	
COPD	Yes	49	4 (8.2%)	0.180†
	No	296	41 (13.9%)	

* Chi-squared test unless stated, †Fischers exact test

Abbreviations; HTN; hypertension, eGFR; estimated glomerular filtration rate (ml/min), MI; myocardial infarction, IHD; ischaemic heart disease, LVF; left ventricular failure, COPD; chronic obstructive pulmonary disease, CVD; cerebrovascular disease.

Table 6.2 Pre-operative clinical variables and peri-operative all cause mortality

		Total (%)	Perioperative Death n=27 (%)	p*
Male Sex	Male	217	19 (8.8%)	0.403
	Female	128	8 (6.3%)	
Age ≥ 70 years	≥ 70 years	165	17 (10.3%)	0.101
	<70 years	180	10 (5.6%)	
Smoker	Yes	145	10 (6.9%)	0.584
	No	200	17 (8.5%)	
Diabetes	Yes	69	11 (15.9%)	0.005
	No	276	16 (5.8%)	
HTN	Yes	196	20 (10.2%)	0.059
	No	149	7 (4.7%)	
eGFR <60	Yes	142	16 (11.3%)	0.047
	No	203	11(5.4%)	
Hyperlipideamia	Yes	110	10 (9.1%)	0.550
	No	235	17 (7.2%)	
Previous MI	Yes	64	6 (9.4%)	0.609
	No	281	21 (7.5%)	
IHD	Yes	104	8 (7.7%)	0.952
	No	241	19 (7.9%)	
LVF	Yes	64	2 (3.1%)	0.090†
	No	281	25 (8.9%)	
Cerebrovascular	Yes	43	4 (9.3%)	0.442†
	No	302	23 (7.6%)	
COPD	Yes	49	7 (14.3%)	0.069
	No	296	20 (6.8%)	

* Chi-squared test unless stated, †Fischers exact test

Legend; HTN; hypertension, eGFR; estimated glomerular filtration rate (ml/min), MI; myocardial infarction, IHD; ischaemic heart disease, LVF; left ventricular failure, COPD; chronic obstructive pulmonary disease, CVD; cerebrovascular disease.

Table 6.3 ECG abnormalities and peri-operative major adverse cardiac event (MACE)

		Total n=345 (%)	MACE n =46 (%)	p*
Abnormal ECG	Yes	141	31 (22.0%)	<0.001
	No	204	15 (7.4%)	
Abnormal Axis	Yes	37	8 (21.6%)	0.116
	No	308	38 (12.3%)	
LVH	Yes	35	6 (17.1%)	0.484
	No	310	40 (12.9%)	
Strain	Yes	43	17 (39.5%)	<0.001
	No	302	29 (9.6%)	
Q-wave	Yes	33	6 (18.2%)	0.389
	No	312	40 (12.8%)	
BBB	Yes	14	3 (21.4%)	0.412†
	No	331	43 (13.0%)	
AF	Yes	32	9 (28.1%)	0.010
	No	313	37 (11.8%)	
PVC	Yes	21	3 (14.3%)	0.750†
	No	324	43 (13.3%)	
HR >100	Yes	40	6 (15.0%)	0.742
	No	305	40 (13.1%)	
QRS >130ms	Yes	12	2 (16.7%)	0.666†
	No	333	44 (13.2%)	
QTc >440ms	Yes	68	19 (27.9%)	<0.001
	No	277	27 (9.7%)	

* Chi-squared test unless stated, †Fischers exact test

Abbreviations; LVH; left ventricular hypertrophy, BBB; bundle branch block, AF; atrial fibrillation, PVC, premature ventricular complex.

Table 6.4 ECG abnormalities and peri-operative all cause mortality

		Total (%)	Perioperative Death n=27 (%)	p*
Abnormal ECG	Yes	141	17 (6.3%)	0.015
	No	204	10 (4.9%)	
Abnormal Axis	Yes	37	3 (8.1%)	1.000†
	No	308	24 (7.8%)	
LVH	Yes	35	5 (14.3%)	0.133
	No	310	22 (71.0%)	
Strain	Yes	43	6 (14.0%)	0.110
	No	302	21 (7.0%)	
Q-wave	Yes	33	4 (12.1%)	0.310†
	No	312	23 (7.4%)	
BBB	Yes	14	2 (14.3%)	0.301†
	No	331	25 (7.6%)	
AF	Yes	32	4 (12.5%)	0.297†
	No	313	23 (7.3%)	
PVC	Yes	21	2 (9.5%)	0.674†
	No	324	25 (7.7%)	
HR >100	Yes	40	6 (15.5%)	0.072
	No	305	21 (6.9%)	
QRS >130ms	Yes	12	1 (8.3%)	1.000†
	No	333	26 (7.8%)	
QTc >440ms	Yes	68	7 (10.3%)	0.398
	No	277	20 (7.2%)	

* Chi-squared test unless stated, †Fischers exact test

Abbreviations; LVH; left ventricular hypertrophy, BBB; bundle branch block, AF; atrial fibrillation, PVC, premature ventricular complex.

6.3.3 Clinical variables and ECG abnormalities - multivariate predictors of adverse outcomes

The clinical variables and ECG abnormalities with a p value of <0.10 from univariate analysis of peri-operative MACE were entered into a logistic regression model [Table 6.5]. The only clinical factors that remained significant on multivariate analysis were hypertension and age > 70 years. From the ECG abnormalities, ventricular strain and QTc >440ms remained significant. An abnormal ECG, eGFR <60 ml/min and AF did not remain significant in the model.

Diabetes, an abnormal ECG, eGFR >60 mls/min, hypertension, COPD and HR>100 were associated with peri-operative mortality on univariate analysis [Table 6.6]. However, only diabetes remained significant after multivariate analysis.

