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Preoperative Cardiac Risk Assessment in Vascular Surgery: Risk Stratification, Novel Cardiac Biomarkers, and their Importance in Abdominal Aortic Aneurysm Surgery

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Dedication

To my wife Linda,

who supported me throughout.

Declaration

Signed

Mr Gavin Bryce

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Br J Cardiol 2009;16:147–150

B-type Natriuretic Peptide (BNP) Predicts Long Term Survival Following Major Non-Cardiac Surgery.

Payne CJ, Gibson SC, Bryce GJ, Jardine A, Berry C and Kingsmore DB.

Br J Anaesth – Accepted for publication, in print 2010.

Reduced LDL-cholesterol levels in patients with coronary artery disease are paralleled by improved endothelial function: An observational study in patients from 2003 and 2007.

Delles C, Dymott JA, Neisius U, Rocchiccioli JP, Bryce GJ, Moreno MU, Carty DM, Berg GA, Hamilton CA, Dominiczak AF.

Atherosclerosis. 2010;211:271-7

Presentations

The Prognostic Value of Raised Preoperative Troponin I in Vascular Surgery – a Case Series.

Bryce GJ, Payne CJ, Gibson SC, Kingsmore DB and Byrne DS

Vascular Society GB & Ireland, EICC, Edinburgh 2006

The Prognostic Value of Raised Preoperative Troponin I in Vascular Surgery.

Bryce GJ, Payne CJ, Gibson SC, Kingsmore DB and Byrne DS

West of Scotland Surgical Association (WOSSA), Glasgow 2006

Raised Preoperative Cardiac Troponin I in Vascular Surgery – What Does It Mean?

Bryce GJ, Payne CJ, Gibson SC, Kingsmore DB and Byrne DS

Greater Glasgow Vascular Audit Meeting, GGH 2006

The Risk And Benefit Of Abdominal Aortic Aneurysm Repair: Can BNP Help?

Bryce GJ, Payne CJ, Gibson SC, Kingsmore DB and Byrne DS

West of Scotland Vascular Society, Glasgow 2006

Abdominal Aortic Aneurysm Repair: Cardiac Risk Stratification.

Bryce GJ, Payne CJ, Gibson SC, Kingsmore DB and Byrne DS

Lanarkshire NHS vascular audit committee, Hairmyres 2006

The Glasgow Aneurysm Score as a Predictor of Immediate Outcome after Elective Abdominal Aortic Aneurysm Repair - in Glasgow.

Bryce GJ, Payne CJ, Kingsmore DB and Byrne DS

Association of Surgeons GB & I (ASGBI), Manchester 2007

BNP Predicts Survival at 1 year in Major Vascular Procedures.

Payne CJ, Bryce GJ, Gibson SC, Kingsmore DB and Byrne DS

ASGBI, Manchester 2007

The Role Of BNP In Cardiac Risk Stratification In Patients Undergoing Aortic Aneurysm Repair – 30 day outcome.

Bryce GJ, Payne CJ, Gibson SC, Kingsmore DB and Byrne DS

ASGBI, Bournemouth 2008

BNP as an Aid to Cardiac Risk Assessment.

Bryce GJ, Payne CJ, Gibson SC, Kingsmore DB and Byrne DS

ASGBI Travelling Fellowship, Glasgow 2008

The Role Of BNP In Cardiac Risk Stratification In Patients Undergoing Aortic Aneurysm Repair – 30 day outcome.

Bryce GJ, Payne CJ, Gibson SC, Kingsmore DB and Byrne DS

WOSSA, Glasgow 2008

Prolonged QTc Interval Can Predict Long Term Survival Following Major Non-cardiac Surgery.

Payne CJ, Payne AR, Gibson SC, Bryce GJ, Jardine A, Berry C, Kingsmore DB.

British Cardiac Society, London 2009

The Preoperative 12 lead ECG; Can it Predict Postoperative Cardiac Complications?

Payne CJ, Payne AR, Gibson SC, Bryce GJ, Jardine A, Berry C, Kingsmore DB.

British Cardiac Society, London 2009

Is There Still a Role for the Preoperative 12-lead Electrocardiogram?

Payne CJ, Payne AR, Gibson SC, Bryce GJ, Jardine A, Berry C, Kingsmore DB.

WOSSA, Glasgow 2010

The Revised Cardiac Risk Index Performs Poorly in Patients Undergoing Vascular Surgery.

Payne CJ, Gibson SC, Payne AR, Bryce GJ, Jardine A, Berry C, Kingsmore DB.

WOSSA, Glasgow 2010

List of Abbreviations

AAA	Abdominal Aortic Aneurysm
ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
AHA	American Heart Association
ASA	American Society of Anaesthesia
AUC	Area Under the Curve
BNP	B-type Natriuretic Peptide
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CCF	Congestive Cardiac Failure
CHF	Chronic Heart Failure
CI	Confidence Interval
CKD	Chronic Kidney Disease
CK-MB	Creatine Kinase Isoenzyme MB
COPD	Chronic Obstructive Pulmonary Disease
CPX	Cardiopulmonary Exercise Testing
CRI	Cardiac Risk Index
CRP	C-Reactive Protein
CRS	Comprehensive Risk Score
CV	Concentration Value
DiPS	Dipyridamole Perfusion Scintigraphy
DiSE	Dipyridamole Stress Echocardiography
DREAM	Dutch Randomized Endovascular Aneurysm Management trial
DSE	Dobutamine Stress Echocardiography
ESC	European Society of Cardiology
Hs-CRP	High Sensitivity C-Reactive Protein
cTnI	Cardiac Troponin-I
ECG	Electrocardiography
E-PASS	Estimation of Physiological Ability and Surgical Stress Score
EVAR	EndoVascular Aneurysm Repair
GAS	Glasgow Aneurysm Score
GP	General Practice/General Practitioner
IQR	Interquartile Range
LVEF	Left Ventricular Ejection Fraction

MACE	Major Adverse Cardiac Event
MET	Metabolic Equivalents
MI	Myocardial Infarction
MPS	Myocardial Perfusion Scintigraphy
NPV	Negative Predictive Value
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
POSSUM	Physiological and Operative Severity Score for enUmeration of Mortality
PPV	Positive Predictive Value
PRS of E-PASS	Preoperative Risk Score of the Estimation of Physiological Ability and Surgical Stress Score
RCRI	Revised Cardiac Risk Index (Lee's)
RNV	RadioNuclide Ventriculography
ROC	Receiver-Operator Characteristics
SD	Standard Deviation
SSS	Surgical Stress Score
TI	Thallium Imaging
V-POSSUM	Vascular Physiological and Operative Severity Score for enUmeration of Mortality
V(p)-POSSUM	Vascular (physiology only) Physiological and Operative Severity Score for enUmeration of Mortality
VBHOM	Vascular Biochemical and Haematological Outcome Model
WHO	World Health Organisation

Summary

Major vascular surgery is associated with a substantial risk of cardiovascular events and death. This risk is of increased importance in prophylactic elective open Abdominal Aortic Aneurysm (AAA) repair, where a balance of risk of rupture and postoperative outcome is assessed prior to management decisions. Further, the UK Small Aneurysm Trial has shown that prophylactic repair of an AAA has no survival benefit for the first three years due to the major adverse cardiac event (MACE) rate of 5-15%. There is however no ideal method of predicting this risk.

Cardiac Troponin I (cTnI) is a contractile protein that is a highly sensitive and specific marker of myocardial necrosis. A few case reports have commented on the finding of preoperative asymptomatic elevated cTnI levels and poor outcome in a small number of patients undergoing major vascular surgery. There are however no studies looking at its incidence in the vascular surgical population or its utility as a preoperative marker.

Several studies have noted that B-type natriuretic peptide (BNP), a diagnostic and prognostic marker of heart failure, may have a role in predicting MACE in settings including major vascular surgery. There are no studies that have investigated this role in AAA repair alone.

The aim of this thesis is to investigate the incidence of, and to determine a possible role for, preoperative elevated cTnI in major vascular surgery. The further aim is to determine if a single preoperative BNP level correlated with MACE and all-cause mortality in elective open AAA repair in both the short and long-term. Comparisons to current accepted risk indices in AAA, and a possible role for BNP in EndoVascular Aneurysm Repair (EVAR) will also be investigated.

Patients were recruited in two cohorts:

Firstly, a prospective, 2 year observational single centre cohort study of all patients undergoing a vascular procedure, with an expected cardiac event rate >5%, recruited patients who had no clinical or ECG evidence of myocardial ischaemia. Preoperative cTnI was performed in all and postoperative screening (clinical assessment, ECG and cTnI) for cardiac events was performed at days 2, 5 and 30.

213 patient were recruited, of whom 11 (5.2%) had an asymptomatic elevated preoperative cTnI (>0.02 ng/ml). Eight of these patients proceeded directly to theatre, and 2 were delayed but later underwent surgery with a persistently elevated cTnI. Of these 10 patients, 5 (50%) died and 4 (40%) suffered MACE. The remaining patient was delayed due to the poor outcome of the preceding patients, and later underwent an uncomplicated aortic bifurcation graft with a normal cTnI level which had been preceded by coronary intervention.

Secondly, a prospective, 2 year observational multi-centre cohort study in the 3 largest vascular units in Glasgow (Gartnavel General Hospital, Glasgow Royal Infirmary and Southern General Hospital) was performed between August 2005 and August 2007, recruiting all patients who were admitted for both elective open AAA repair and EVAR. Preoperative BNP levels were performed and batch analysed at the end of the study. Postoperative screening for cardiac events was performed as described above. Data was collected to allow calculation of risk indices associated with outcome in AAA repair (Glasgow Aneurysm Score [GAS], Vascular physiology only Physiological and Operative Severity Score for enUmeration of Mortality [V{p}-POSSUM], Vascular Biochemical and Haematological Outcome Model [VBHOM], Revised Cardiac Risk Index [RCRI] and Preoperative Risk Score of the Estimation of Physiological Ability and Surgical Stress Score [PRS of E-PASS]). Follow-up was continued to a minimum of 3 years, where possible, with cause of death recorded.

106 of 111 patients were recruited. The median [interquartile range] BNP concentrations in the 16 patients (15%) who suffered immediate postoperative MACE was 206 [118-454] vs 35 [17-61] pg/ml in the remainder (p=0.001). ROC analysis indicated a BNP concentration of 99.5 pg/ml best predicted MACE (area under the curve 0.927), with sensitivity of 88% and specificity of 89%. The BNP in patients who suffered cardiac death was significantly higher than in those that did not (median BNP 496 [280-881] vs 38 [18-84] pg/ml, p=0.043). ROC analysis revealed a cut-off of 448 pg/ml (AUC 0.963), with sensitivity 80%, specificity 100%, positive predictive value 100% and negative predictive value 99%.

Not only did higher values of BNP predict MACE, but it was also found to predict all-cause mortality in the immediate (median BNP 100 [84-521] vs 35 [17-81], p=0.028), intermediate (median BNP 201 [97-496] vs 35 [17-73], p<0.001) and long-term (median BNP 98.5 [58-285] vs 32 [17-71.5], p<0.001) postoperative periods. ROC analysis revealed decreasing BNP levels to predict outcome over time, with a BNP of >60.5 pg/ml (AUC 0.761) found to best predict death at 3 years.

Whilst BNP was found to predict outcome, most risk indices performed poorly. The GAS, VBHOM and RCRI performed poorly and did not predict any outcome measure. V(p)-POSSUM was, however, found to predict all outcome measures (p=0.028, p=0.030, p=0.038 for MACE, cardiac death and all-cause mortality respectively). The PRS component of E-PASS was found to predict MACE (p=0.019) and cardiac death (p=0.017). BNP performed better than any risk index.

During the study period only 40 of 42 patients admitted for elective EVAR were recruited. Of these 40, only 3 suffered a non-fatal MI and 1 died of respiratory failure. BNP was not found to predict MACE or death in this cohort, and due to the small number of patients, and events, no strong conclusions could be drawn.

Whilst preoperative elevated cTnI was found to identify patients that were at an increased risk of both postoperative MACE and death following their major vascular surgical procedure, its use in elective open AAA repair is limited due to infrequent occurrence. Preoperative serum BNP concentration, however, predicted postoperative MACE, cardiac death and all-cause mortality in patients undergoing elective open AAA repair on immediate, intermediate and long term follow-up. Further, BNP performed better than any current risk index for elective open AAA surgery. This simple blood test, therefore, offers valuable information regarding risk stratification of prospective surgical patients and should be considered a part of routine preoperative assessment in this prophylactic procedure.

Chapter 1

Introduction

1.1 Perioperative Cardiac Events – the Extent of the Problem

Patients undergoing major non-cardiac surgery are at significant risk of cardiovascular morbidity and mortality. It is estimated that in Europe 40 million surgical procedures are performed annually with a postoperative myocardial infarction (MI) rate of 1% (400,000) and a cardiovascular mortality rate of 0.3% (133,000).[1] The true extent of the problem is likely to be considerably worse with further pooled analysis of several large studies finding a 30-day incidence of cardiac events (perioperative MI or cardiac death) of 2.5% in unselected patients over the age of 40 years.[2] These complications were highest in vascular surgery patients, who had an incidence of 6.2% for cardiac events.[3] The high frequency of perioperative cardiac complications reflects the high prevalence of underlying coronary artery disease, present in severe form in 28% of patients undergoing infrainguinal arterial reconstruction and 36% of patients undergoing abdominal aortic aneurysm repair

. Screening asymptomatic individuals for perioperative cardiac events following high risk vascular procedures can further amplify these figures, with abdominal aortic aneurysm (AAA) repair resulting in cardiac event rates of up to 25%.[4]

In Scotland the problem is exacerbated by the high incidence of coronary artery disease due in part to the high levels of obesity, hypertension and cigarette smoking, making Scotland a high risk population. The impact on those that suffer a perioperative cardiac event is considerable with hospital mortality rates of 15-25% following non-fatal MI[5,6] and 65% following a cardiac arrest.[7] For those that survive, the length of hospital stay increases and health costs swell. In addition the risk of further non-fatal MI and cardiac death in both the short and long term following surgery is greater than before.[8,9] Perioperative cardiac risk should therefore be a serious consideration prior to planning any surgical procedure.

1.2 Abdominal Aortic Aneurysm Repair – A Unique Problem

An abdominal aortic aneurysm is defined as an abnormal dilatation of the abdominal aorta with a maximal diameter ≥30mm.[10] AAAs are a common disease in the elderly affecting some 4-10% of males and 0.5-1.5% females aged 65-79 years old.[11,12] Over time, despite the vast majority remaining asymptomatic, AAAs expand in size. The risk of rupture of an AAA increases with size with an estimated 25% per year rupture rate for aneurysms ≥6 cm and a 25% 5-year rupture rate for those >5.5 cm [Figure 1.1].[13]

The mortality after AAA rupture is high at approximately 80% for those who reach hospital and 50% for those undergoing emergency surgery for ruptured aortic aneurysm.[15,16] This is reflected in that 1.5% (7000) of all UK male deaths are attributable to AAA mortality.[15]

The rationale for elective surgical treatment of AAAs is based on the natural history of aneurysms, progressive expansion leading to rupture, and in the absence of established effective medical therapy. Symptomatic AAAs require surgical repair to relieve symptoms and to reduce the risk of impending rupture. Asymptomatic aneurysm management is dependent on size. The risk of rupture of an AAA <4 cm is in the order of 2%/year which makes elective open repair with its perioperative mortality of around 5-6% an unattractive option.[17, 18] Large AAAs with a maximal diameter of >6 cm are generally considered for repair as the risk of rupture outweighs the surgical risk.