Table 6.5 Cox regression analysis of clinical variables and ECG abnormalities and post-operative major adverse cardiac event (MACE)

	Univariate		Multivariate*	
Factor	HR (95% CI)	p	HR (95% CI)	p
Ventricular Strain	6.12 (2.92-12.66)	<0.001	4.93 (2.30-10.58)	<0.001
QTc >440ms	3.59 (1.85-6.96)	<0.001	2.92 (1.44-5.96)	0.003
Hypertension	3.13 (1.50-6.53)	0.002	2.79 (1.28-6.01)	0.010
Age ≥ 70 years	2.85 (1.46-5.57)	0.002	2.26 (1.11-4.60)	0.025
Abnormal ECG	3.21 (1.73-5.95)	<0.001		
AF	2.92 (1.26-6.78)	0.010		

Abbreviations; HR - hazard ratio, CI - confidence interval, AF- atrial fibrillation,

Table 6.6 Cox regression analysis of clinical variables and ECG abnormalities and post-operative mortality

	Univariate		Multivariate*	
Factor	HR (95% CI)	p	HR (95% CI)	p
Diabetes	3.08 (1.36-6.99)	0.007	2.56 (1.10-5.95)	0.029
Abnormal ECG	2.66 (1.18-6.00)	0.018		
eGFR >60	2.22 (0.99-4.93)	0.051		
Hypertension	2.31 (0.95-5.61)	0.065		
COPD	2.20 (0.92-5.77)	0.076		
HR >100	2.39 (0.91-6.32)	0.080		

Abbreviations; HR - hazard ratio, CI - confidence interval, eGFR - estimated glomerular filtration rate (mls/min).

6.3.4 Relationships between a history of IHD and the presence or absence of an abnormal ECG

The relationship between a history of IHD and an abnormal ECG was examined. Patients with a history of IHD and a normal ECG had the lowest MACE rate (2.4%) compared with no IHD and a normal ECG (8.6%), IHD and an abnormal ECG (24.2%) and no IHD and an abnormal ECG (20.3%) (p=0.001). The preoperative prescription of an antiplatelet agent, a statin and a beta-blocker within these groups is summarised in Table 6.7. Patients with known IHD and a normal ECG have a significantly higher rate of antiplatelet therapy, statin and beta-blocker prescription compared with the other groups. Multiple ECG abnormalities were encountered in 54 (15.7%) patients (37 (10.7%) patients had 2 and 17 (4.9%) had 3 or more). The rate of peri-operative MACE was higher in patients with 2 (35.1%) and 3 or more (23.5%) abnormalities, compared with 1 (16.1%) and a normal ECG (7.4%) (p<0.001).

Table 6.7 Prescription rate of best medical therapy in patients with or without ischaemic heart disease (IHD) and a normal or abnormal ECG

		Normal ECG		Abnormal ECG		p*
		No IHD n = 162 (%)	IHD n=42 (%)	No IHD n=79 (%)	IHD n=62 (%)	
Antiplatelet Agent	Yes	64 (39.5)	32 (76.2)	44 (55.7)	39 (62.9)	<0.001
	No	98 (60.5)	10 (23.8)	35 (44.3)	23 (37.1)	
Statin	Yes	65 (40.1)	32 (76.2)	41 (51.9)	37 (59.7)	<0.001
	No	97 (59.9)	10 (23.8)	38 (48.1)	25 (40.3)	
Beta-blocker	Yes	22 (13.6)	25 (59.5)	20 (25.3)	19 (30.6)	<0.001
	No	140 (86.4)	17 (40.5)	59 (74.7)	43 (69.4)	

* Chi-squared test.
Abbreviations; IHD - Ischaemic heart disease

6.4 Discussion

This study has two key findings: Firstly, a standard pre-operative ECG has stronger predictive value for peri-operative events than clinical characteristics, such as IHD. Secondly, patients with an abnormal ECG, but without a prior history of ischaemic heart disease represent an otherwise unrecognised high risk group. This finding is important since this group could potentially be amenable to risk reduction intervention.

Although a number of other studies have examined the relationship between the pre-operative ECG and post-operative outcomes, we believe this study has a number of strengths. This was a prospective study in consecutive patients who were screened for post-operative cardiac events. The relatively high MACE rate may be explained by the fact that 'all-comers' were included and no patients were excluded on clinical grounds. By so-doing, we were also able to collect information on patients without a prior diagnosis of heart disease

Noordzij and colleagues retrospectively computer interpreted ECGs from 23036 patients undergoing non-cardiac surgery.[86] Since this study was performed retrospectively using cardiac death as their only endpoint, non-fatal cardiac events were not included in the analysis. This may explain their conclusion that an ECG is not necessary in lower risk procedures. Similarly Lui and colleagues concluded that the preoperative ECG was of limited value in a prospective study of more than 500 elderly patients (aged >70).[88] They found a high prevalence of ECG abnormalities (75.2%) and concluded that the ECG had no discriminatory value. They did however examine far more ECG abnormalities than in this study (22 variables), and this may reflect the reduction in specificity. Van Klei and colleagues examined 2422 patients, enrolled in a previous study, for post-operative MI and all cause mortality.[87] They found that on univariate analysis bundle branch block predicted outcome, but was not significant on regression modelling. Again this study was performed retrospectively. They concluded that in their study group an ECG did not improve prediction beyond risk factors identified on a careful history. Landesberg and colleagues carried out a prospective study of 405 patients undergoing vascular surgery.[90] They carried out rigorous post-operative screening for cardiac events (daily cardiac enzymes). Despite this, they found a low rate of MACE (4.7%), perhaps reflecting a

healthier population. However they did find that LVH and ST segment depression was more predictive of poor outcome than standard clinical variables. Correll and colleagues performed a case-control study comparing a cohort of 95 patients with an abnormal pre-operative ECG, matched to 195 patients without an abnormality.[89] They concluded that risk factors obtained from a careful history predicted ECG abnormalities and therefore questioned the value of the routine ECG.

With regard to our second key finding, we were surprised to find such a high event rate in patients with an abnormal ECG but without a prior history of IHD. In fact, the MACE rate in these patients (20.3%) was higher than in patients with known IHD and a normal ECG (8.6%), and nearly as high as the MACE rate in IHD patients with an abnormal ECG (24.2%). There may be several explanations for this surprising result. Firstly, the rate of antiplatelet agent, statin and beta-blocker use was lower in this group. These drugs improve prognosis after major surgery.[228] Secondly, since these patients had ECG abnormalities, it seems likely that some of them had undiagnosed heart disease. Thirdly, since these patients had no history of IHD, it seems plausible that prior risk assessment, such as stress testing or coronary arteriography, would not have been performed. Thinking ahead, this group of patients with unrecognised or subclinical cardiac illness represent a group who might benefit from a targeted pre-operative intervention, such as more aggressive risk assessment and improved best medical management.