Figure 1.1 Survival without abdominal aortic aneurysm (AAA) rupture by size category of last measured aortic diameter.
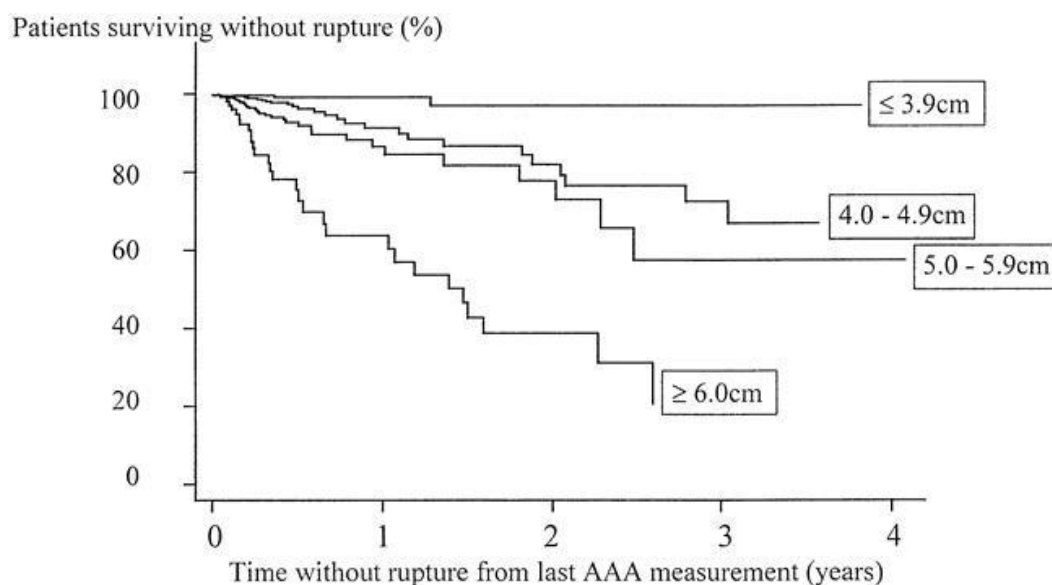
The above graph shows survival without AAA rupture from the last measurement of aortic diameter up to the time of aneurysm repair, death, AAA rupture, or cessation of follow-up. This analysis does not provide an estimate of rupture rates but allows assessment of how the risk of rupture varies with the last known AAA diameter. The much-higher risk of rupture in patients with aneurysms ≥6.0 cm is shown clearly. The number of ruptures per 100 patient-years increased from 0.3 for AAA ≤3.9 cm to 1.5 and 6.5 for patients with AAAs in the diameter ranges 4.0 to 4.9 cm and 5.0 to 5.9 cm, respectively. The person-years of follow-up for patients with AAAs ≥6.0 cm was so restricted by censorship at surgery that no estimate of rupture rate was calculated, although the rate of rupture appeared very high. Figure adapted from [14].

The decision on whether to repair AAAs with a diameter of between 4 and 5.5 cm (the 'small' aneurysm) is a more difficult one. The only appropriate randomised controlled trial that has been designed to address this question is 'The UK Small Aneurysm Trial'.[18] This study recruited greater numbers than originally powered for and obtained 100% follow-up. The trial included 1090 men and women aged 60-76 years with asymptomatic AAAs of anteroposterior diameter 4.0-5.5cm. Patients were identified in centres throughout the UK and were randomised (using computerised allocation) to open elective surgery or routine ultrasound surveillance every 6 months (3 months if diameter 5.0-5.5cm). This high operative mortality (5.8%), primarily cardiac in origin[19], meant that there was a greater risk of death from surgery than from any other cause in the observation group for the first three years of follow-up. Survival was subsequently worse in the surveillance group so that the survival curves crossed at about 3 years, although this has never reached statistical significance even after 12 years of follow-up [Figure 1.2].[20] Thus, the evidence to date does not support the routine surgical repair of aneurysms <5.5cm in diameter.

Attempts to reduce the high level of cardiac postoperative mortality associated with open elective AAA repair led to the development of endovascular aneurysm repair (EVAR), where stenting of the aneurysm using similar interventional techniques to that of angiography is performed. Major trials of EVAR have shown that whilst perioperative mortality is lower (1.7% 30-day mortality in EVAR 1 trial)[21], there is a constant level of device failure which requires regular surveillance with consequent increased cost (postoperative complications at 4 years 41% EVAR group vs 9% open group).[22] In addition the all cause mortality at 4 years was found to be similar in both groups. This led to the realisation that EVAR would not be the first choice for all patients given the lower morbidity and greater long term survival after open elective repair, especially in the young fit patient.

Figure 1.2 Overall survival by treatment group.
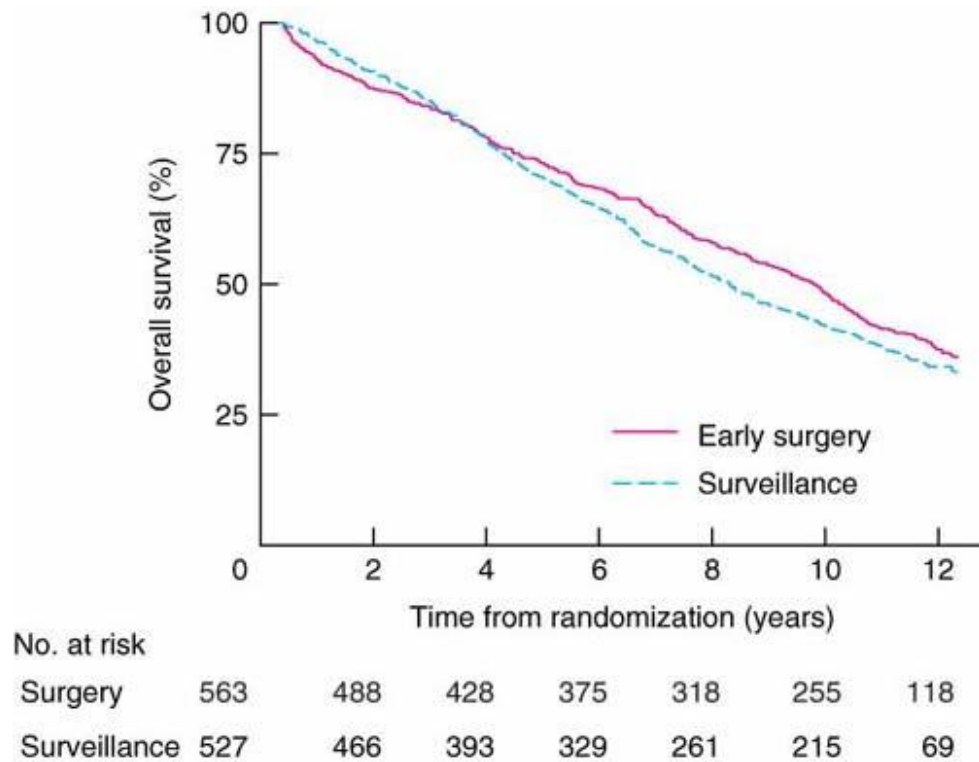
At 3 years mortality after early surgery was less than that of ultrasound surveillance, however this difference did not reach statistical significance. After 12 years, mortality in the surgery and surveillance groups was 63.9 and 67.3 per cent respectively, unadjusted hazard ratio 0·90 (p=0.139). Figure adapted from [20].

In view of the findings of the 'UK Small Aneurysm Trial' and EVAR 1 trial, any development that would allow the identification of those at high risk of perioperative cardiac morbidity or mortality would greatly improve management. Low risk patients could be offered open elective repair of even small aneurysms, leading to longer survival and the avoidance of the long-term morbidity associated with EVAR use. Equally, identification of high risk patients who would not survive an open procedure could lead to them being offered an endovascular repair or of delaying surgery altogether until the risk of rupture was felt to outweigh that of prophylactic repair.

1.3 The Pathophysiology of the Perioperative MI

1.3.1 Non-Cardiac Surgery

The pathophysiology of perioperative cardiac events is not entirely clear with little data on the topic; however, it is believed that in the perioperative period around half of all cardiac complications are caused by coronary plaque rupture with subsequent thrombus formation and coronary artery occlusion[23] and the remainder by prolonged myocardial ischaemia.[24] This distinction occurs as a result of histopathological autopsy analyses of coronary arteries and the myocardium of patients who suffered perioperative fatal MIs, revealing direct evidence of plaque disruption (fissure or rupture of plaque and haemorrhage into the plaque cavity) in 55% of cases, with the site of infarction commonly correlating with the affected vessel.[24] Similar autopsy results were found in further histological analyses of 1841 autopsy records with 26 cases of postoperative MI of whom 46% had plaque rupture with confirmed transmural infarctions within their territory.[25]

The evidence for severe or prolonged myocardial ischaemia is based on a number of findings. The presence of a circumferential distribution of infarction on pathological specimens is consistent with myocardial supply/demand mismatch as the trigger of myocardial injury.[25] Further, most perioperative MIs are asymptomatic and are characterised by ST-segment depression, reflecting subendocardial ischaemia.[26] In addition, almost all perioperative MIs are non-Q-wave rather than Q-wave with complete reversal of ECG changes to baseline in nearly all patients with ischaemia (including those with infarction).[27] The likelihood however is that myocardial ischaemia and plaque rupture are not mutually exclusive and that MIs can develop by different mechanisms at different locations in the same patient. For this reason it is the triggers of perioperative MIs that are the key to these cardiac events.

Surgery, with its associated trauma, anaesthesia and analgesia, intubation and extubation, pain, hypothermia, bleeding and anaemia, and fasting, is analogous to an extreme stress test. Increasing grades of surgical trauma and general anaesthesia can initiate inflammatory and hypercoagluable states which may have a role in plaque fissuring and acute coronary thrombosis.[28, 29] The stress state involves increased levels of catecholamines and cortisol resulting in increases of blood pressure, heart rate and coronary artery sheer stress.[30] Coronary artery sheer stress may trigger plaque fissuring and coronary thrombosis, while the haemodynamic changes may be responsible for increased myocardial oxygen demand resulting in perioperative myocardial ischaemia. Further to this a hypoxic state can be initiated by anaemia, hypothermia (through shivering) and analgesia (through respiratory depression).[31-33] Perioperative hypoxia can result in further myocardial ischaemia in the setting of haemodynamically significant coronary artery stenosis. Further research is awaited to determine which triggers are most important in preventing perioperative MIs [Figure 1.3].

Figure 1.3 Potential triggers of states associated with perioperative elevations in troponin levels, arterial thrombosis and fatal myocardial infarction.
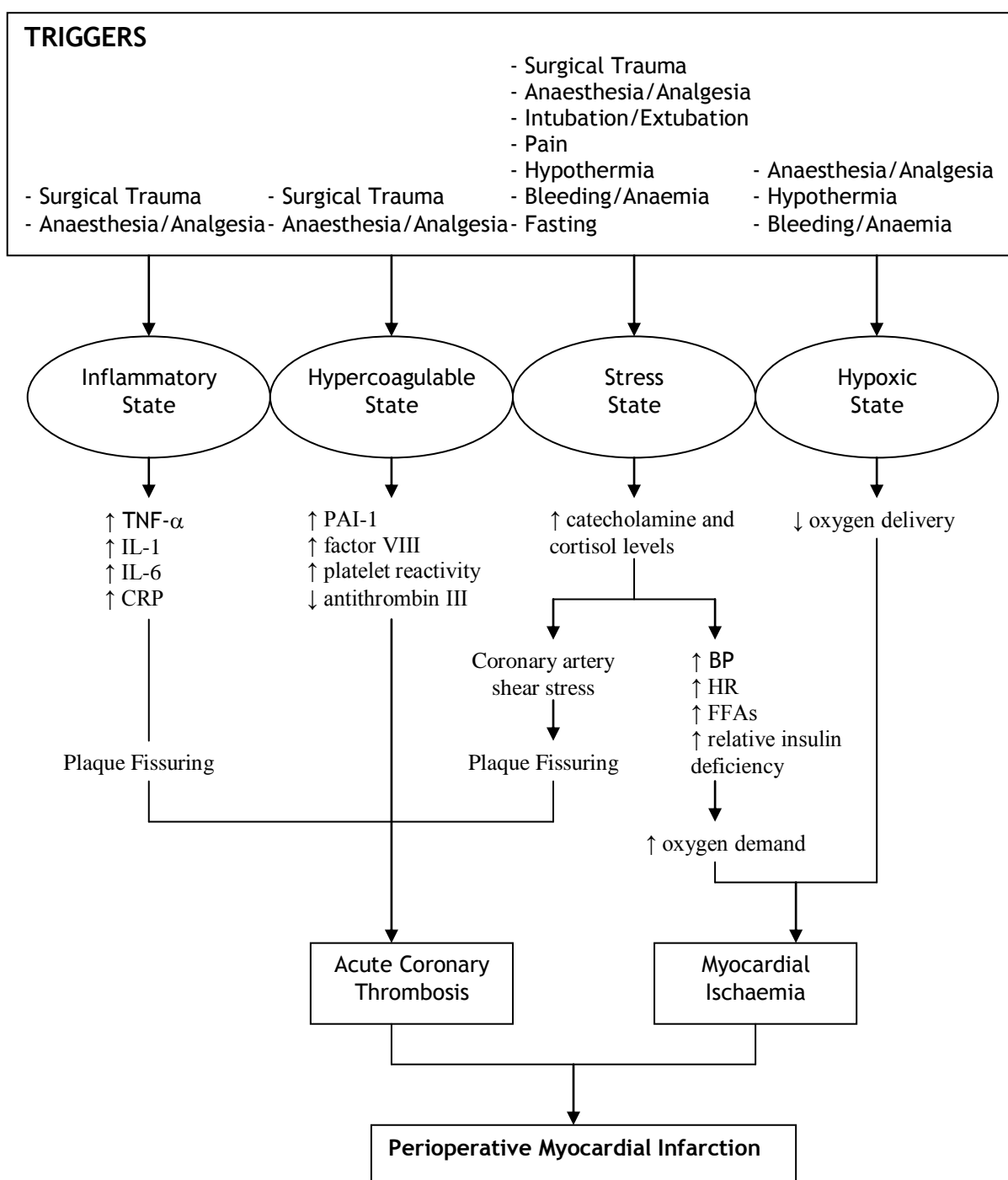
The numerous potential triggers of a perioperative myocardial infarction impact in different ways when considering the pathophysiology of a cardiac event. It remains unknown which factor/trigger is most important. TNF-α = tumour necrosis factor-α, IL = interleukin, CRP = C-reactive protein, PAI-1 = plasminogen activator inhibitor-1, BP = blood pressure, HR = heart rate, FFAs = free fatty acids. Figure adapted from [34].

1.3.2 Abdominal Aortic Aneurysm Repair

Surgical repair of an AAA provides further haemodynamic changes that further risk the myocardium. The basic surgical procedure in open repair of an AAA includes clamping the aorta, opening the aortic sac, suturing in a prosthetic graft to replace the aneurysmal artery and then unclamping the aorta. The initial response to clamping the aorta is arterial hypertension due to impedance of aortic flow and left ventricular ejection producing increased afterload, with no significant effect on heart rate. The more proximal the clamp placement the greater the rise in blood pressure. Infrarenal clamping can increase blood pressure 7-10% with an increase in afterload. The systemic vascular resistance can increase up to 40% and the effect on cardiac filling pressures, further exacerbated by reduced preload due to a decreased venous return, is variable resulting in a reduction of cardiac output by 9-33%.[35] Infrarenal clamping is often well tolerated in patients with preserved ventricular function, but in the presence of significant dysfunction it can precipitate ischaemia and heart failure.[36]

Unclamping the aorta after repair causes a reduction in blood pressure due to an abrupt decrease in systemic vascular resistance, and central hypovolaemia secondary to sequestration of blood into reperfused tissues. There is also a reperfusion injury with mild acidaemia, and circulation of released vasodilators and myocardial depressants. This all contributes to hypotension and myocardial dysfunction. To counteract this surgeons and anaesthetists frequently ensure that their patients are volume-loaded prior to releasing the cross-clamp, and that cross clamping times are kept to a minimum.[37]

The effects of cross-clamping and unclamping with regards to myocardial function and coronary blood flow are well documented. Increased preload and afterload associated with aortic cross-clamping lead to an increase in myocardial oxygen demand. In patients without coronary artery disease, the myocardial oxygen supply is usually adequately increased by increased coronary blood flow and preservation of myocardial autoregulation and endocardial-epicardial flow rates, thereby avoiding severe myocardial ischaemia and maintaining myocardial contractility.[38] However, in patients with atherosclerotic coronary artery disease, both left and right filling pressures increase, and ECG evidence of myocardial ischaemia can be demonstrated[39-41] indicating an inability to increase subendocardial blood flow in response to an increase in intra-ventricular pressure. Echocardiography and ventriculography findings in post-myocardial infarction patients after cross-clamping reveal that those with pre-existing impaired myocardial contractility or increased left ventricular end-diastolic volumes cannot further mobilise the Frank-Starling mechanism. A decrease in the velocity and contraction of myocardial fibres can then occur and they then proceed to develop left ventricular failure in response to myocardial ischaemia and release of myocardial depressant factors from ischaemic tissue.[42] It is clear therefore that open AAA surgery provides a substantial threat to cardiac outcome in patients who are often already high risk candidates.