One limitation of our study is that the ECGs were assessed by a cardiologist which is rarely routinely performed on all pre-operative ECGs. However, this study examined standard ECG characteristics, many of which are routinely described in the automated computer report provided on the ECG print-out. Therefore, we believe our findings are relevant to everyday practice. Bedside interpretation of the ECG by a non-cardiology trained staff member is standard in most settings. More complex analyses performed in some other studies may not allow this relevance. This study included consecutive patients undergoing major surgery in our unit, and reflects the case load we encounter. The heterogeneous nature of our cohort could also be considered as a limitation, although we feel this allows the findings to be applicable to general clinical practice. Finally, it is worth remembering that a pre-operative ECG remains the

optimal baseline comparison in the event of a post-operative MI, and without it, the timely diagnosis of a cardiac event may be hampered.

In conclusion, we show that in this study group, the ECG remains an important tool in the pre-operative assessment of patients undergoing major non-cardiac surgery.

7 The performance of the Revised Cardiac Risk Index (RCRI) in patients undergoing major vascular surgery

7.1 Introduction

The pre-operative assessment of the likelihood of a post-operative cardiac event is complex[229]. The Revised Cardiac Risk Index (RCRI) is a commonly used scoring system for the stratification cardiac risk of patients undergoing major non-cardiac surgery.[6] The RCRI scores patients according to 6 clinical categories; high risk surgery (thoracic, abdominal and supra-inguinal vascular surgery), history of ischaemic heart disease, history of congestive heart failure, cerebrovascular disease, insulin-dependent diabetes and renal failure. The RCRI defines Class 1 as no factors present, Class 2 as 1 factor present, Class 3 as 2 factors present and Class 4 as 3 or more factors present. Results from the validation cohort of the original study suggest that the risk of a major adverse cardiac event (MACE) in Class 1, 2, 3 and 4 was 0.4%, 0.9%, 7% and 11% respectively.

Since the publication of the original paper in 1999, the RCRI has become a widely used stratification tool for cardiac risk. Indeed the most recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines on peri-operative cardiovascular evaluation for non-cardiac surgery stress the use of risk stratification, in particular the RCRI, in its recommendations.[69] The RCRI has, to date, been cited in over 400 papers, although very few of these papers have focused on validating its findings.

Several attempts have been made to directly validate the RCRI.[101,102,230,231] A recent meta-analysis has examined the predictive value of the RCRI in these studies.[103] It concluded that the RCRI performed moderately well at discriminating between low and high peri-operative risk. However the authors felt it performed poorly in vascular cohorts, and that the studies included were of variable quality. This report highlights the need for further studies evaluating the RCRI. Therefore, we aim to prospectively assess the predictive value of the RCRI in patients undergoing vascular surgery in a West of Scotland setting.

7.2 Methods

7.2.1 Patients Selection

This is a single centre observational study in patients undergoing major vascular surgery. Consecutive patients undergoing aortic surgery, lower limb bypass surgery and amputation were selected for inclusion in the study. All patients had standard pre-operative assessment including a 12-lead ECG. Further cardiac assessment was carried out at the discretion of the operating team. Ethical approval for this study was provided by the West of Scotland Research Ethics Committee. All patients gave written consent to the study following a verbal explanation and written information

The patients were pre-operatively scored according to the RCRI using the following criteria.[6] High risk surgery was defined as thoracic, abdominal or supra-inguinal bypass surgery. Ischaemic heart disease was defined as a previous myocardial infarction, a positive exercise tolerance test, the use of nitrate therapy or the presence of pathological Q-waves on ECG. Previous congestive cardiac failure, cerebrovascular disease (stroke or transient ischaemic attack) and pre-operative treatment with insulin was noted. Renal failure was defined as a serum creatinine of >2.0mg/dl (176.8umol/l).

The presence of other risk factors such as smoking, hyperlipidaemia, and chronic obstructive airways disease (COPD) were obtained from the patient's history and medical records. Hypertension was considered present if antihypertensive medication was taken. The glomerular filtration rate (eGFR) was estimated using the MDRD equation.[192] An eGFR of greater than 60 mls/min was considered normal. This was used as a separate variable from the definition for renal failure in the RCRI. Pre-operative anaemia was defined as a haemoglobin of <13.0 g/dl for males and <11.0 g/dl for females. Operations were recorded as elective or urgent (surgery during an unplanned admission). Patients operated as an emergency, within 24hrs of an unplanned admission were excluded.

7.2.2 Post-operative Surveillance

Post-operative screening for cardiac events was performed. This consisted of daily clinical assessment and serial ECGs and troponin I measurement on day 2, day 5 and 6 weeks following surgery. All patients were followed-up for the first post-operative year, either at outpatient clinic or with the general practitioner (GP). In the absence of follow-up data, the patient was directly contacted. The primary outcomes were MACE (non-fatal myocardial infarction and cardiac mortality), all-cause mortality within the post-operative period (6 weeks) and 1 year all-cause mortality. The definition of a non-fatal MI was that used by The Joint European Society of Cardiology/American College of Cardiology Committee[34]: a typical rise and gradual fall of serum troponin with at least one of the following: ischaemic symptoms, development of pathological Q waves on the ECG, ECG changes indicative of ischaemia (ST segment elevation or depression) or coronary artery intervention. Cardiac death was defined as death secondary to MI, cardiogenic shock or intractable arrhythmia.

7.2.3 Statistical Analysis

Statistical analysis was performed using SPSS (Version 15) statistical software package (SPSS, Chicago, Illinois, USA). A p-value of less than 0.05 was considered significant. Categorical variables are presented with totals and percentages, and analysed with chi-squared, Fishers exact test or Mann-Whitney test as appropriate. Receiver operating characteristic (ROC) curves were plotted to model the efficacy of the RCRI. The area under the curve (AUC) was calculated.

7.3 Results

A total of 252 patients undergoing major vascular surgery were included in the study. Sixty-five patients underwent aortic surgery (25.8%), 100 had lower limb bypass surgery (39.7%) and 87 had a lower limb amputation (34.5%). Thirty-nine patients (15.5%) had a post-operative MACE, and twenty patients (7.9%) died within the post-operative six week period. The one year mortality rate was 22.6%.