1.4 Diagnosing Perioperative Cardiac Events

1.4.1 The Difficulty in Detection

It is already known that MIs occur unnoticed outwith the operative setting. A review of eight large cohort studies with samples over 100 evaluating the frequency of unrecognised MIs (based on the appearance of new diagnostic Q waves) revealed that of 65,000 people 3,237 MIs occurred, of which 945 (29%, 95% CI 28-31%) were not detected at the time of the event.[43] In addition patients experiencing an unrecognised MI were shown to have a prognosis similar to that of patients with a recognised MI.[44]

The scale of the problem of perioperative clinically unrecognised MI is demonstrated by three large prospective cohort studies of non cardiac surgery. The studies, all with sample sizes greater than 300 and unrestricted surgery type, with at least one postoperative measurement of cardiac enzyme/biomarker and accountability of signs/symptoms revealed that only 14% (95% CI 3-25%) of patients complained of chest pain and 53% (95% CI 38-68%) had clinical signs or symptoms recognised by medical staff to imply an MI.[5,6,45] Although the total number of events was small (38/1309, 3%), the large proportion of these events which were clinically unrecognised is concerning. This can however be reasoned as most perioperative MIs occur during the first 3 days after surgery[6,46] during which time most patients receive analgesics blunting cardiac pain perception. Further, patients experiencing potential signs (tachycardia, hypotension etc.) may have these mistaken for other more common postoperative explanations such as hypovolaemia, epidural anaesthesia, bleeding, medication effects, atelectasis or sepsis. Some patients may remain intubated and sedated in this high risk period leading to difficulty in communicating the development of an event.

1.4.2 Methods of Diagnosis

Currently there are no standard agreed diagnostic criteria for perioperative MI in patients undergoing noncardiac surgery. For MI in general the World Health Organisation (WHO) definition, described in the mid-80s, requires at least two of three criteria to be met including 1) ischaemic type chest pain lasting greater than 20mins, 2) change in serial ECG tracings including the development of pathological Q waves and 3) increased concentration of serum creatine kinase-MB (CK-MB) fraction.[47] The development of assays for the cardiac troponins T (cTnT) and I (cTnI) that are highly specific and sensitive to myocardial injury led to a revision by the European Society of Cardiology and the American College of Cardiology (ESC/ACC) [Table 1.1].

This gave more prominence to cardiac biomarkers so that the definition of an acute, evolving or recent MI required a typical rise and gradual fall of cardiac troponin or a rapid rise and fall of creatine kinase isoenzyme MB (CK-MB) accompanied by at least one of 1) typical ischaemic symptoms; 2) pathological Q waves; 3) ECG changes indicative of ischaemia; 4) coronary intervention (including percutaneous intervention or coronary artery bypass graft).[48] Of the cardiac biomarkers named, the use of CK-MB in the perioperative setting has been avoided as measurements are prone to false-positive and false-negative values. This is in part due to surgical trauma resulting in the release of CK-MB from skeletal muscle and a false–positive CK-MB value for MI.[49,50] Furthermore, a significant proportion of perioperative MIs occur early after surgery, when creatine kinase values will be high following surgical trauma. These high values of creatine kinase can therefore result in a low ratio of CK-MB to creatine kinase levels resulting in false negative measurements.[50,51]

Table 1.1 Diagnostic criteria for non-perioperative MI of the ESC/ACC.

Definition of MI.

Criteria for acute, evolving or recent MI -
Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI:

1. Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:

    - Ischaemic symptoms
    - Development of pathologic Q waves on the ECG
    - ECG changes indicative of ischaemia (ST segment elevation or depression)
    - Coronary artery intervention (e.g. coronary angioplasty).

2. Pathologic findings of an acute MI.

Criteria for established MI -
Any one of the following criteria satisfies the diagnosis for established MI:

1. Development of new pathologic Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed.
2. Pathologic findings of a healed or healing MI.

The redefined definition of an MI published in 2000 highlights the importance of new and established cardiac biomarkers. Adapted from [48].

As described, perioperative MI is often silent and clinicians may not be alerted to the possibility. In addition, many patients have an uninterpretable ECG due to bundle branch block, chronic ST changes and pacing. Some will have infarcts in areas where conventional ECG lacks sensitivity (e.g. posterior) and some will have significant ST-segment changes that resolve by the time the ECG is repeated the following day. In an attempt to reduce the risk of missing MIs use of echocardiography has been advocated. The evidence for this is however contradictory since echocardiography has been shown to be insensitive due to the requirement of a myocardial injury involving >20% of the wall thickness to detect a wall motion abnormality.[48] This is challenged by a study revealing a new wall-motion abnormality in 8 of 9 patients who suffered a perioperative MI from 108 noncardiac surgery patients.[50] None of the remaining 99 patients had new wall-motion abnormalities although those that were considered to have had a perioperative MI were based on criteria of elevated troponin and significant ECG changes. This makes it difficult to know if echocardiography would pick up a new perioperative MI that was not picked up by conventional criteria. It is not unreasonable, however, that when clinicians come across a patient with an elevated troponin after surgery without either ischaemic symptoms or a diagnostic ECG, they should consider obtaining an echocardiogram. Further research is needed to evaluate the diagnostic criteria for a perioperative MI and to clear inconsistencies.

1.5 Risk Stratification

For over 40 years researchers have been studying perioperative cardiac risk and how best to estimate it. The goal of improved risk stratification is important for allowing accurate informed decisions, both by the patient and their physicians. Although no research has documented its benefits, risk stratification has taken on an important role in clinical decision-making. Accurate risk estimates provide guidance for perioperative management, including the choice of surgical techniques and the location and intensity of postoperative care. Improved accuracy is considered especially critical today with the demands for cost containment and the increasing age of the population.

Preoperative clinical evaluation is an important part of the routine workup to any operative procedure. In non-cardiac vascular patients a thorough history, physical examination and routine ECG can aid assessment of cardiac risk. Patients in this group without a previous MI, angina, diabetes, congestive cardiac failure and with a normal resting ECG have been reported to be at very low cardiac risk (<1%) for major perioperative cardiac complications.[52,53] This can therefore identify a subgroup of low risk patients; however, separating the remaining patients into categories based on degree of risk can be more complicated.

Clinical history can also help estimate functional status in order to calculate perioperative risk. Functional capacity can be expressed in metabolic equivalents (METs). Multiples of the baseline MET value can be used to express aerobic demands for specific activities [Table 1.2].[54] One MET is equivalent to the oxygen consumption of a resting 70 kg 40-year-old male, while 10 METs would be equivalent to participation in strenuous sports such as swimming or singles tennis. A low functional capacity is defined as the inability to perform more than 4 METs of activity. A decreased functional capacity (inability to walk 600m or climb 2 flights of stairs) has been shown to be an independent predictor of perioperative cardiac events,[55] with a positive predictive value (PPV) of 89% for cardiopulmonary complications.[56] Patients with severe limitations of function, such as those who are close to or bedridden, have been shown to have a greater risk of cardiac events.[57] With its emphasis on identifying high risk patients this system is a poor predictor of complications in patients at intermediate risk. A number of risk identification strategies have therefore been developed to help further separate these groups.

Table 1.2 Estimated energy requirements for various activities.

1 MET	• Eating, dressing and using toilet.
	• Walking indoors around the house.
	• Walking around a block or 2 on level ground at 2 to 3 mph (3.2 to 8.4 kph).
	• Doing light work around the house such as dusting or washing dishes.
4 METs	• Climbing a flight of stairs or walking up a hill.
	• Walking on level ground at 4mph (6.4kph).
	• Running a short distance.
	• Doing heavy work around the house like scrubbing floors or lifting or moving heavy furniture.
	• Participating in moderate recreational activity like golfing, bowling, dancing or doubles tennis.
Greater than 10 METs	• Participating in strenuous sports like swimming, singles tennis, football or skiing.

Calculating metabolic equivalents based on daily activities makes estimation of functional status in the clinical situation uncomplicated, although this relies on subjective information. kph - kilometres per hour, MET - metabolic equivalent, mph - miles per hour.

1.5.1 Risk Index Systems

The original stratification system for perioperative risk assessment was the Dripps Index of the American Society of Anaesthesia (ASA), published in 1961 [Table 1.3].[58] It remains in clinical use today, classifying patients into 5 physical status classes, with class 1 being a completely healthy patient and class 5 being patients considered moribund and in whom surgery is undertaken as a last resort. Limitations of the ASA physical status are that it is a subjective index and that it has been found not to be predictive of cardiac outcome.[59]

The more recent clinical indices can be split into two types – generic and Bayesian. The published generic indices (Lee, Goldman, Eagle) estimate a patient's risk through determination of how many predictors of risk (e.g. diabetes, angina, congestive cardiac disease) the patient has. The published Bayesian risk indices (Detsky) modify the hospital's average cardiac event rate for a specific surgery (pretest probability) through use of a patient's individual index score (likelihood ratio), which is based on how many predictors of risk the patient has. This results in an estimate of the patient's risk of a perioperative cardiac event (post-test probability).

Table 1.3 ASA grading and mortality in the anaesthetised general population.

ASA	Grade Definition	Mortality (%) - in general
I	Normal healthy individual	0.05
II	Mild systemic disease that does not limit activity	0.4
III	Severe systemic disease that limits activity but is not incapacitating	4.5
IV	Incapacitating systemic disease which is constantly life-threatening	25
V	Moribund, not expected to survive 24 hours with or without surgery	50

Postoperative mortality associated with increasing degrees of ASA class, published in 1961 and based on subjective information. ASA – American Society of Anaesthesia. Adapted from [58].

The first generic multifactorial risk index for cardiac complications was published by Goldman in 1977. [60] Goldman's cardiac risk index based on 1001 consecutive patients (>40 years of age) was the first validated multivariate model to be used in non-cardiac surgery for predicting cardiac morbidity and mortality. Nine risk factors were identified and weighted, based on their ability to predict postoperative cardiac death or MI, congestive cardiac failure or ventricular tachycardia. A history of a previous MI or the presence of an S3-gallop rhythm were the strongest predictors. A patients cardiac risk score was calculated on the basis of the number and corresponding weight of risk factors, with scores ranging from 1 to 4 (4 representing the highest risk). The most obvious limitation of this cardiac index was the lack of ability to take into account the specific risk of any given surgical procedure.

In order to improve the predictive accuracy in patients undergoing major vascular surgery, Detsky produced a modified cardiac risk index in 1986 using a Bayesian approach.[61] Surgical risk was incorporated into the index using the institution's average cardiac event rate for particular surgical procedures (as the pretest probability) which was then modified by a number of patient-specific risk factors. The presence of significant angina was included and the presence of an old or recent MI was differentiated. To simplify further, the number of risk classes was decreased from 4 to 3. This modified index fulfilled the methodological criteria of a clinical prediction rule study and has shown consistent results in a separate setting. This validation however is limited to one high-quality single-centre study[62] and the current predictive accuracy of the Detsky index is uncertain. This is due in part to the Bayesian approach where the defined average surgical risk for a particular hospital for a particular procedure at a particular time is used. It is not known at present if the complication rates at one institution are transferable to others when using the same defined risk factors. The advances in medical therapy for cardiac disease and improvement in anaesthetic and surgical techniques also question the applicability in the modern age.

More recent risk scoring systems have been developed by Eagle[63] and Lee.[64] Both systems use multivariate analysis to identify preoperative clinical factors that are predictive of perioperative cardiac events. Both arrived at 6 similar risk factors although the Eagle score included the findings of myocardial thallium scanning in patients presenting for major vascular surgery. Due to limited thallium scanning availability and cost the Revised Cardiac Risk Index (RCRI), developed in 1999 by Lee et al, has become the most widely used model of risk assessment in noncardiac surgery. This risk index assigns one point each for the presence of 6 independent risk factors for major cardiac complications in patient undergoing major elective surgery [Table 1.4]. The incidence of major adverse cardiac events in patients with 0, 1, 2 or 3 risk factors were 0.4%, 0.9%, 7% and 11% respectively in the validation cohort. Recently it was demonstrated in 108,593 patients undergoing all types of noncardiac surgery that this RCRI was indeed predictive of cardiovascular mortality but could be substantially improved by adding age and a more detailed classification of type of surgical procedure.[65] This is especially relevant to AAA surgery as open abdominal aortic surgery carries a higher risk than either intraperitoneal or intrathoracic surgery.[62, 66]

Table 1.4 Risk factors from the Revised Cardiac Risk Index.

- High-risk surgery
– Intraperitoneal, intrathoracic or suprainguinal vascular procedures
- Ischaemic heart disease
- History of congestive heart failure
- History of cerebrovascular disease
- Insulin therapy for diabetes mellitus
- Preoperative creatinine level > 2.0 mg/dl (>176μmol/l)

Ischemic heart disease was defined as those with major cardiac complications included any of the following: history of myocardial infarction, history of a positive exercise test, current complaint of chest pain considered to be secondary to myocardial ischaemia, use of nitrate therapy, or ECG with pathological Q waves. Congestive heart failure was defined as the presence of any of the following: history of congestive heart failure, pulmonary oedema, or paroxysmal nocturnal dyspnoea; physical examination showing bilateral rales or S3 gallop; or chest radiograph showing pulmonary vascular redistribution. Cerebrovascular disease was defined as a history of transient ischemic attack or stroke.

1.5.2 ACC/AHA Algorithm

The American College of Cardiology (ACC) and the American Heart Association (AHA) published a consensus statement on the preoperative cardiac evaluation of patients presenting for noncardiac surgery in 1996,[67] which was updated in 2001[68] and again in 2007.[69] This was based on expert opinion to help clarify an important step of operative work-up, given that there were few meaningful trials existing on the topic. The consensus produced an algorithm that included factors about the patient and their medical history whilst also taking into account the specific type of surgery [Figure 1.4]. The first step in the algorithm was to establish if there was a need to assess cardiac risk based on the urgency of surgery. In patients undergoing elective surgery, the need existed and so the next stage was to identify those with active unstable cardiac conditions including acute or recent MI (<1 month), severe or unstable angina, decompensated heart failure, significant arrhythmia or severe valvular heart disease. In these conditions, intensive management was recommended with surgical delay or cancellation if necessary.