7.3.1 Utility of Revised Cardiac Risk Index (RCR)I for prediction of peri-operative MACE, peri-operative mortality and 1 year survival

Applying the RCRI to the cohort as a whole, the rate of MACE for RCRI class 1, 2, 3 and 4 was 13.4%, 14.9%, 18.6% and 16.7% respectively (p=0.858) [Table 7.1]. Similarly, the rate of peri-operative mortality for these groups was 7.3%, 9.2%, 6.8% and 8.3% (p=0.951). The one year mortality in each group was 17.1%, 24.1%, 25.4% and 29.2% (p=0.492).

Table 7.1 Primary Endpoints by Revised Cardiac Risk Index (RCRI) Class

	n	MACE (%)	Peri-operative Mortality (%)	1 Year Mortality (%)
Total	252	39 (15.5)	20 (7.9)	57 (22.6)
RCRI Class 1	82	11 (13.4)	6 (7.3)	14 (17.1)
RCRI Class 2	87	13 (14.9)	8 (9.2)	21 (24.1)
RCRI Class 3	59	11 (18.6)	4 (6.8)	15 (25.4)
RCRI Class 4	24	4 (16.7)	2 (8.3)	7 (29.2)
p-value*		0.858	0.951	0.492

* Chi-Squared Test
Abbreviations: MACE - Major Adverse Cardiac Event, RCRI - Revised Cardiac Risk Index

7.3.2 Revised Cardiac Risk Index; individual *component analysis for endpoints.*

Analysis of the RCRI components revealed that no individual factor predicted post-operative MACE after univariate analysis [Table 7.2]. Insulin therapy was higher in patients that died in the peri-operative group (18.2% vs. 6.4%, p=0.020). Patients with a pre-operative creatinine >2mg/dl had higher peri-operative mortality (30.0% vs. 7.0%, p=0.036), and 1 year mortality (60.0% vs. 21.1%, p=0.004). Patients undergoing high risk surgery had a significantly lower 1 year mortality (10.8% vs. 26.7%, p=0.008).

7.3.3 Operative subgroup analysis and predictive utility of Revised Cardiac Risk Index

The predictive value of the RCRI was then examined within the three individual operative groups [Table 7.3]. Due to small numbers, the two highest risk groups (class 3 and 4) were combined for analysis. In no subgroup was the RCRI predictive of peri-operative MACE. The RCRI did stratify 1 year mortality in the patients undergoing lower limb bypass surgery; class 1, 2 and ≥3 with mortality rates of 9.6%, 18.5%, 33.3% (p=0.049) respectively. In the amputation group, patients in RCRI class 1 had peri-operative mortality rate of 13.3%, compared with 17.9% in class 2 and 6.9% in class 3.

Table 7.2 Predictive value of individual RCRI components for peri-operative major adverse cardiac event (MACE), peri-operative mortality and 1 year mortality

		n	Peri-operative MACE	p*	Peri-operative mortality	p*	1 Year Mortality	p*
High Risk Surgery	Yes	65	9 (13.8)	0.673	3 (4.6)	0.300†	7 (10.8)	0.008
	No	187	30 (16.0)		17 (9.1)		50 (26.7)	
IHD	Yes	82	12 (14.6)	0.797	7 (7.6)	0.807	23 (28.0)	0.152
	No	170	27 (15.9)		13 (7.6)		34 (20.0)	
CCF	Yes	57	11 (19.3)	0.364	2 (3.5)	0.263*	17 (29.8)	0.139
	No	195	28 (14.4)		18 (9.2)		40 (20.5)	
CVD	Yes	38	7 (18.4)	0.586	3 (7.9)	1.000†	12 (31.6)	0.152
	No	214	32 (15.0)		17 (7.9)		45 (21.0)	
IDDM	Yes	33	7 (21.2)	0.328	6 (18.2)	0.020	11 (33.3)	0.115
	No	219	32 (14.6)		14 (6.4)		46 (21.0)	
Creat	Yes	10	3 (30.0)	0.189†	3 (30.0)	0.036†	6 (60.0)	0.004
>2 mg/dl	No	242	36 (14.9)		17 (7.0)		51 (21.1)	

Legend;
* Chi-Squared Test unless otherwise stated.† Fisher's Exact Test.
Abbreviations: MACE - Major Adverse Cardiac Event, IHD – Ischaemic Heart Disease, CCF – Congestive Cardiac Failure, CVD – Cerebrovascular Disease, IDDM – Insulin Dependant Diabetes Mellitus. Creat - Creatinine.

Table 7.3 Predictive value of Revised Cardiac Risk Index (RCRI) Class within Operation Groups

	RCRI Class	n	MACE (%)	Peri-operative Mortality (%)	1 Year Mortality (%)
Aortic Surgery	1	0	-	-	-
	2	32	5 (15.6)	2 (6.3)	4 (12.5)
	≥3	33	6 (18.2)	1 (3.0)	3 (9.1)
	p value*		0.683	0.536	0.658
Bypass	1	52	5 (9.6)	2 (3.8)	5 (9.6)
	2	27	3 (11.1)	1 (3.7)	5 (18.5)
	≥3	21	3 (14.3)	3 (14.1)	7 (33.3)
	p value*		0.846	0.198	0.049
Amputation	1	30	6 (20.0)	4 (13.3)	9 (30.0)
	2	28	5 (17.9)	5 (17.9)	12 (42.9)
	≥3	29	8 (27.6)	2 (6.9)	12 (41.4)
	p value*		0.644	0.456	0.539

* Mann-Whitney test.
Abbreviations: MACE – Major Adverse Cardiac Event

7.3.4 Clinical predictors of primary endpoints not included in the revised cardiac risk index

Analysis of other risk factors not included in the RCRI showed that age ≥ 70 years (p=0.002), a history of hypertension (p=0.010), pre-operative anaemia (p<0.001) and urgent (p=0.024) had a significantly higher rate of post-operative MACE (table 4). Furthermore, age ≥ 70 years (p=0.028), diabetes (type I and II) ((p=0.013), GFR <60mls/min (p=0.009), COPD (p=0.043), pre-operative anaemia (p=0.025) and expedited surgery (p=0.020) were associated with an increased rate of post-operative death. The following factors were associated with lower one year survival rates; age ≥ 70 (p=0.024), diabetes (type I and II) (p=0.044), hypertension (p=0.023), GFR <60mls/min (p=0.031), expedited surgery (p<0.001) and pre-operative anaemia (p<0.001).