Figure 1.4 ACC/AHA 2007 preoperative cardiac evaluation before non-cardiac surgery.
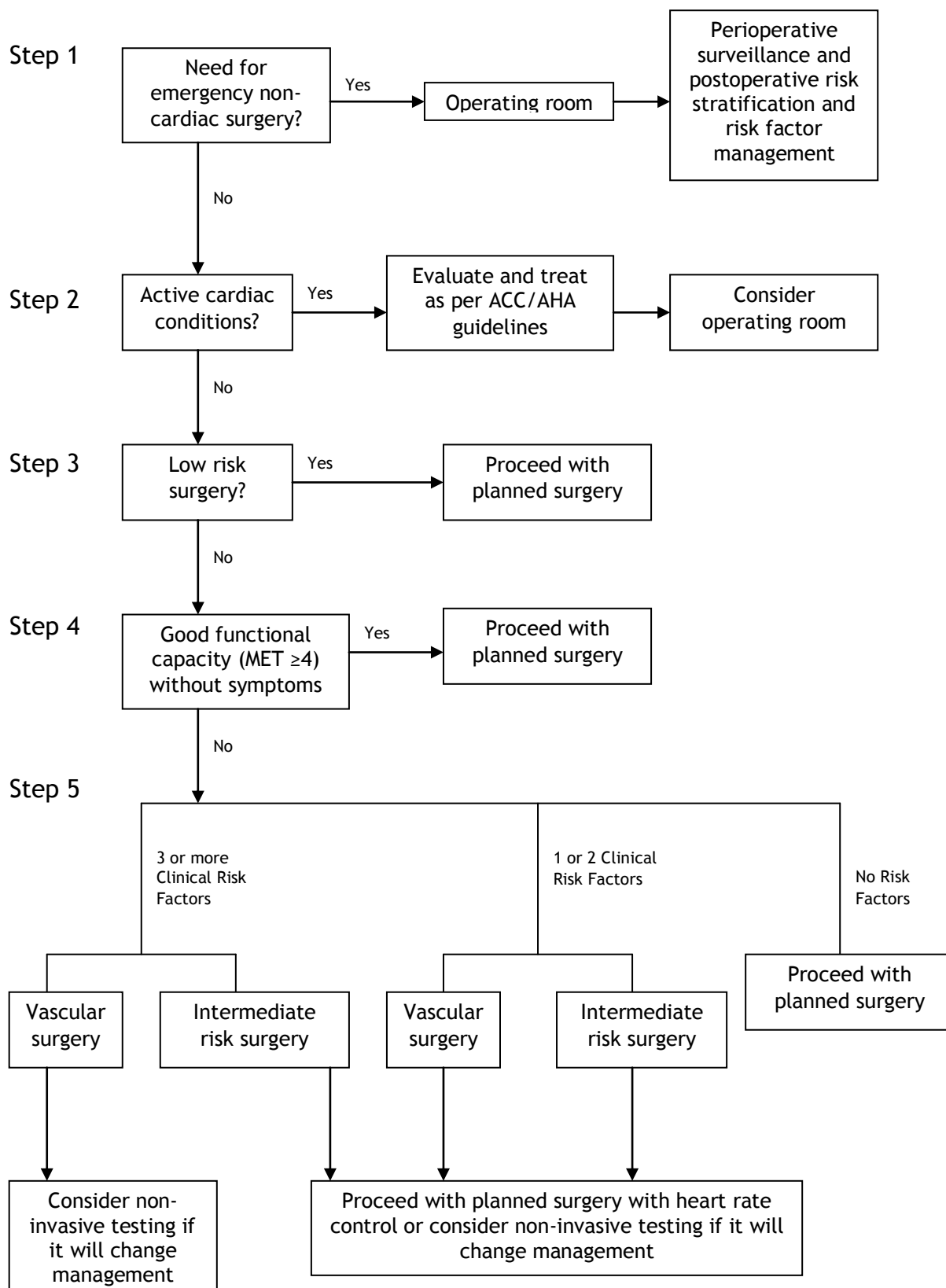
Adapted from [69].

In those presenting for low risk surgery, the procedure could take place as planned. If however the procedure was of higher risk, then an estimation of functional status was made. Only those patients achieving a MET level of ≥4 would then proceed to surgery. For the remainder, an estimation of patient specific clinical risk was required using the Lee RCRI, adapted to exclude the type of surgery which was incorporated elsewhere in the algorithm. Patients were then divided into groups based on the number of clinical risk factors (those of Lee's revised cardiac risk index excluding high risk surgery) and the surgical risk. The recommendation was for preoperative cardiac testing for elective vascular surgery patients with ≥3 clinical risk factors and poor functional capacity. Preoperative testing could also be considered in those with 1-2 clinical risk factors and poor functional capacity for intermediate risk non-cardiac surgery, or good functional capacity undergoing vascular surgery. Preoperative testing was not recommended for patients without clinical risk factors undergoing intermediate- or low-risk non-cardiac surgery.

The validity of these guidelines has been evaluated in only a few prospective or randomised studies. One prospective evaluation published in 1997 was performed using a similar protocol to the ACC/AHA guidelines in 203 patients presenting for aortic surgery.[70] In this study patients identified as being at intermediate risk (n=79) with an estimated functional capacity of <4 METs and all patients at high risk (n=23) underwent non-invasive testing and/or subsequent medical care. The results showed that the algorithm predicted outcome with total cardiac morbidity in the low, intermediate and high-risk categories of 9%, 14% and 24% respectively. In a similar retrospective study the use of dobutamine stress echocardiography (DSE) was studied in accordance with ACC/AHA guidelines in 85 patients undergoing non-cardiac surgery.[71] This study found that the ACC/AHA guidelines had a positive predictive value of 4.7% for selecting patients with a positive DSE. During the perioperative period no patients had a cardiac complication related to myocardial ischaemia. These findings prompted a conclusion that the current ACC/AHA guidelines for non-invasive testing result in a low frequency of positive tests and were of limited value in the clinical setting.

1.5.3 Preoperative Non-Invasive Testing

If indeed it is deemed necessary to perform further non-invasive cardiac stress testing there are a number of options available. The exercise ECG is the most common method of non-invasively evaluating individuals for the presence of coronary artery disease with pooled data from 7 studies indicating a sensitivity of 74% and specificity of 69% for predicting a major adverse cardiac event (MACE, being a non-fatal MI or cardiac death) in major vascular surgery.[72] Exercise ECG testing can be safely performed in the outpatient setting and is considered the least expensive non-invasive test for detecting myocardial ischaemia and providing a good estimate of functional capacity. The limitations of this test are inherent in its nature. Those that cannot reach the target heart rate for age have an inadequate investigation which is common in patients with peripheral vascular disease (claudication), diabetes mellitus (peripheral neuropathy), prior cerebrovascular event, or beta-blockade. Up to 40% of patients also have pre-existing ECG abnormalities such as ST-segment/T wave abnormalities, underlying left-bundle branch blocks or ventricular paced rhythms that may preclude reliable ST-segment analysis.[73] In addition, no information regarding ventricular function can be obtained.

As an alternative to exercise induced stress, pharmacological non-invasive testing is often required in patients undergoing major vascular surgery. Coronary artery vasodilators such as dipyridamole, combined with nuclear imaging or echocardiography, or the use of agents that increase myocardial oxygen demand such as dobutamine combined with echocardiography have both been advocated. The most extensively researched of these is dipyridamole perfusion scintigraphy (DiPS) which has been shown in a meta-analysis of 23 studies to have a sensitivity of 83% and a specificity of 49% for predicting MACE in major vascular surgery.[72] The major limitation of this type of test is the frequent occurrence of false-positive results owing to attenuation artefacts (breast tissue, diaphragm etc.) that can produce apparent perfusion defects.

The most recent recommended non-invasive test is dobutamine stress echocardiography (DSE). Review of 6596 stress tests has shown it to be safe, revealing a low incidence of side effects with cardiac arrhythmias (8%) and hypotension (3%) the most common.[74-76] The feasibility of DSE in patients with abdominal aortic aneurysm has also been confirmed in 98 patients in whom there was no evidence of aneurysm rupture or haemodynamic instability.[77] The sensitivity and specificity on a review of 8 studies of DSE in major vascular surgery were 85% and 70% respectively for predicting MACE [Figure 1.5].[72]

There are only a few studies comparing the prognostic accuracy of these tests used for preoperative cardiac risk assessment. A meta-analysis of 20 studies by Mantha et al[78] comparing the predictive value of DiPS, radionuclide ventriculography (RNV), ambulatory ECG and DSE for perioperative MACE showed that, with the exception of DSE, each test demonstrated a bias for better predictive value in earlier studies. Although DSE appeared to be the best among these tests and ambulatory ECG the least predictive, the analysis was not sufficient to determine the optimal test.[79] A subsequent meta-analysis studied data from 15 papers regarding perioperative screening using DiPS and DSE in 2439 patients undergoing vascular surgery. The development of MACE with a negative DiPS was 3% versus 18% in patients with a reversible defect. The positive predictive value (PPV) of DSE for cardiac death and myocardial infarction were 17% and 26% respectively, while the negative predictive value (NPV) was 99%.

Figure 1.5 Results of meta-analysis evaluating ability of non-invasive cardiac tests to predict risk of perioperative cardiac events in patients undergoing major vascular surgery.
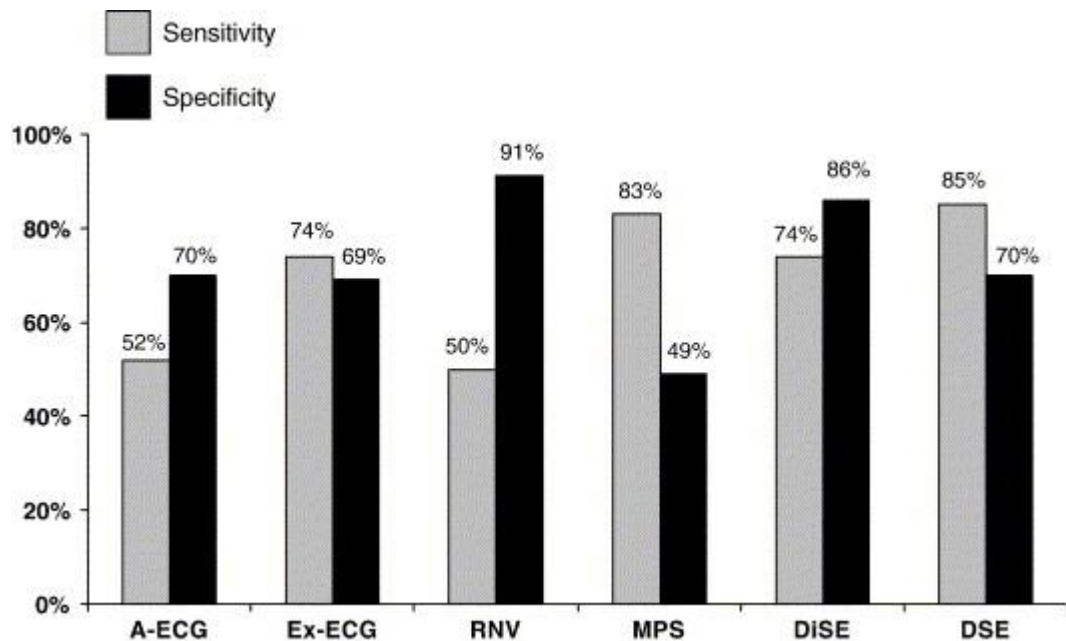
Meta-analysis results of 8119 patients including 8 studies on ambulatory electrocardiography (A-ECG), 7 on exercise electrocardiography (Ex-ECG), 8 on radionuclide ventriculography (RNV), 23 on myocardial perfusion scintigraphy (MPS), 8 on dobutamine stress echocardiography (DSE), and 4 on dipyridamole stress echocardiography (DiSE). Positivity was considered as ST segment depression of ≥1 mm or ST elevation ≥2 mm after J point (measured at 60 ms) lasting at least one minute in A-ECG, development of exercise induced horizontal or down sloping ST depression of 1 mm or more in Ex-ECG, ejection fraction ≤35% in RNV, one or more fixed or reversible thallium-201 myocardial defects in MPS, and new or worsening ventricular wall motion abnormalities in both DiSE and DSE. DSE showed a positive trend towards better diagnostic performance than the other tests, but this was only significant in the comparison with myocardial perfusion scintigraphy. The conclusion of the meta-analysis was that DSE may be the favoured test in situations where there is valvular or left ventricular dysfunction. Adapted from [34] and [72].

Recently Kertai et al compared the predictive value of DSE and dipyridamole stress echocardiography (DiSE) with DiPS in 2204 patients undergoing major vascular surgery.[80] There was no statistically significant difference in the predictive value of a positive test result for either DiSE (OR 37.1, 95%CI 8.1-170.1) or DSE (OR 9.6, 95%CI 4.9-18.4). A positive test result for DiPS however had a significantly lower odds ratio and prognostic capability (OR 1.9, 95%CI 1.2-3.2). In the most recently published meta-analysis by Beattie et al 68 studies including over 10,000 patients undergoing non-cardiac surgery were reviewed.[81] The likelihood of a positive stress echocardiography predicting a cardiac complication was twice that of thallium imaging (OR 4.09, 95%CI 3.21-6.56 vs OR 1.83, 95%CI 1.59-2.10). While one third of all cardiac events occurred in patients with negative cardiac testing, the proportion was significantly higher in those with a negative thallium scan. In addition, the rate of referral for angiography where coronary intervention was not required was twice as high in those that received thallium imaging than in the remainder. Despite these findings no statistically significant difference between thallium imaging and stress echocardiography could be found for either positive or negative tests [Table 1.5].

Table 1.5 Meta-analytic comparison of stress echocardiography versus thallium imaging as a preoperative screening tool.

Variable Analysed	Stress Echocardiography		Thallium Imaging		
	Studies	Likelihood ratio (95% CI)	Studies	Likelihood ratio (95% CI)	p-value
All studies	25	4.09(3.21-6.56)	50	1.83(1.59-2.10)	0.0001
Vascular studies only	19	4.75(3.44-6.56)	39	1.83(1.57-2.13)	0.0001
Studies with blinding only	4	5.52(3.45-8.85)	11	1.73(1.11-2.71)	0.0001
Studies completed after 1995	19	3.75(2.89-4.87)	29	1.79(1.45-2.21)	0.001
Studies with routine screening for MI	12	4.11(2.85-5.93)	10	1.60(1.22-2.08)	0.0001
Direct comparisons of SE to TI	7	3.78(2.10-6.79)	7	1.73(0.96-3.11)	0.16
Quantitative studies (Comparison of ROC*)	9	0.80(0.75-0.84)	13	0.75(0.70-0.80)	0.35
Proportion revascularised†	9	57.5(34.0-81.0)	23	29.0(18.0-30.1)	0.05

Meta-analysis of 68 studies including 10,049 patients, with 25 of Stress Echocardiography (SE) and 50 of Thallium Imaging (TI). Results reveal that positive SE has a likelihood ratio that is 2 times more predictive than a positive TI. SE was found overall to be superior. Further, preoperative SE was shown in this meta-analysis to have a better negative predictive value than thallium scintigraphic imaging (not shown above). MI – Myocardial Infarction, TI – Thallium Imaging, SE – Stress Echocardiography, * - expressed as receiver operating characteristic curve (95% CI), † - expressed as percentage of patients (95% CI). Adapted from [81].

Despite the studies and meta-analyses available there remains a considerable number of limitations. Most of the data available is from small studies, many of which were retrospective with blinding taking place in less than 20% of patients. Screening for MI was not routinely performed and there was no protocol for interventions for a positive test in any study. In addition the data spanned 20 years during which time single-photon computed tomography and magnetic resonance imaging has become the current standard rather than thallium scanning, and significant advances in perioperative management have taken place. As a result there is currently no conclusive evidence to support one cardiac stress test over another. It appears that DSE has a better PPV and NPV than both exercise ECG and nuclear imaging. The degree of positivity of a test also appears important with moderate to large defects on nuclear imaging being associated with a nine-fold increase in MI or cardiac death. Patients with weakly positive nuclear imaging had no significantly increased risk over those with negative tests.[81]

1.5.4 Preoperative Biochemical Markers of Outcome

1.5.4.1 B-type Natriuretic Peptide

Brain (or B-type) natriuretic peptide (BNP) is one of a family of cardiac peptides secreted almost exclusively by the myocardium in a non-specific response to wall stress in association with ventricular dilatation and pressure overload.[82] The physiological effects of BNP include the augmentation of urinary volume (diuresis), sodium excretion (natriuresis), aldosterone antagonism through inhibition of the renin-angiotensin system, sympathetic autonomic nervous system inhibition and direct antiproliferative effects on the cardiac myocytes.[83] These effects result in relaxation of vascular smooth muscle, counteraction of hypertrophy and destruction of the myocyte sarcomere structure.

The synthesis of BNP occurs through a preprohormone. Once produced in the myocardial cells from preproBNP, proBNP is cleaved into the inactive N-terminal fragment (NT-proBNP) and the active hormone BNP_{1-32}. Variable amounts of BNP_{1-32}, NT-proBNP and proBNP itself are released into the circulation. BNP_{1-32} rapidly undergoes breakdown to form the biologically active fragments BNP_{3-32} and BNP_{7-32}. During periods of cardiac strain, up regulation of BNP production occurs with levels of BNP clearly reflecting significant change within 2-12 hours.[84] Although NT-proBNP and BNP (or BNP_{1-32}) are secreted in a 1:1 ratio, serum levels differ due to the longer half life of NT-proBNP. Pre-analytical factors that need consideration include stability of BNP and renal clearance as its parts are cleared by the kidney and thus levels rise as renal function deteriorates.[85] Based on early investigations, it has been commonly accepted that the plasma clearance of NT-proBNP is more dependent on renal function than is that of BNP.[86, 87] More recently however it has been demonstrated that BNP and NT-proBNP correlate well when examined across the spectrum of renal disease and that no clear difference can be shown in chronic renal disease.[85, 88] For each 30 ml/min reduction in creatinine clearance (from 150-30 ml/min) BNP increased by 9%, 22%, 44% and 89% and NT-proBNP increased by 9%, 24%, 46% and 95% respectively.[85] It is recommended that BNP should be analysed within 4 hours of collection due to its short half-life. If not, then it should be tested within 24 hours when at 2 to 8°C, or stored at -22°C. Testing recommendations for NT-proBNP include analysis within 2 hours of collection

because of possible evaporation effects.[89] Despite these initial recommendations, a later study has shown no statistical difference between results obtained for NT-proBNP or BNP when EDTA anticoagulated blood was aliquoted and stored at room temperature or 4°C in glass or plastic tubes for 48 hours.[90] Age is also a variable to take into consideration when interpreting BNP. Age-related ventricular changes, subclinical cardiac dysfunction and decreases in renal function all contribute to normal values of BNP increasing with age.[91-93] BNP increases from 40 pg/ml (95th percentile reference) in age 55-64 years to 86 pg/ml in patients aged ≥75 years.[93]

The physiological role of BNP is to effect an adaptive response to cardiovascular strain through natriuretic peptide receptors A and B.[94] It modulates the cardiovascular system by limiting myocardial hypertrophy, causing peripheral vasodilatation and increasing endothelial permeability. At a renal level, inhibition of renin and aldosterone production occurs, with resulting natriuresis and diuresis. In the central nervous system the inhibition of salt and water intake, in addition to vasopressin secretion, takes place. Type C receptors and neutral endopeptidases act as scavengers and clear the peptides from the circulation.[95] Pharmacological reproduction has resulted in natriuretic peptide analogues which have been used in the treatment of renal failure and congestive cardiac failure with varying degrees of success.[96-98]

The close association of BNP levels with myocardial stress and its expression in cardiac failure has resulted in its development as a biomarker of cardiac failure. Levels are directly related to left ventricular mass and inversely related to left ventricular ejection fraction.[99-101] BNP has also been described as a diagnostic tool, for example in the evaluation of acute dyspnoea where it can help to differentiate cardiac failure from other causes of dyspnoea: a serum BNP value of <100 pg/ml was thought to make congestive cardiac failure unlikely, and a value >500 pg/ml made it highly likely [Figure 1.6].[101]

Figure 1.6 BNP values in evaluation of acute dyspnoea.
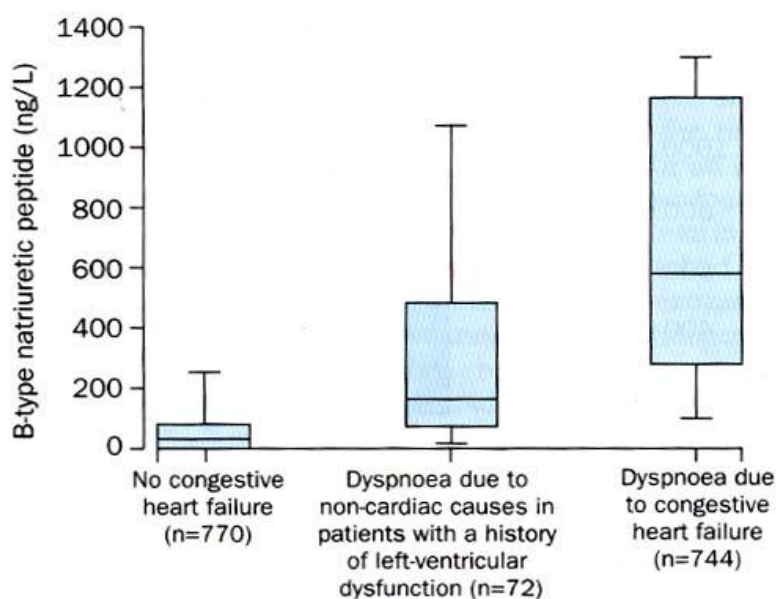
Boxplots from a prospective study of 1586 patients who attended an emergency department with acute dyspnoea and whose BNP was measured with a bedside assay. Final diagnosis was dyspnoea due to congestive heart failure in 744 patients (47%), dyspnoea due to noncardiac causes in 72 patients with a history of left ventricular dysfunction (5%), and no finding of congestive heart failure in 770 patients (49%). The difference among groups was significant for each pair wise comparison (p<0.001). Patients with a diagnosis of acute congestive heart failure had mean (±SD) BNP levels of 675±450 pg/ml, whereas those without congestive heart failure had BNP levels of 110±225 pg/ml. The 72 patients who had base-line ventricular dysfunction without an acute exacerbation had a mean BNP 346±390 pg/ml. Adapted from [101].

In patients with chronic cardiac failure BNP has been used to monitor disease progression and prognosis. A single NT-proBNP level has been shown to independently predict both mortality and subsequent hospitalisation.[102] Response to treatment with diuretic, angiotensin-converting-enzyme inhibitor or vasodilator therapy, can be monitored by a decrease in BNP levels, and an increase on their withdrawal.[103] A rise in BNP is closely linked to myocardial ischaemia and the degree of damage sustained with large amounts of cardiac muscle damage resulting in significant rises in BNP levels.[104, 105] In a subset of patients presenting with symptoms of acute coronary syndrome (ACS) without heart failure, BNP levels were significantly different between acute MI (median 203.5 pg/ml), unstable angina (77.9 pg/ml) and patients without ACS (27.7 pg/ml). In the presence of cardiac failure, BNP levels did not discriminate between those who had an acute MI or those who did not.[106] Other causes of raised BNP are listed below [Table 1.6].

Table 1.6 Non-cardiac failure causes of raised BNP.

Cardiac	Pulmonary	Other
Heart muscle disease	Pneumonia/Bronchitis	Anaemia
Acute cardiomyopathy	COPD	GI tract pathology
Myocarditis	Lung carcinoma	Cancer
Hypertrophic	Pulmonary embolism	Critical illness
cardiomyopathy	Pulmonary hypertension	Septic shock
Arrhythmias	ARDS	Burns
Atrial fibrillation		Ischaemic stroke
Atrial flutter		Sleep apnoea
Acute coronary syndrome		Hyperthyroidism
Pericarditis		
Valvular heart disease		

BNP levels are a continuous variable, with even mildly elevated levels being associated with increased risk of death, heart failure, atrial fibrillation and stroke. Further, even mildly elevated levels of serum BNP are associated with an increased mortality risk in comparison to those below the cut-off levels, irrespective of the cause of the increase in BNP. The many possible causes of an elevated BNP level, other than congestive cardiac failure, are similar to those seen to cause elevations of cTnI [Table 3.3]. COPD – Chronic Obstructive Pulmonary Disease, GI – Gastrointestinal, ARDS – Acute Respiratory Distress Syndrome. Adapted from [107].

Interest in BNP as a biomarker for risk in non-cardiac surgery has recently accelerated. This interest was catalysed by the well-recognised and acknowledged finding that preoperative ventricular dysfunction is a strong risk factor for perioperative cardiac morbidity and mortality as identified by Goldman in 1977.[108] Further to this, risk-adjusted operative mortality and 30-day readmission rates have been found to be higher in those with cardiac failure than those with known coronary artery disease (11.7% vs 6.6% and 20% vs 14.2% respectively, p<0.001).[109, 110] It is therefore being increasingly recognised that there is a significant mortality and morbidity associated with the diagnosis of cardiac failure. As a result, initial trials, reported in 2005 and 2006, found that elevated preoperative NT-proBNP concentrations were associated with cardiac events after non-cardiac and major vascular surgery.[111, 112] A further study in 2006 of 1590 patients undergoing non-cardiac surgery showed that preoperative elevated concentrations of BNP were an independent biomarker of postoperative cardiac events.[113] BNP levels were also found to be a superior predictor of cardiac outcome to the Goldman multifactorial clinical index, with preoperative BNP concentrations >189 pg/ml identifying those at highest risk. An additional publication this year in the British Journal of Anaesthesia further supported this evidence reporting that patients with raised preoperative BNP levels were more likely to suffer perioperative cardiac death or myocardial injury during the first 3 postoperative days.[114]

In Glasgow, a recent prospective single-centre derivation study was performed in high-risk patients undergoing major non-cardiac surgery, with a subsequent validation study. Forty one patients were recruited to the derivation cohort in whom 11 suffered a postoperative cardiac event. The median (interquartile range) pre-op BNP in those that had an event was 240 (172-344) pg/ml compared with 39 (15-70) pg/ml in those with no cardiac complication (p<0.001) [Figure 1.7].

Figure 1.7 BNP concentrations by cardiac event incidence.
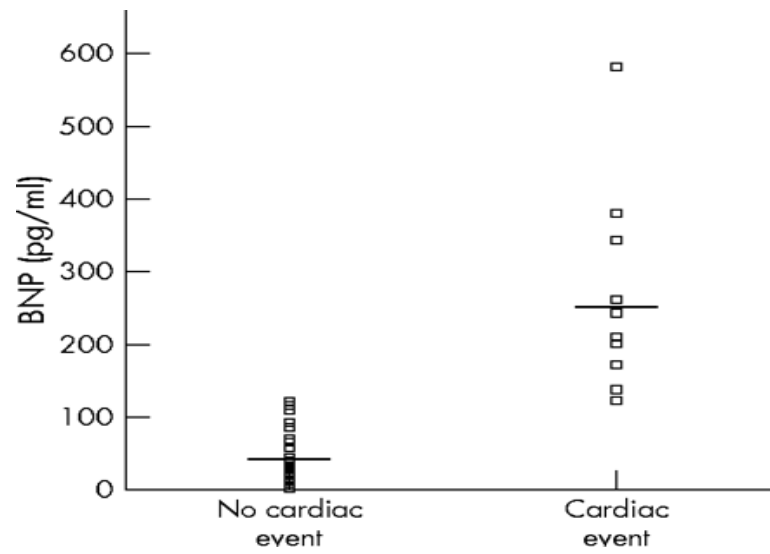
The median (interquartile range) plasma BNP concentration in patients who experienced a fatal or non-fatal MI (n = 11) was 240 (172–344) pg/ml, compared with 39 (15–70) pg/ml in those who did not (n = 30). All patients who experienced an event had a preoperative BNP concentration > 120 pg/ml. Adapted from [115].

In the validation cohort, the median (interquartile range) BNP concentration in the 15 patients who had a cardiac event was 351 (127-1034) pg/ml, compared with 30.5 (11-79.5) pg/ml in the remainder (p<0.001). Using an ROC curve analysis it was calculated that a BNP concentration of ≥108.5 pg/ml best predicted the likelihood of cardiac events, with a sensitivity and specificity of 87% each. Postoperative BNP concentrations above this value were a significant outcome predictor even after adjustment for confounders using multivariate analysis. The conclusion, therefore, was that preoperative serum BNP concentration predicted postoperative cardiac events in patients undergoing major non-cardiac surgery independently of other risk factors.[116]

As a result of the many studies examining the perioperative role of BNP in non-cardiac surgery [Table 1.7] it is clear that there is a direct association between increasing levels of BNP and risk of postoperative events. Clearly, the wildly divergent quoted discriminatory thresholds for BNP make interpretation difficult. Variations in patient cohorts with respect to age, gender (males have consistently lower levels of BNP compared to females), co-morbidity, BMI and degree of pre-existing cardiac failure almost certainly account for this. This therefore makes the identification of a single universally-applicable BNP discriminatory point unlikely, and the optimal discrimination will be influenced by the prevalence of cardiac pathology in the population being examined.

A single preoperative BNP level as part of routine workup in patients presenting for major or intermediate risk surgery allows preoperative risk stratification that is equal to, or possibly better than, current prognostic tools. There is, however, no study to date that looks at elective abdominal aortic aneurysm patients as a single group with an emphasis on appropriate sample size and long term outcome.

Table 1.7 Characteristics of studies examining the perioperative role of BNP in non-cardiac surgery.

First author [reference]	Surgery	Urgency of surgery	Study period	Patient numbers	Optimal discrimination point
BNP					
Dernellis [113]	Mixed vascular/non-vascular	Elective	Short term < 30 days	1590	189 pg/ml
Cuthbertson [117]	Mixed vascular/non-vascular	Emergency	6 months (emergency surgery)	40	170 pg/ml
Leibowitz [119]	Non-vascular	Mixed Elective/Emergency	Short term < 30 days	44	165 pg/ml
Gibson [116]	Mixed vascular/non-vascular	Elective	Short term < 30 days	190	108.5 pg/ml
Cuthbertson[114]	Mixed vascular/non-vascular	Elective	Short term < 30 days	204	40 pg/ml
Cuthbertson [118]	Mixed vascular/non-vascular	Elective	Median 654 days	204	35 pg/ml
NT-proBNP					
Feringa [112]	Vascular	Elective	Short term < 30 days	170	533 pg/ml
Goei [121]	Vascular	Elective	Short term < 30 days	356	478 pg/ml
Yeh [111]	Mixed vascular/non-vascular	Elective	Short term < 30 days	190	450 pg/ml
Feringa [120]	Vascular	Elective	14 months	335	319 pg/ml
Mahla [122]	Vascular	Elective	Median 826 days	218	280 pg/ml

Most of the studies that have been conducted thus far have looked at determining optimal cut-off points for predicting postoperative cardiac events including cardiac death, non-fatal myocardial infarction, heart failure, acute pulmonary oedema and haemodynamic compromise from cardiac arrhythmias, as well as composites of the above. Adapted from [107].