Table 7.4 Patient Characteristics and predictors of major adverse cardiac event (MACE), peri-operative mortality and 1-year mortality

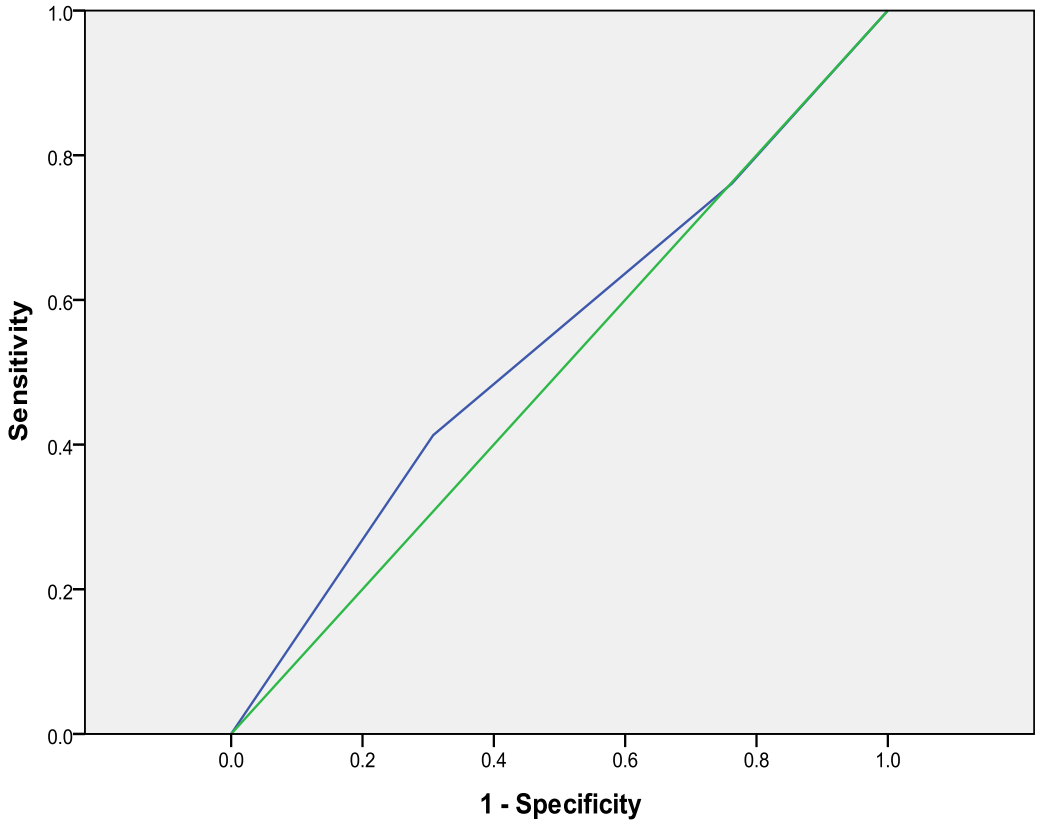
Factor	n (%) n=252	MACE (%) n=39	p*	Perioperative Mortality (%) n=20	p*	1 year Mortality (%) n=57	p*
Male Sex	166 (65.9)	26 (66.7)	0.909	16 (80.0)	0.165	38 (66.7)	0.886
Age ≥ 70	135 (53.6)	27 (69.2)	0.002	14 (70.0)	0.028	35 (61.4)	0.010
Smoker	126 (50.0)	19 (48.7)	0.862	9 (45.0)	0.641	29 (50.9)	0.880
Diabetes (I and II)	57 (22.6)	10 (25.6)	0.624	9 (45.0)	0.013	18 (31.6)	0.066
Hypertension	154 (61.1)	31 (79.5)	0.010	16 (80.0)	0.071	42 (73.7)	0.027
Hyperlipidaemia	82 (32.5)	11 (28.2)	0.530	8 (40.0)	0.458	21 (36.8)	0.431
eGFR <60mls/min	107 (42.5)	22 (56.4)	0.055	14 (70.0)	0.009	31 (54.4)	0.038
Previous MI	50 (19.8)	8 (20.5)	0.909	6 (30.0)	0.235	18 (31.6)	0.012
COPD	46 (18.3)	4 (10.3)	0.160	7 (35.0)	0.043	12 (21.1)	0.534
Beta-Blocker	68 (27.0)	11 (28.2)	0.852	6 (30.0)	0.751	18 (31.6)	0.374
Antiplatelet	150 (59.5)	22 (56.4)	0.667	9 (45.0)	0.168	33 (57.9)	0.776
Statin	139 (55.2)	21 (53.8)	0.858	9 (45.0)	0.341	34 (59.6)	0.438
Pre-operative Anaemia	116 (46.0)	29 (74.4)	<0.001	14 (70.0)	0.025	41 (71.9)	<0.001
Urgent Surgery	153 (60.7)	30 (76.9)	0.024	17 (85.0)	0.020	50 (87.7)	<0.001
Blood loss >500mls	32 (12.7)	7 (17.9)	0.284	2 (10.0)	0.706	5 (8.8)	0.311

* Chi-Squared Test unless otherwise stated. † Mann-Whitney test.
Abbreviations: eGFR – Estimated Glomerular Filtration Rate, MI – Myocardial Infarction, COPD – Chronic Obstructive Pulmonary Disease.

7.3.5 Receiver operator curve analysis of the performance of the RCRI

The area under the ROC curve for the RCRI score was calculated for the endpoints. The AUC for peri-operative MACE was 0.538 [Figure 7.1], 0.501 for peri-operative mortality and 0.562 for 1 year mortality. The same analysis was performed, amending the RCRI to consider all included vascular operation groups as high risk. The AUCs were not improved for peri-operative MACE, mortality or 1 year mortality respectively (0.507, 0.473 and 0.525). However if this category in the RCRI was replaced by age ≥ 70 years, the AUCs were improved (0.614, 0.622 and 0.665).