1.5.4.2 Cardiac Troponin-I

Cardiac troponins are regulatory proteins that control the calcium-mediated interaction of the thin actin and myosin filaments of the cardiac muscle. The troponin portion of this cardiac contractile apparatus consists of 3 subunits: cardiac troponin T (cTnT), cardiac troponin I (cTnI) and cardiac troponin C (cTnC).[123] Although troponins are present in skeletal muscle, myocardium contains cTnT and cTnI isoforms that are not present in skeletal muscle, allowing separation by immunologic techniques.[124] Troponin I has 3 isoforms: cardiac muscle (cTnI), and fast-twitch skeletal muscle and slow-twitch skeletal muscle (sTnI) each encoded by an individual gene. Located exclusively in the mammalian heart, cTnI is never expressed in skeletal muscle.[125]

Many factors determine the rate of appearance in the blood of a marker such as cTnI, including molecular weight, charge, binding, degradation and clearance by the renal, hepatic or reticulo-endothelial systems.[126] Following an insult (ischaemic or other) myocytes can recover, succumb or hibernate. In all cases, be it by survivable ischaemia, necrosis or apoptosis, cTnI degradation products are released.[127, 128] After acute MI, approximately 50% of patients have a rise in their cTnI within 3-4 hours, with a peak at 10-24 hours.[129] Levels remain elevated for 4-10 days because of gradual degradation of myofibrils and release of the troponin complex.[130, 131] This results in cTnI having a wider diagnostic window than CK-MB, which peaks at 18-24 hours.[132] The clinical sensitivity of cTnI for detection of myocardial injury has been reported to be as high as 100% at 36 hours following the onset of symptoms, compared to 81.8% for CK-MB mass at the same time point.[133] Debate continues as to the appropriate cut-off values of troponin concentrations for defining a clinically relevant MI. Initial cut-off values (cTnI >1.5 ng/ml and cTnT >0.1 ng/ml) were derived from titration of troponin concentrations to a population of patients with a clinically diagnosed MI. However, even small increases in serum concentrations of cardiac troponins are associated with adverse cardiac outcome in patients with or without ST-segment elevation.[134, 135] Considering the high specificity of cardiac troponins for myocardial cell injury, the consensus document of the European Society of Cardiology and the American College of Cardiology Committee on the re-definition of MI states that in the presence of documented myocardial ischaemia, even minor increases in troponin serum concentration to >99th

percentile of the normal population should be regarded as indicative of MI. As most troponin assays lack adequate precision to allow this at such low concentrations, slightly higher cut-off values based on ≤10% imprecision are recommended.[48, 136]

In the frequent absence of typical symptoms and ECG changes of acute MI, the diagnosis of a perioperative MI is difficult and has to rest heavily on changes in biochemical markers. Cardiac troponins appear to be well suited to identifying these events and have been shown to be more sensitive than CK-MB.[27, 137, 138] In one study of 1175 noncardiac surgery patients, abnormal levels of cTnT were detected in 87% of patients with MI and in 16% patients without MI. Among this latter group, cTnT was abnormal in 62% of patients with and 15% of those without other major cardiac complications, with the highest rates being observed in those undergoing AAA repair or other vascular surgery. Although CK-MB had a similar diagnostic performance with regards MI, cTnT was better in detecting other cardiac complications.[137] A further paper also identified abnormal postoperative cTnI levels in patients undergoing vascular surgery. In total, 18% of 100 patients had elevated cTnI levels, highest in those undergoing ruptured AAA repair (67%), elective open AAA repair (20%) and infrainguinal bypass surgery (15%). Again CK-MB was less sensitive in detecting cardiac complications other than MI.[139]

Whilst cardiac troponins are of use in diagnosing a perioperative MI, the difficulty is in defining these cardiac events and therefore identifying their true incidence. This can depend not only on the cut-off value, but also on the rigour with which perioperative MIs are looked for. In one paper, had biochemical monitoring for ischaemic events not taken place, only 3.6% of patients would have met criteria for a perioperative MI rather than the 5.6% actually identified. Similarly, whereas 12% of patients had increased cTnT concentrations during routine postoperative monitoring, only 3% had a perioperative MI by the WHO definition.[140] The dilemma remains whether a reported incidence of perioperative myocardial injury based on traditional definition underestimates the true incidence of clinically relevant myocardial injury, or whether a reported incidence based on serum concentrations of cardiac troponins overestimates it.

The dilemma of defining perioperative MI seems less critical when the significance of elevated cardiac troponins is investigated. Several investigations have shown that abnormal levels of perioperative cardiac troponins identify patients at increased risk of perioperative and long-term cardiac complications.[50, 137, 140-142] Indeed, even postoperative cardiac troponin elevations below the conventional cut-off levels for the diagnosis of myocardial infarction and without clinical complications have been associated with significantly worse long-term survival after major vascular surgery.[140-143] One study demonstrated that asymptomatic elevation of cTnT in non-cardiac surgery was associated with a 4-fold increased in the risk of cardiac events during a 6-month follow-up.[141] Furthermore, a 6-fold increased risk of 6-month mortality has been found in patients with abnormal elevations of cTnI following vascular surgery in 229 patients.[140] More recently, a positive association between abnormal levels of cTnI after vascular surgery and all-cause mortality over 2.5 years has been reported.[143] It seems therefore that measurement of postoperative cardiac troponin levels provide important short- and long-term prognostic information, and perioperative routine cardiac troponin measurements in high risk patients can be useful for identifying patients at increased risk of perioperative and long-term morbidity and mortality. With regard to preoperative cardiac risk stratification, there is no paper published that quantifies this risk based on cardiac troponin measurements, although preoperative elevations have been reported.

1.5.4.3 C-reactive Protein and D-dimers

C-reactive protein (CRP), in particular when measured using high-sensitivity assays (hs-CRP), has been suggested as a potentially useful prognostic marker for cardiovascular disease. Atherosclerosis is an inflammatory disease,[144] and patients with elevated inflammatory markers (such as CRP) have a worse prognosis following acute coronary events.[144, 145] A number of publications have suggested that this link may extend to predicting adverse cardiac events following vascular surgery. To investigate this association further and to compare its usefulness with that of DSE and BNP, a meta-analysis of 10 prospective patient cohort studies was published looking at CRP as a predictive test in early, intermediate and long term cardiac outcomes in vascular surgery.[146] Unfortunately due to small sample size it was not possible to

determine the prognostic value of preoperative CRP for early cardiac outcome. It was also not possible to compare CRP to BNP or DSE due to differing cardiac risk profiles and to the inclusion of patients undergoing surgical procedures with low or intermediate risk (carotid endarterectomy, peripheral angioplasty or EVAR). The same held for intermediate outcomes. A CRP >3 mg/l was, however, associated with a significantly increased risk of late all-cause mortality, cardiac death and MACE (OR 2.4, 5.65 and 2.76 respectively). Only one study reported on short-term MACE after AAA surgery.[147] Of the 34 patients included, 3 suffered a non-fatal MI or cardiac death, only one of whom had an elevated CRP (although the cut off level was not recorded). This led to an OR of 1.22 (95% CI 0.1-15.23). However, the wide 95% CI exposes the true impact of this result, with little being added by this paper.

As CRP levels are affected by local or systemic infection, due to its role as an acute phase protein, there is doubt about its ability to predict cardiac outcome.[148] This is certainly the case in vascular surgery where patients often have infectious pathologies, such as infected ischaemic ulcers. Further, there is a published link between aortic aneurysm diameter and CRP levels, where CRP is elevated compared to controls when AAA is present and the levels rise with increasing aortic diameter.[149, 150] With this and the limited data it is not possible to make positive conclusions on CRP as a preoperative marker, especially in the setting of AAA surgery.

Hypercoagulability has also been suggested as an important factor in perioperative myocardial infarction. This is supported by the association between raised preoperative fibrin D-dimer levels and a higher risk of perioperative cardiac events found in 110 patients undergoing peripheral vascular surgery.[151] In both univariate and multivariate analysis, D-dimer levels were found to be predictors of MACE, cardiac failure, unstable angina and arrhythmias combined. When the study was limited to MACE alone, although there was a significant difference in D-dimer levels (2.75 vs 2.47, p=0.003), this did not hold in regression analysis. There were also a number of limitations in the study including only a 49% inclusion (297/647) with 106 patients excluded due to 'logistics preventing work-up'. Although one other published paper found fibrinogen, von Willebrand factor and fibrin D-dimer levels to strongly predict poor outcome after infrainguinal bypass in 184 consecutive patients,[152] another small study of 42 patients undergoing vascular surgery found no correlation.[153] More importantly neither commented specifically on cardiac outcome and there is no published data at this time in relation to AAA surgery.

1.5.5 Risk Scores in AAA Repair

There are a number of mathematical models available to aid risk prediction in elective abdominal aortic aneurysm repair in both the open and EVAR setting. There is however no consensus as to which scoring system should be considered the most predictive whilst questions about validity and transference between populations remain. Of the scoring systems available only three are frequently used to predict risk in the abdominal aortic population. These are the Glasgow Aneurysm Score (GAS), the Physiological and Operative Severity Score for enumeration of Mortality (POSSUM) and the Vascular Biochemical and Haematological Outcome Model (VBHOM). A number of other scoring systems have been published including the Estimation of Physiological Ability and Surgical Stress (E-PASS), Leiden score, Vanzetto score, the Australian Audit Risk Model for EVAR and the Society of Vascular Surgeons co-morbidity score.

In 1994 the Glasgow Aneurysm Score (GAS) was constructed by Samy et al following retrospective analysis of 500 patients undergoing AAA repair in Glasgow between 1980 and 1990. Logistic regression was used and identified preoperative shock, myocardial dysfunction, renal impairment and cerebrovascular disease as significant factors in determining postoperative outcome.[154] The GAS comprised a weighted score for each of these risk factors in addition to age and was validated by the author after its conception, confirming the accuracy of the method in both the elective and emergency settings for open surgery.[155] Further validation was carried out in the Scandinavian population in 2003 on two separate occasions, including use of the Finnvasc registry (a national registry of vascular surgery in Finland).[156, 157] Analysis of the Finnvasc registry demonstrated that the predictive power for mortality was lower than previously suggested with an area under the curve (AUC) of only 0.668 (p<0.001) suggesting that the GAS was inaccurate in this context. Subsequently the GAS has been shown to be accurate in predicting mortality (AUC>0.80) by teams in the UK and the Netherlands.[158,159]

The GAS is a relatively easy score to collate and its simplicity makes it user friendly. It has also been validated successfully numerous times and predicts in-hospital mortality with acceptable accuracy in open AAA repair. A definite drawback is that the GAS does not reliably identify individual high-risk patients due to a low-positive predictive value[160] and is consistently inaccurate when used to predict morbidity, and specifically cardiac morbidity. Further to this it has been found to perform relatively poorly compared to more recent models despite an acceptable AUC of 0.749 (p=0.01).[161]

The Physiological and Operative Severity Score for enUmeration of Mortality (POSSUM) prediction models score, created in 1991 as an audit tool, contains both physiological and operative components, and can only be used to predict mortality preoperatively if the physiological component is used alone.[162-164] This score has been applied to a number of surgical groups including orthopaedic patients, head and neck surgery, GI/Colorectal surgery and vascular surgery. The original POSSUM score using exponential analysis was evaluated and an early report claimed that POSSUM over-predicted death in their group of patients especially in low-risk patients. In an effort to counteract this effect the original POSSUM equation was modified leading to the Portsmouth predictor equation for

mortality (P-POSSUM) utilising the same physiological and operative variables, but using linear analysis. Modifications were subsequently suggested to improve the predictive accuracy of POSSUM for vascular surgical procedures including AAA repair (V-POSSUM). This score was developed following a meeting of the Vascular Surgical Society of Great Britain and Ireland where additional factors that were potentially of use were added to the standard P-POSSUM database. This new model was validated using data from the UK national vascular database and was shown to be predictive of outcome when physiological data were used alone or in combination with operative details, although this only applied to elective aneurysm repair.[165]

The various POSSUM-based scores have produced variable results when undergoing validation as preoperative scores, which raises the point that the score was intended as an audit tool. Use of the physiology-only scores yielded inconsistent results when used to predict outcome in AAA repair. The true validity may also be clouded by the complexity of the system where unknown scores are recorded as normal, potentially underestimating risk, and where potential observer bias may result in subjectivity.

As an alternative score to the POSSUM score, a logistic regression model based on a minimal dataset derived from the UK national vascular dataset haematology and biochemistry results was described called the Vascular Biochemical and Haematological Outcome Model (VBHOM).[166] This VBHOM was also initially designed as an audit tool but was validated using a population of patients undergoing both elective and emergency AAA repair, and appeared to have a good predictive value, failing nevertheless to show statistical "goodness-of-fit", indicating poor calibration.[167] In response, a new VBHOM model was constructed using two years of data from the vascular dataset as opposed to 1 year as in the original, amounting to 2718 patients.[168]

External validation suggested a high degree of accuracy when used to predict death using entirely objective data, suggesting that any model based on a single preoperative blood sample could accurately predict outcome. However, once again the results of validation studies have not been consistent. Validation of the revised VBHOM as yet is not available.

The use of risk scores to predict outcome in AAA surgery is clearly in its infancy. Those that are available are not user friendly enough for clinical use and lack sufficient validation. There are no further cardiac risk prediction models for AAA surgery other than those mentioned in previous chapters.

1.5.6 Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (CPX) is a non-invasive, integrated assessment of cardiovascular and pulmonary function both at rest and under stress. During the test patients are exposed to incremental physical exercise up to their maximally tolerated level, dictated either by exhaustion or symptom related cessation (i.e. shortness of breath or angina). A number of physiological variables are recorded during the test including blood pressure, ECG, ventilatory parameters and inspiratory/expiratory gases from which the body's maximum oxygen uptake ($VO_{2\ max}$) and the point at which metabolism exceeds aerobic capacity (Ventilatory Anaerobic Threshold or VAT) are derived. Together these broadly indicate the ability of the cardiovascular system to deliver oxygen to the peripheral tissues and the ability of the tissues to utilise that oxygen. CPX should therefore be able to determine a patient's physiological capacity to cope with the metabolic demands created by the trauma of major surgery.

CPX has been widely researched in cardiac and pulmonary medicine and surgery, including in lung resection and cardiac transplantation.[169, 170] However, few studies have investigated the role of CPX in the preoperative assessment of patients undergoing non-cardiopulmonary thoraco-abdominal surgery. In particular, despite increasing interest, its use in AAA repair or vascular surgery is limited to only a few papers. Of those, the 2 better conducted studies showed only a weak relationship between $VO_{2\ max}$ and postoperative morbidity and mortality in patients undergoing open elective AAA repair.[171, 172] One study investigated the role of anaerobic threshold in elective AAA repair and found it to be a strong predictor[171], however there was no comment on cardiac morbidity or its ability to predict MACE, and for the purposes of this thesis, despite its increasing popularity as a research tool CPX did not appear to have research or clinical benefits in predicting postoperative cardiac outcome.

1.5.7 Preoperative Cardiac Assessment in Glasgow

In Glasgow, at the time of writing, there is no standardised assessment of cardiac risk. There are no published papers or other forms of literature that help shed light on what is currently practised locally. From personal experience and from discussions with consultant vascular surgeons throughout Glasgow, it is apparent that in almost all surgical cases there is a clinical assessment made in the outpatient clinic at the time of discussing surgical options and making the decision to proceed to surgery. This takes the form of case note review, with special attention to past medical history and drug history, and focused questioning regarding functional status and metabolic equivalents. An experience- and knowledge-based assessment is then made of the patients' likely risk of surgery. This will often prompt an anaesthetic review and sometimes lead to a cardiology opinion, where risk of surgery is estimated and attempts to optimise cardiac status may be made. No documented attempts at risk scoring are made, although RCRI scores are often mentally estimated. No other form of risk scoring is attempted.

Although all patients undergo a preoperative ECG, it is unlikely that any other form of cardiac investigation will be directed by surgical staff other than the transthoracic echocardiogram which is increasingly requested. Anaesthetic or cardiology opinion may rarely result in preoperative non-invasive cardiac imaging. In the present studies, this author has found that of 106 patients proceeding to theatre only 3 had a DSE performed and 2 had thallium scanning. Despite these low numbers, it was noted that 12 patients had had a preoperative coronary angiogram, with or without intervention, in the preceding year. Four of these resulted in percutaneous intervention and 3 in coronary artery bypass grafting. Undoubtedly, modification of cardiac medication and commencement of beta-blocker therapy occurred, however what medication changes were made and for what reason is outwith the scope of this research.

As discussed there is no set preoperative pathway for assessing cardiac risk. The most likely reason for this is the complex nature of preoperative cardiac risk stratification. There is no simple assessment that can be implemented at the time of clinic review, and often those assessments that are made in the surgical outpatient setting are the simplest available, such as questioning functional capacity and reviewing past medical history. Undoubtedly a quick method of accurately assessing that risk would be beneficial in deciding the appropriateness of surgery, or what surgical option to employ. The possible cardiac interventions aimed at optimising cardiac status when surgery is deemed necessary despite apparent high risk, are discussed in the following section.

1.6 Intervention in the High Risk Patient

The goal of improved cardiac risk stratification is to allow accurate informed decisions to be made both by the patient and the surgeon. This important role is not only useful in predicting outcome and making a decision about proceeding to theatre, but also in guiding the choice of interventions. A range of strategies are employed aimed at reducing the incidence of perioperative cardiac complications of which the simplest is delaying or cancelling surgery. Other interventions include preoperative coronary revascularisation, modification of medical therapy or adjustment of anaesthetic technique. Closer perioperative monitoring could also aid the detection of cardiac complications.

1.6.1 Preoperative Coronary Revascularisation.

The use of coronary revascularisation before noncardiac surgery is based on the assumption that perioperative MIs occur primarily in coronary arteries with haemodynamically significant stenoses, and that revascularisation will therefore prevent infarction. As discussed above, the pathophysiology of a perioperative MI may make this assumption false. Controversy therefore is widespread about the effectiveness of preoperative revascularisation and it is unsurprising that there have been numerous studies looking at the use of percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG) in patients undergoing major noncardiac surgery. This is especially true in the vascular surgical population. A number of early studies collected retrospective hospital data of patients who underwent PTCA before surgery in order to relieve symptomatic angina or to treat myocardial ischaemia identified by non-invasive testing.[173-175] The results of these studies showed that the incidence of perioperative cardiac death and myocardial infarction was low, but these studies failed to use a comparison group of patients with coronary artery disease not treated with PTCA. A follow-up study compared adverse cardiac outcomes after noncardiac surgery among patients with prior PTCA, patients with preoperative coronary revascularisation and normal control subjects.[176] The findings of the study showed that patients treated with PTCA within 90 days of surgery had a similar incidence of perioperative events to matched patients with CAD in the control group. Patients revascularised more than 90 days before surgery had a

lower risk of cardiac events than those revascularised within 90 days. This rate however was not as low as that in the control group. Furthermore, the effect of revascularisation was limited to a reduction in the incidence of angina and congestive heart disease. There was no reduction in MI or cardiac death.

In 2000 a study was published highlighting the hazards of noncardiac surgery following percutaneous coronary stent placement.[177] Perioperative coronary thrombosis and major bleeding complications were reported in 40 patients treated with PTCA and coronary stenting less than 6 weeks before major noncardiac surgery. In the perioperative period 7 nonfatal MIs, 11 major bleeding episodes and 8 deaths were observed. All the deaths and MIs, as well as 8 of the 11 bleeding episodes occurred in those who underwent surgery within 14 days of stenting. Fatal cardiac events were mostly caused by stent thrombosis, which was associated with interruption of antiplatelet medication 1-2 days before surgery. In contrast, severe bleeding occurred in patients whose antiplatelet medication was continued. These findings were also confirmed in a group of 207 patients who underwent noncardiac surgery within 60 days of coronary stent placement.[178] Eight of the 207 patients had MACE. Six patients died, 2 of whom suffered a periarrest myocardial infarction. The risk of MACE therefore persisted for 6 weeks after stent placement. No major complication was observed in 39 other patients who had surgery 7-9 weeks after stent placement.

Where former evidence was based on small observational studies and expert opinion, a number of recent randomised controlled trials have clarified the issue. The Coronary Artery Revascularisation Prophylaxis (CARP) trial was the first randomised trial that investigated the benefit of coronary revascularisation in patients presenting for AAA repair or lower extremity revascularisation.[179] A total of 510 patients with significant coronary artery stenosis were randomised to either revascularisation or intensive medical therapy perioperatively. Of the 316 patients enrolled who had nuclear stress imaging, 72% had moderate-to-large reversible defects (44.3% of total cohort). The incidence of death or MI within 30 days of the vascular procedure was high but similar in the two groups, with an incidence of 14.7% in those revascularised and 17.7% with medical therapy. Long-term mortality was high but similar between the groups, averaging 22.5% [Figure 1.8].

Figure 1.8 Prophylactic coronary revascularisation – long-term survival from the CARP trial.
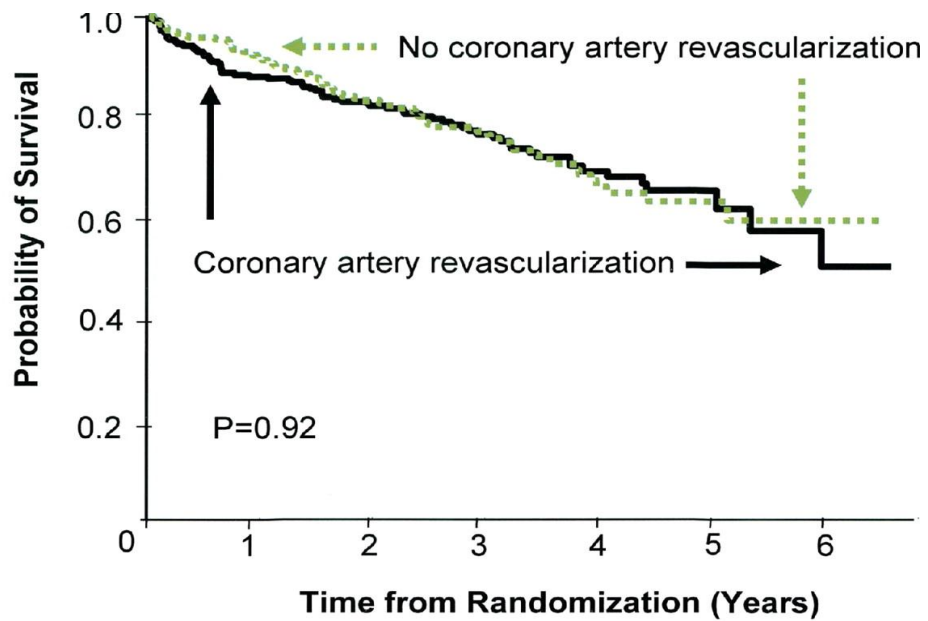
No. at Risk						
Revascularization	226	175	113	65	18	7
No revascularization	229	172	108	55	17	12

The median follow-up time for mortality was 2.8 years (interquartile range 1.7-3.9) in the revascularization group and 2.6 years (1.6-3.8) in the no-revascularisation group. There were 137 deaths (70 in the revascularisation group and 67 in the no-revascularisation group). At a median of 2.7 years after randomization, mortality was 22 percent in the revascularization group and 23 percent in the no-revascularisation group (relative risk, 0.98, 95% CI 0.70-1.37; P=0.92). Adapted from [175].

Although these results appear impressive, there were a number of limitations: there was no subgroup analysis investigating the impact of CABG versus PCI; patients undergoing CABG had, on average, 3 vessels revascularised versus 1.3 in the PCI group, with the completeness of revascularisation reported as 61.9% for PCI versus 98% for CABG; acute or sub-acute stent thrombosis posed an additional risk with prophylactic PCI compared to CABG; and premature termination of antiplatelet therapy may have skewed results as discussed above. In 2006 a follow-up study revealed that both short and long-term outcome was significantly better in those receiving CABG compared to PCI.[180] This study involved 91 patients undergoing prophylactic CABG and 131 patients undergoing PCI before major vascular surgery using the same enrolment criteria as the CARP trial. In the CABG group, the 30-day mortality and MI rate was 2.2% and 6.6% versus 3.8% and 16.8% for PCI. Mortality at 2.7 years was 16% for CABG and 21% for PCI. The most significant criticism of the CARP trial relates to the inclusion (coronary stenosis of >69% in at least 1 major coronary vessel suitable for revascularisation) and exclusion criteria (severe co-existing illness, >50% left main coronary stenosis, severe aortic stenosis or LVEF <20%). Therefore the optimal preoperative management for patients with the above exclusion criteria was not determined. The authors of the CARP trial considered most patients in their cohort to be high risk, but only 7.3% had severe perfusion defects and multiple risk factors whilst those with triple CAD plus mildly depressed LV function represented only 14.5%. In response a subgroup analysis was performed and a trend towards improved outcome with revascularisation was seen in patients with a large burden of ischaemia and multiple clinical risk factors.[181]

Further evidence of this trend was shown by 3 other studies. The first retrospective study involving patients with moderate-severe defects on thallium imaging showed improved long-term mortality outcomes in those patients who underwent vascular surgery following coronary revascularisation.[182] There was a significantly higher incidence of triple vessel and left-main vessel disease in the group who underwent revascularisation, suggesting that revascularisation in this particular pattern of disease was protective in high risk patients. A follow-up retrospective study identified a number of predictors of long-term survival of which only prophylactic coronary revascularisation and statin use were positive predictors of increased long-term survival.[183] Finally, in a prospective study of

patients undergoing major vascular procedures, prophylactic revascularisation in those with moderate-severe defects on thallium imaging decreased the incidence of low-level troponin release and of elevations consistent with a diagnosis of MI from 49% to 22.4% and 23.4% to 6.4% respectively.[184]

While much of the above work by Landesberg has gone against that found in the CARP trial, results from the pilot study of the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group (DECREASE)-V trial implied that revascularisation, even in patients with multiple risk factors and severe CAD, does not improve outcome as long as best medical therapy is instituted preoperatively.[185] Of the 1888 suitable patients, undergoing elective open AAA repair, screened prior to thallium imaging or DSE, 430 proceeded to cardiac testing and 101 were found to have extensive ischaemia and randomised to revascularisation or medical therapy. Of the 49 patients revascularised, 12 had 2-vessel CAD, 33 had 3-vessel CAD and 4 had left main disease. In addition 43% had a LVEF <35%. Complete revascularisation was achieved in 86% with 32 patients receiving PCI and 17 CABG. The 30-day incidence of MI and all-cause mortality after their subsequent aneurysm surgery was 42.9% in the revascularisation group and 32.7% in the control group. There was no significant difference in outcome at 1 year (49% vs 44.2%). There was a "catch-up" effect noted by 1 year where the number of cardiac events in the medically managed group approached that of the revascularisation group. With or without revascularisation the 30-day operative mortality was 33-43% despite medical management, leading to the question over the need for revascularisation in AAA patients.

While the argument that revascularisation does not improve outcome is compelling, there remains sufficient doubt about this conclusion that, given the current literature, it is difficult to advise against prophylactic revascularisation in the highest risk patients. There is mounting evidence that the completeness of revascularisation is the most important variable[180] and that CABG may confer benefit over PCI, particularly in patients with extensive CAD or in those with ischaemic cardiomyopathy. In long-term outcome studies, CABG is associated with an improved outcome.

1.6.2 Pharmacological Treatment

The beneficial effect of preoperative treatment of a coronary stenosis is limited because of the unpredictable behaviour of non-significant coronary lesions with regards to plaque rupture, thrombus formation and subsequent coronary occlusion. Plaque instability is driven by the stress of surgery and any therapy aimed at plaque stabilisation may benefit in both the short and the long-term. Perioperative use of beta-blockers, statins and aspirin have all shown promise.

1.6.2.1 Beta-blocker Therapy

The benefit from beta-blockade (specifically beta1-selective blockade) is with restoration of the oxygen supply/demand mismatch by decreasing myocardial contractility, heart rate and arterial pressure. The complexity of the interactions between the heart, sympathetic nervous system and inflammation also contribute to the beneficial effect of beta-blockade.[186] Furthermore, beta-blockers decrease the release of intracardiac noradrenaline during ischaemia reducing cardiac toxicity, attenuate exercise-induced coronary vasoconstriction improving exercise capacity, and have antiarrhythmic properties, increasing the threshold for ventricular fibrillation during myocardial ischaemia.

Despite wide-scale use of beta-blockers perioperatively there has remained

some debate about their protective effect. This was intensified by the results of the PeriOperative ISchaemic Evaluation (POISE) trial in 2007.[187] Prior to this publication a number of papers showed clear evidence in favour of the use of beta-blockers. These included a randomised controlled trial of 200 patients receiving either perioperative (induction and 7 days therapy) atenolol or placebo.[188] Over the 2-year follow-up period, overall mortality after hospital discharge was significantly lower in the atenolol (10%) than in the placebo group (21%) amounting to a relative risk reduction of 55%. Criticism was concentrated on the exclusion of a number of in-hospital deaths (n=4) associated with atenolol use which, if included, would have negated the significance of the observed difference. In addition, the tolerance to beta-blockade therapy was poor, with a trend towards a more severe cardiac history in the control group. A subsequent study (DECREASE-I), looking at perioperative bisoprol (30 days pre-op and 30

days post-op with heart rate titration) in patients with documented CAD undergoing major vascular surgery, randomised 112 from 1351 screened patients.[189] This paper reported a 10-fold reduction in the rate of perioperative cardiac events in the bisoprolol group (3.4% vs 34%). Limitations included a small sample size resulting in only 20 events, early termination of the trial due to unexpectedly large beneficial effects, lack of blinding, and the lack of representation from the broader population. A recent large meta-analysis including 15 studies (1,077 patients) showed a significant beneficial effect of beta-blockers in non-cardiac surgery [Table 1.8].[190]

The recently presented POISE study showed a benefit of high-dose metoprolol controlled-release therapy on the risk of MI but an increased risk of stroke and overall mortality. These results have been questioned due to widespread criticism relating to the dose and timing of beta-blocker use, the choice of beta-blocker, criteria for dose adjustment and patient inclusion. The starting dose of metoprolol was between 2 and 8 times that commonly prescribed, with initiation of therapy immediately before surgery and therefore an extremely narrow window for titration. Further, titration was based not only on heart rate control but on a single blood pressure measure, with therapy discontinued when levels fell below a systolic pressure of 100 mmHg. No consideration was taken to preoperative blood pressure or the actual drop, with the potential for patients to drop blood pressure from a high systolic pressure down to 105 mmHg and still be included in the study. It has therefor been hypothesised that dose-related hypotension in patients naïve to beta-blockers, and in whom without prior knowledge of their cardiac status could have asymptomatic left ventricular dysfunction, could account for much of the adverse outcome associated with this trial. Indeed 49 of the 60 strokes in POISE were proven ischaemic in origin. The inclusion of emergency patients, those that had signs of preoperative sepsis, and the use of 'individual physician's judgement' on choosing the type of surgery to be included further questions the true clinical impact of these results.

Table 1.8 Comparison of patients treated with perioperative beta-blocker therapy versus no drug or placebo.

End point	Treated (n=551)	Control (n=526)	OR	95% CI	Rx effect	P value	
Cardiac death	0.54%	2.22%	0.55	0.25 – 1.22	< 45%	0.140	
All-cause death	1.27%	1.85%	0.79	0.36 – 1.76	< 21%	0.568	
Cardiac death or MI	1.09%	6.10%	0.33	0.17 – 0.67	< 67%	0.002	
Nonfatal MI	0.54%	3.88%	0.44	0.20 – 0.97	< 56%	0.043	
Ischemia	10.98%	25.55%	0.35	0.23 – 0.54	< 65%	< 0.0001	
Summary OR	2.45%	7.00%	0.42	0.32 – 0.56	< 58%	< 0.0001	

Forest plot axis: 0.1 0.2 0.5 1 2 5 10 — Lower risk / Higher risk

Ischaemic event data available from 11 of 15 studies (n=410 treated and n=407 controls). Beta-blocker use resulted in a 67% relative reduction in the combined endpoint of cardiac death and non-fatal MI (1.1% vs 6.1%, OR 0.33, 95% CI 0.17-0.67; p=0.002, NNT = 20). OR - odds ratio, Rx – treatment, MI - myocardial infarction, CI – confidence interval, NNT – number needed to treat. Adapted from [190].

The importance of the initiation time of beta-blocker therapy before surgery can be argued based on its physiological effects. The acute effects include reduction of myocardial oxygen demand as describe above. Otherwise, the further suggested benefits may be related to anti-inflammatory properties possibly observed only after prolonged use as seen in acute MI patients who require to be on beta-blocker therapy for at least 48 hours before a clear reduction in the inflammatory response is seen.[191] It is unclear whether the effect on coronary plaque stabilisation can be achieved immediately on commencement of beta-blocker therapy. As described above, a randomised trial of 200 patients using atenolol at anaesthetic induction revealed a long-term benefit. There was, however, no difference in perioperative cardiac events.[188] The Metoprolol After Vascular Surgery (MAVS) trial randomised 496 patients to metoprolol or placebo starting 2 hours before surgery until a maximum of 5 days post-op.[192] No significant difference in outcome was observed at 30 days; or at 6 months after surgery. The Perioperative Beta-Blockade (POBBLE) trial randomised 103 patients undergoing vascular surgery to metoprolol or placebo, starting less than 24 hours prior to surgery and continuing to 7 days.[193] This trial again showed no benefit on 30 days outcome with a cardiac event rate of 32% in the metoprolol group versus 24% in the placebo group. The Diabetic Postoperative Mortality and Morbidity (DIPOM) trial started therapy at the earliest on the evening prior to surgery, and again no benefit was seen.[194] The POISE trial randomised patients to receive either controlled-release metoprolol or placebo starting 2-4 hours before surgery and continued for 30 days.[187] In contrast the DECREASE-I trial started bisoprolol at an average of 37 (range 7-89) days before surgery with careful titration of therapy and revealed a significant benefit with bisoprolol use in the perioperative period.[189] The long-term beneficial effects were recently confirmed by a study which demonstrated a decreased progression of coronary atherosclerosis in patients receiving beta-blocker therapy using pooled analysis from four intravascular ultrasonography trials.[195] The use of beta-blockers was significantly associated with a decrease of atheroma volume at follow-up, not seen in those without therapy.