Figure 7.1 ROC curve analysis: RCRI and post-operative major adverse cardiac event (MACE)



7.4 Discussion

The prediction of post-operative cardiac morbidity is challenging. Patient co-morbidity, operation type, peri-operative stress and post-operative factors are all influential in the pathogenesis of post-operative MACE.[4,232] Extensive research has examined a plethora of pre-operative stratification tools. Many cardiac scoring systems have been devised that aim to stratify and quantify risk.[229]

The RCRI includes patients factors (IHD, cardiac failure, cerebrovascular disease and insulin dependent diabetes), pre-operative renal impairment (Creatinine >2mg/dl) and type of surgery. These factors were found to be the most significant predictors of post-operative MACE in a derivation cohort of 2893 patients and the model was validated in a cohort of 1422 patients. Procedure types included thoracic, orthopaedic, vascular and abdominal surgery. The rates of major cardiac morbidity in the derivation and validation cohorts were 2% and 2.5% respectively. These rates are considerably lower than in our study group, perhaps reflecting the heterogeneous nature of the procedures examined and a healthier study population.

Why then has it performed so poorly in our cohort? Firstly, the RCRI defines high risk surgery as, intrathoracic, intraperitoneal and suprainguinal vascular surgery. In our cohort, patients undergoing high risk surgery, as defined by the RCRI, had a lower MACE rate, improved peri-operative survival and lower 1 year mortality. This can be explained as the high risk patients were undergoing elective aortic surgery, yet patients undergoing lower limb revascularisation or amputation were considered as low risk surgery. However, removing this 'high risk surgery' parameter from the model did not improve the predictive efficacy. Secondly, patients with peripheral vascular disease have a notoriously high level of subclinical cardiac disease.[10] The absence of clinical manifestations of cardiac disease may in part be due to their physiological exercise limitations.[233] This is likely to 'underscore' patients with vascular disease, therefore underestimating the risks of post-operative cardiac events.

We did not include patients undergoing endovascular aortic aneurysm repair (EVAR) in our analysis. EVAR is associated with lower post-operative mortality

and reduced cardiac event rates,[176] however it is uncertain whether these patients should still be considered as 'high risk surgery'. Archan et al examined the predictive value of the RCRI in 225 EVAR patients.[58] They found a low cardiac event rate (6.2%), and no in-hospital cardiac deaths. Patients with a RCRI Class 4 had a higher cardiac event rate and lower 1 year survival on univariate analysis; however this was not the case over the longer follow-up periods. Similarly, patients undergoing other forms of minimally invasive surgery, such as laparoscopic colorectal resection have an improved peri-operative morbidity profile.[234] It is unclear if traditional risk assessment tools apply to these patients.

Boersma et al retrospectively analysed the post-operative mortality of over 100,000 patients undergoing non-cardiac surgery.[101] The study cohort included orthopaedic (20%), abdominal (15%), ear, nose and throat (14%), gynaecological (14%) and urological surgery (10%). Due to the retrospective nature of the study, mortality (1.7%), and in particular cardiac mortality (0.5%) was the primary endpoint. They concluded that the RCRI was "probably suboptimal for identifying patients with greater cardiac risk". The authors improved the performance of the scoring system by adding age to the model. Welten et al retrospectively reviewed the outcome of 2730 patients undergoing open vascular surgery (aortic, carotid and lower limb revascularisation).[102] They also found that the predictive value of the RCRI was improved by an adjustment for age. These findings are reproduced in the present study.

Ford and colleagues have performed a meta-analysis examining the uses of the RCRI.[103] The majority of the studies included simply use the RCRI as a stratification tool to display data. Only five high quality, prospectively performed studies were found that specifically aimed to validate the findings of the RCRI. The authors conclude that the RCRI demonstrated moderate performance in differentiating low and high cardiac risk within mixed surgical cohorts. However, a significantly inferior predictive value was found within specific vascular cohorts.

The validation of scoring systems with large cohorts has largely been performed retrospectively. While large numbers of patients are available for analysis, accurate end points are difficult. Boersma and colleagues' paper examined only

cardiac death, as the determination of post-operative non-fatal MI was not possible.[101] In a recent editorial, Goldman identified a number of limitations in the published studies investigating the efficacy of the RCRI.[235] These included the inability to accurately document pre-existing risk factors on retrospective chart analysis, variable post-operative screening for cardiac events and the inconsistent end-points used. He reminds the reader that the RCRI was designed to predict only post-operative MACE.

A limitation of this study is that routine screening for post-operative MI will inevitably lead to a higher event rate than experienced in day-to-day practice. However, the RCRI index was derived and validated on data extracted from a similarly screened population. In addition, the importance of a silent infarction is well recognised.[14] Asymptomatic myocardial injury leads to increased inpatient complications and reduced survival.[32]

The reliance on the RCRI has been questioned in the recently published combined European Society of Cardiology (ESC) / European Society of Anaesthesiology (ESA) guidelines on the preoperative cardiac risk assessment and for patients undergoing non-cardiac surgery, due to its 'suboptimal' performance in patients with multiple risk factors.[180] With this in mind, we conclude from our prospectively gathered cohort study, that the RCRI performs poorly in predicting post-operative cardiac morbidity and mortality following vascular surgery. The inclusion of an age category improves efficacy. Caution should be used when applying this index to vascular patients.

8 Discussion

8.1 Cardiac risk assessment in patients undergoing major non-cardiac surgery (NCS)

The assessment and prediction of cardiac risk during and after non-cardiac surgery is multi-factorial. There is no simple and universally available assessment technique that is effective for all surgical populations. Ultimately, grouping clinical factors and assessment measures together as an easy to use scoring system should be superior to using individual factors in isolation. Identification of both simple to perform and easy to interpret tests are crucial. With this in mind, the studies presented in this thesis have several important findings;

8.1.1 BNP is a powerful predictor of peri-operative cardiac morbidity, mortality and long term survival

This study shows that an elevated pre-operative BNP is associated with an increased peri-operative MACE rate, increased peri-operative mortality and a reduced long term survival, independent of other factors. The short-term findings reported in this thesis are supported by several trials published subsequently[132,203,204,220,223]. The long-term outcome study represents the longest follow-up data available in the literature.

BNP appears to be a surrogate marker for a number of medical co-morbidities; however BNP has a far superior predictive value than the individual factors alone. What then are the predictive strengths of BNP? While patients with an elevated BNP have a high chance of an adverse outcome, patients with a 'normal' BNP have an extremely low chance of an adverse event. For example, over 40% of patients with an elevated BNP in our study had a MACE and 18% died in the peri-operative period. The negative predictive values for MACE and mortality were 96% and 97% respectively. Thus, these studies demonstrate that BNP is a predictor of adverse outcomes; however, of greater importance, a low BNP is highly indicative of an uneventful post-operative period. This finding of a high NPV is supported by meta-analysis of other published studies.[216]

We found that a cut-off BNP level of 88 pg/ml provided the best sensitivity and specificity for peri-operative MACE, 107 pg/ml for peri-operative mortality and 87.5 pg/ml for all cause long-term mortality. It is difficult to extract a

consensus regarding the optimal BNP cut-off point from the existing literature. Although several studies have been published examining the relationship between BNP and peri-operative MACE rate, there is considerable variation in study population and methodology. The cut-off points derived from the individual studies range from 39-174 pg/ml.[132,136,203,204,223] Studies from non-surgical populations have demonstrated 100pg/ml as a suitable cut-off point and the various analyses in this thesis would support the adoption of this cut-off point for the purposes of surgical risk stratification.[217,218]

8.1.2 Traditional cardiac variables perform poorly in prediction of peri-operative and long term mortality

With the exception of a history of hypertension, none of the recorded cardiac variables predicted an adverse short-term post-operative outcome. Likewise, with the exception of a history of LVF in a sub-group analysis of peri-operative survivors only, none of the cardiac variables predicted long-term survival. Therefore, neither IHD nor a history of a previous MI had any predictive value in the various analyses presented in this thesis. There are several possible reasons for this.

The first reason may be the influence of best medical therapy prescription in patients with a past cardiac history. Patients with known stable heart disease are likely to be receiving optimal medical therapy. The use of APAs, statins and beta-blockers are associated with reduced peri-operative MACE and mortality in patients undergoing major NCS.[45,78,143,144,155] Secondly, the presence of subclinical heart disease may explain the lack of difference of MACE rate between patients with cardiac risk factors and those without. A high rate of asymptomatic LVSD has previously been demonstrated in the general population in the West of Scotland.[205] Therefore, some patients in our cohort will present for surgery with 'latent' CAD or LVSD. Also, a proportion of our cohort was undergoing vascular surgical procedures. This group has a notoriously high prevalence of CAD, of which a subgroup will have asymptomatic disease.[10]

8.1.3 Anaemia and urgent surgery are strong predictor of adverse outcome

Pre-operative anaemia and urgent surgery, defined as surgery performed during an unplanned admission, were both significant predictors of peri-operative MACE on multivariate analysis.

Pre-operative anaemia has been identified as a predictor of poor post-operative survival. Large database analyses (>200,000 patients) have also shown pre-operative anaemia rates of up to one third, and a significant association with peri-operative mortality.[213,214] In light of the considerable limitations of retrospective database analyses and the insufficient data we collected regarding the aetiology of anaemia, it remains unclear if anaemia represents a modifiable variable or simply acts as an indicator of other chronic diseases.

Urgent surgery is also known to predict adverse outcome from previous studies.[39,47] Although urgency of surgery proved a powerful predictor of both reduced short and long term survival, the opportunities for optimisation and intervention are more limited than in patients undergoing elective surgery and therefore these patients pose a particular challenge. In these studies, we defined urgent as requiring non-elective surgery during an unplanned admission. Patients who underwent surgery within 24hrs of an unplanned admission were excluded. Therefore, these patients had a minimum of 24hrs in hospital prior to surgery and in some cases several days of in-patient care preceding surgery. This period should allow adequate risk assessment and at least a short period of optimisation before surgery. Risk stratification may also guide appropriate modifications in surgical or anaesthetic techniques and in certain cases, consideration of alternatives to operative intervention.

8.1.4 ECG is a better predictor than traditional cardiac variables

The results of this research demonstrate that, in this cohort, a standard 12-lead ECG has a superior predictive utility for peri-operative cardiac events than standard cardiac characteristics. This study also highlights a sub-group of patients who have an abnormal ECG, but no known history of heart disease that is at particularly high risk of cardiac morbidity and may potentially benefit from risk reduction intervention.

8.1.5 The revised cardiac risk index performed poorly in the vascular sub-group analysis

The Revised cardiac risk index is a commonly used assessment tool and is recommended in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines on peri-operative cardiovascular evaluation for non-cardiac surgery.[6,179] Analysis of the vascular group of patients showed that the RCRI offered no predictive accuracy for peri-operative MACE, mortality or 1 year survival. This confirms concerns regarding the use of this scoring system in vascular patients.[103] Despite the poor performance in our vascular cohort, the RCRI remains a well validated tool for the stratification of risk in the non-vascular setting. The RCRI is simple to use, and is certainly the best currently available scoring system. However, there appears to be a 'gap in the market' for a scoring system derived from, and validated entirely in, a vascular-only cohort.

8.2 Study Strengths and Limitations

This was a prospective study in consecutive patients who were screened for post-operative cardiac events. This resulted in a high yield of peri-operative cardiac events. The study was performed in a single centre by a small group of investigators to limit bias and variation. All the long term follow-up was performed by a single investigator.

Since consecutive patients were included in our study, there is considerable heterogeneity in patient characteristics. Thus, our patients had a broad range of co-morbidities and the surgical problems involved acute illness and critical chronic disease, such as that due to chronic progressive limb ischaemia. While the prognostic value of BNP may be greater in particular subgroups, we suggest that the heterogeneity in our population may in fact make our results more transferable to ordinary clinical practice.

We used all-cause mortality, rather than cardiac death and non-cardiac death, as the endpoint for analysis of our long-term results. All-cause mortality was chosen as it was not possible to obtain accurate 'cause of death' for all patients, particularly when the death occurred in the community. Nor was it possible to adjudicate on these events. However, we feel that 'all cause mortality' is a very robust endpoint. Arguably, knowledge that BNP predicts death in any form in the longer term after surgery represents 'the bottom line', and perhaps this result above all is most important if our research with BNP (and work done by others) is to be translated into clinical practice.

During analysis of the database for this thesis, I encountered several data points that I considered inadequate to perform secondary post-hoc analysis. If I were to repeat this study I would improve recording of the following variables;

- Smoking status. We recorded only for presence or absence of smoking at the time of admission for surgery. I would like to have recorded packs smoked per day or prior smoking history. However, self reporting of cigarette use is notoriously inaccurate and additional data collected may be inaccurate.

- Status of previous MI. We recorded a history of MI as a dichotomous variable; we did not record specific data regarding timing of MI in relation to surgery or the use of coronary angiography at the time of MI.

- Improved data collection for anaemia. As previously mentioned, the identification of anaemia as a powerful predictor of MACE and long-term mortality was not anticipated as a major finding of this study. Therefore, no specific data was collected other than pre-operative haemoglobin. In retrospect, data about chronicity of anaemia, categorisation of anaemia (i.e. haematinic assessment) or previous investigations for anaemia would be helpful.

8.3 Implications for care of patients undergoing major non-cardiac surgery (NCS)

It is clear from the review of current literature and the results presented in this thesis that risk stratification based on standard clinical variables collected at pre-operative assessment alone is unsatisfactory. Likewise, the utility of scoring systems, such as the RCRI, in certain circumstances is questionable. Identification of high-risk patients, with the use of cardiac biomarkers or by other techniques, allows targeted pre-operative assessment and appropriate risk modification.

8.3.1 Multidisciplinary approach

A multidisciplinary team (MDT) approach to the management of many conditions, such as cancer, is now routine. A multidisciplinary approach standardises investigation, intervention and follow-up of such patients. Standardisation of the very same steps (investigation, intervention and follow-up) seems crucial for improved care of high risk patients undergoing major surgery.

A similar multidisciplinary approach to such patients would have a number of likely benefits. Firstly, the patient would be offered evidence-based optimisation of co-morbidities by informed clinicians and the patient would have timely access to appropriate cardio-respiratory investigations.

Secondly, a patient-centred MDT decision regarding progression to surgery in high risk patients would have the 'corporate backing' of the combined team in the event of an adverse outcome. This should be useful for clinicians, surgeons and anaesthetists alike; particularly as individualised mortality figures are shortly to become publicly available, as they currently are in cardiac surgery. It should reduce the occurrence of an inappropriate patient undergoing a surgical procedure based on a single clinician's assessment. Therefore, it is good for patients, good for individual clinicians and good for healthcare providers.

With ongoing controversy regarding the role of non-invasive cardiac imaging, peri-operative beta-blockers and dual-antiplatelet therapy and the constantly evolving field of peri-operative medicine, these decisions should be made by an

experienced team of clinicians equipped with the current best evidence in the field of cardiac risk modification.

8.3.2 Bundle of Care for High risk patients

'Bundles of care' have become popular in several areas of medicine. Enhanced recovery after surgery (ERAS) is an example of this.[165] While individual components of the ERAS protocol are 'unproven' to improve post-operative outcomes after surgery, when examined in its entirety, the ERAS bundle has been shown in numerous trials to significantly improve outcome.[166–168] The surviving sepsis bundle is another example of standardising the assessment and treatment of a clearly defined population, with an easy to follow pathway that has demonstrated improvements in patient outcomes.[236]

Pathways, checklists and bundles are helpful tools for the standardisation of care. Pre-operative assessment and risk stratification should lend itself to this approach. Accordingly, a simple evidence-based care pathway, specifically for patients at higher than normal risk of cardiac morbidity, should be investigated with prospective clinical trials.

8.4 Areas for Future Research

8.4.1 Natriuretic peptides

While our study agrees with several other studies in demonstrating natriuretic peptides as powerful predictors of MACE and mortality, there is currently no consensus regarding which marker to use (BNP or NT-proBNP), or which cut-off point to use.[141,142] Hopefully, the ongoing Vascular Events In Noncardiac Surgery Patients Cohort Evaluation Study (VISION) will answer these questions. This ambitious multicentre project intends to recruit 40,000 patients undergoing major NCS.[237] The study aims to document MACE rates in this large prospective cohort and identify predictors of adverse outcome. The utility of BNP is one of the objectives of the study.

8.4.2 Improved risk prediction scoring system

This thesis questions the utility of the most commonly used risk prediction scoring system, the revised cardiac risk index (RCRI), within the vascular group. However, the concept of an easy to use scoring system containing several simple-to-record variables remains attractive. The cohort described in this thesis could be used as a derivation cohort to construct a new scoring system. A further observational study would be required to validate these findings.

8.4.3 Risk reduction with High Risk Bundle

The development of a high risk bundle or care pathway, that would require the multi-disciplinary involvement of various specialties, is discussed above. The efficacy of such an approach, particularly with the likely increased costs incurred per patient would require a randomised clinical trial in order to establish its role in peri-operative medicine.

8.4.4 Management of Peri-operative Myocardial Infarction

Finally, in the absence of prospective trials examining the management of PMI, there is an opportunity to perform a study that would inform clinicians regarding the management of PMI in an evidence based fashion. When combining MACE and asymptomatic troponin rise, 1 in 5 patients in our cohort had a cardiac

injury. High event rates such as this, within a large centralised surgical service, would allow a prospective trial to be performed. Furthermore, until such a study is performed, the management of asymptomatic troponin elevation remains unclear.

8.5 Conclusion

Accurate and individualised cardiac risk stratification remains an elusive goal. A single pre-operative blood test to measure BNP offers valuable information in the prediction of peri-operative adverse outcomes and long-term survival after surgery. The predictive value of BNP appears to be superior to the traditional cardiac variables examined in this thesis. The presence of anaemia at the time of surgery and urgency of surgery also predict adverse outcome. However, the exact role of anaemia in this population requires more research.

The continued value of the pre-operative ECG has been demonstrated in this cohort, and an abnormal ECG predicts adverse outcome compared with standard cardiac risk factors. The presence of an abnormal ECG in patients with no history of heart disease may help identify a high risk group who would benefit from medical optimisation.

The exact course of action to pursue after identification of a patient who is at higher than normal risk of cardiac morbidity is unclear. However, further assessment followed by medical optimisation with anti-platelet agents, statin and cautious beta-blockade should be considered. Alterations of surgical approaches or anaesthetic techniques, as well as an improved level of care after surgery are additional measures that may further reduce risk of cardiac morbidity.

Finally, as surgeons, we are very focused on clear documentation of the surgical risks of individual procedures. Quantification of these risks has become routine in the informed consent process. More accurate assessment of the non-surgical complications should be included in this process in order to allow patients to make a truly informed decision about proceeding to or declining major surgery.

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