The different beta-blockers have various plasma half-lives and peak ratios. Bisoprolol and atenolol are long-acting agents with half-lives of 10-11 hours and 6-7 hours respectively, whereas metoprolol has a short duration of action of about 3.5 hours. Beta-blockers with short half-lives will increase the risk of a cardiovascular event on sudden withdrawal as seen in elderly patients undergoing elective surgery where long-acting beta-blockers are associated with higher cardioprotective benefits.[196] Additional consideration is required with metoprolol and atenolol which are only moderately beta1-adrenoreceptor selective. As described, beta1 blockade is beneficial during the perioperative period where high adrenaline and noradrenaline levels create increased heart rates and blood pressure whilst stimulating an inflammatory process putting vulnerable plaques at risk. Blocking beta2-receptors in addition to beta1 leads to uncontrolled alpha stimulation and a subsequent adverse rise in blood pressure.[197] Therefore the highly beta1-selective bisoprolol is the favoured agent in the perioperative setting.

In addition to initiation time and type of beta-blocker, dose adjustment for heart rate control is important. This is based on the fact that cardiovascular and sympathetic suppression is required to produce cardiac protection. As the extent of such suppression is difficult to assess clinically, heart rate is taken as a physiological surrogate of sympathetic tone.[188, 189] Two studies have confirmed this by showing positive results using strict heart rate control in the perioperative setting with a reduction in perioperative myocardial ischaemia, troponin T release and improved long-term outcome.[198, 199] The POISE trial randomised treatment of controlled-release metoprolol just before surgery, and the maximum recommended therapeutic dose was already achieved within the first day after surgery. This is in contrast to the DECREASE studies, where a low dose of bisoprolol at an average 12.5% of the maximum recommended therapeutic dose was carefully up-titrated during a mean of 30-days. Although the POISE trial showed a reduction of perioperative MI, there was an excess of overall mortality and increased risk of stroke. The message may be that if beta-blockade is to be used it should be carefully titrated with guidelines on discontinuation of therapy. It may also be that the beneficial effect of beta-blockers is best seen in high risk patients, as shown in a retrospective cohort study of 782,969 patients who underwent major noncardiac surgery.[200] Beta-

blocker use showed no benefit but possible harm in low-risk patients, but had a significant beneficial effect in high risk patients. This may account for the negative outcome of the MAVS and DIPOM trials which included many low risk patients including 60% of the MAVS cohort.

At present, the weight of evidence suggests that beta-blockers lower rates of perioperative myocardial ischaemia or infarction and cardiovascular death among high risk patients undergoing major vascular surgery. However, there appears to be a concurrent risk of adverse events associated with these medications if patients are not monitored properly during the perioperative period. Despite this, it seems clear that perioperative beta-blockers, where adequately titrated and monitored, should continue to occupy a prominent role in the therapeutic armamentarium for improving outcomes among high-risk patients undergoing major vascular surgery.

1.6.2.2 Statins

Statins are widely prescribed to patients to decrease low-density lipoprotein (LDL) cholesterol in patients with, or at risk of, coronary artery disease, and have been shown to decrease the number of future cardiovascular events. Besides lowering cholesterol, statins have other important effects, known as pleiotropic effects. These effects include atherosclerotic plaque stabilisation, oxidative stress reduction and a reduction of vascular inflammation.[201] In human carotid plaques, statins have been demonstrated to decrease lipids, lipid oxidation, inflammation, matrix metalloproteinases and cell apoptosis, and to increase tissue inhibitors of metalloproteinases and collagen. These properties of statins may stabilise coronary artery plaques, thereby preventing plaque rupture and subsequent MI in the perioperative period.[202]

A number of large clinical trials have shown a beneficial effect of statins with regards to safety and long-term outcome, whilst improving symptoms related to peripheral non-coronary atherosclerosis.[203, 204] There is however only one published blinded, placebo-controlled, randomised clinical trial evaluating the effects of statin therapy on perioperative cardiovascular complications in which 100 patients were randomised to 20mg atorvastatin or placebo.[205] After 6 months the incidence of cardiac events (cardiac death, non-fatal MI, stroke or unstable angina) was more than 3 times higher with placebo than with atorvastatin (26% vs 8%, p=0.031). This study suggested that even short-term treatment with a statin could significantly reduce the incidence of major cardiovascular events in vascular surgery.

There have been a number of other case-control and retrospective trials published that evaluate the effect of statin therapy on perioperative cardiac outcomes, all of which demonstrate some benefit. The earliest case-control study, published in 2003, concluded that statin therapy reduced perioperative mortality in patients undergoing major vascular surgery with statin therapy less common among cases than controls (8% vs 25%) and similar results in subgroups of patients according to other cardiac therapy or risk factors.[206] A later retrospective study of 570 patient who underwent AAA repair revealed that 30-day mortality and non-fatal MI (overall 8.9%) were lower in statin users than in nonusers (3.7% vs 11%).[207] Although the statin users had a different risk profile, the reduced risk remained after adjustment for this difference and was independent of beta-blocker use. A large retrospective cohort study of 780,591 patients undergoing major noncardiac surgery at 329 hospitals revealed that after correction for baseline differences, the 70,159 statin users had a 1.4 fold reduced risk of in-hospital mortality.[208] In addition, the long-term benefit of statins was reported in patients undergoing AAA repair when followed up over a median of 4.7 years.[209]

Reviews of studies to determine the strength of data have again demonstrated a benefit with statin therapy. One meta-analysis found that preoperative statin therapy was associated with a 4.4% absolute reduction in the risk of early mortality after vascular surgery (1.7% vs 6.1%, p<0.001).[210] When including noncardiac surgery, a 1.1% absolute reduction in the risk of early mortality was observed (2.2% vs 3.3%, p<0001). A further comprehensive review of 11 papers on perioperative statin use concluded that all demonstrated an improved postoperative cardiac outcome.[211]

A major concern of statin therapy is the potential side effects, such as statin-induced myopathy and rhabdomyolysis. Perioperatively, patients might be unaware of these symptoms, owing to sedation and analgesic agents. There is also a concern regarding the possible increased risk of statin induced myopathy in the perioperative period due to impaired renal function and multiple drug use during anaesthesia, risking the subsequent development of rhabdomyolysis and acute renal failure. No studies have however been published supporting these concerns, except for a few case reports.[212-214] One retrospective study of 981 consecutive patients undergoing vascular surgery has been published.[215] This study measured CK blood levels and clinical status in those already on statins or recently commenced. After correcting for cardiac and clinical risk factors for myopathy, length of surgery remained the only independent predictor of myopathy. No cases of rhabdomyolysis were observed.

The optimal dosing and timing of statins for the prevention of perioperative events has still to be elucidated. An important concern is the continuation of statins in the perioperative period. Unintended interruption in the immediate postoperative period is a well-known phenomenon because of the unavailability of an intravenous formula of statins. From patients with CAD, it is known that sudden withdrawal can be harmful,[216] with a similar risk recently demonstrated in vascular surgery patients in whom statin withdrawal was associated with an increased risk for postoperative troponin release and cardiac events.[217] The extended release of fluvastatin appeared to have beneficial effects over other statins when discontinued in this same study.

1.6.2.3 Other Pharmacological Therapies

Acetylsalicylic acid (ASA) is one of the cornerstones in the primary and secondary prevention of cardiovascular diseases. The evidence of ASA in the perioperative period in patients undergoing noncardiac surgery is less clear. In a randomised trial of carotid endarterectomy patients, ASA was shown to be effective in preventing intraoperative and postoperative stroke but with no effect on death or non-fatal MI.[218] In another trial comparing low-dose and high-dose ASA in carotid surgery, there was an observed reduced mortality, MI and stroke in the low-dose group.[219] A meta-analysis of 10 trials using antiplatelet therapy during lower limb bypass surgery showed a reduction in serious vascular events and vascular death in patients with peripheral vascular disease, although this did not reach statistical significance.[220] No randomised trial exists of preoperative discontinuation of ASA. A meta-analysis of 41 studies observed that ASA increased the risk of bleeding complications 1.5-fold but did not lead to higher levels of severe bleeding complications.[221] A systematic review in subjects at risk for or with CAD demonstrated that ASA non-adherence/withdrawal was associated with a 3-fold higher risk of MACE.[222]

Alpha-2-adrenergic agonists (clonidine, mivazerol) dilate post-stenotic coronary vessels and attenuate the severity of perioperative haemodynamic abnormalities, an effect which may reduce cardiovascular complications.[223, 224] Previous small scale studies have failed to demonstrate that clonidine reduces the incidence of cardiac death or non-fatal MI compared with placebo.[225, 226] A number of meta-analyses performed claim to demonstrate a reduced incidence of myocardial ischaemia,[227, 228] however these reviews were dominated by one large-scale randomised trial of 2854 patients in whom there was no overall effect on the endpoints of cardiac death and nonfatal MI.[229]

The prophylactic use of intravenous nitroglycerin and diltiazem for the prevention of cardiac complications after non-cardiac surgery has also been studied. These small-scale randomised studies failed to find any difference in the incidence of intraoperative and perioperative myocardial ischaemia in patients receiving nitroglycerin or diltiazem compared with placebo.[230-232]

1.6.3 Anaesthesia and Monitoring Techniques

In recent years, the attention in cardiac risk reduction has been focused on preoperative cardiac risk assessment to modify cardioprotective medication or consider revascularisation in an attempt to improve perioperative outcome. Less attention has been given to the role of anaesthesia and monitoring techniques in the cardiac management of high-risk patients. Despite this, evidence exists to support the theory that adequate operative haemodynamic control such as prevention of tachycardia, hypotension and possibly hypertension with the use of modern monitoring techniques may prevent myocardial ischaemia and reduce the incidence of perioperative cardiac complications.

1.6.3.1 Inhalational Anaesthesia

A number of laboratory studies have shown that halogenated volatile anaesthetics have a protective effect on the ischaemic myocardium. In these studies, volatile anaesthetic use was associated with improved post-ischaemic recovery and smaller myocardial infarction size.[233, 234] This has been termed pharmacological preconditioning, similar to ischaemic preconditioning, of which the exact mechanism appears to be protection of the cardiomyocytes via an effect on ATP-regulated potassium channels.[235] Volatile anaesthetics may also exert 'post-conditioning', directly on the myocyte but also indirectly through modulation of neutrophil-mediated damage, protecting against myocardial reperfusion injury.[236, 237] The key issue however is haemodynamic stability and a number of volatile anaesthetics have been studied. A large scale study of 4 anaesthetic agents (isoflurane, enflurane, fentanyl and halothane) looked at perioperative outcome in 17 201 surgical patients.[238] The incidence of death, myocardial infarction and stroke (0.04%) was so low that no definite conclusions could be made, although marked differences in their haemodynamic properties were noted. Halothane use was associated with ventricular dysrhythmia, fentanyl with severe hypertension and bronchospasm and isoflurane with severe tachycardia. Further clinical studies comparing sevoflurane and isoflurane suggest that both have similar cardiovascular effects, and do not alter outcomes such as myocardial infarction and death in patients with coronary artery disease.[239-241] The choice of agent is therefore often based on other factors such as experience, availability and the ease of emergence from anaesthesia.[242]

1.6.3.2 Epidural Anaesthesia/Analgesia and Intraoperative Normothermia

Early studies of epidural anaesthesia claim that, due to better suppression of surgical stress, positive effects on postoperative nitrogen balance, more stable cardiovascular haemodynamics, reduced blood loss, better peripheral vascular circulation and postoperative pain control, perioperative outcomes may be improved with this anaesthetic modality.[243, 244] A number of later studies involving more than 600 patients who underwent aortic surgery have failed to demonstrate any benefit with epidural anaesthesia and analgesia in the prevention of myocardial ischaemia, myocardial infarction and mortality.[245-249] In contrast a systematic review of all randomised controlled trials using data from 9559 patients revealed a 30% reduction in all-cause mortality and a 33% reduction in myocardial infarction compared to standard therapy in non-cardiac surgery.[250] The use of neuraxial blockade also reduced the risk of all-cause mortality by 34% in a subgroup of patients who underwent vascular surgery. More recent randomised controlled trials have attempted to readdress this issue. The first clinical trial involved 1021 patients scheduled for abdominal aortic, gastric, biliary or colonic surgery, who were randomly assigned to general anaesthesia and postoperative analgesia with parenteral opioids or a combination of epidural and light general anaesthetic with postoperative epidural morphine.[251] The results showed no significant difference in the incidence of 30-day mortality and major complications between the two groups. However, subgroup analysis of the AAA group revealed a significantly lower incidence of major cardiovascular (10% vs 18%), pulmonary (14% vs 28%) and cerebral complications (0.5% vs 5%) compared to patients without epidural anaesthesia. This was felt to be due to the high-risk status of the aortic surgical patients many of whom had a history of hypertension or chronic obstructive pulmonary disease, and to the longer mean operating time. In a similar study of 915 high risk patients undergoing abdominal surgery the use of epidural anaesthesia and analgesia did not reduce the incidence of morbidity (57% vs 61%) or mortality (5% vs 4%).[252] The incidence of respiratory failure was significantly lower in patients managed using epidural techniques (23% vs 30%). Nevertheless, these studies suggested that by improvement in analgesia, reduction in respiratory failure and the observed low risk of serious adverse consequences, many high-risk patients undergoing major abdominal surgery would receive substantial benefit from an intraoperative

combination of general and epidural anaesthesia with continuing postoperative analgesia.

Hypothermia is common around the perioperative period and triggers sympathetically-mediated hypertension resulting from an increase in circulating levels of noradrenaline and generalised systemic vasoconstriction.[253] Decrease in the core body temperature by approximately 1.0 $^{\circ}$C results in shivering and increased total-body oxygen consumption, which places increased demands on the cardiovascular system. These adrenergic and metabolic responses to hypothermia can lead to an imbalance in myocardial oxygen supply and demand, resulting in myocardial ischaemia or infarction.[33, 254, 255] Two clinical trials have explored the issue of unintentional hypothermia and postoperative myocardial ischaemia. The first studied 100 patients undergoing lower extremity vascular reconstruction and revealed that a larger proportion of patients in the hypothermic group (temp. <35 $^{\circ}$C) developed ischaemic ECG changes than in the normothermic group (36% vs 13%, p=0.008).[33] In a subsequent study of 300 patients undergoing abdominal, thoracic or vascular surgical procedures the perioperative maintenance of normothermia was associated with a significantly lower incidence of cardiac events compared to those with hypothermia (1.4% vs 6.3%, p=0.02).[255] It seems, therefore, that measures used to ensure normothermia would benefit, especially in those at high risk of suffering perioperative MACE.

1.7 Aims of the Thesis

The need for adequate preoperative cardiac risk stratification in major vascular surgery is clearly demonstrated in the above chapters, not only in identifying high risk patients that may benefit from those interventions described above, but in surgical decision making. The importance of this in a prophylactic operation to prevent rupture of an AAA, where a balance of risks is essential prior to making a decision regarding surgery, is further emphasised, especially in the case of the small AAA.

A number of case reports have described preoperative elevation in cTnI in vascular surgery and described the associated poor outcome in these patients. At the time of writing, there is no published research that has further investigated this and therefore the initial aims of this thesis are to investigate the true incidence of preoperative elevated cTnI in asymptomatic individuals prior to undergoing a major vascular procedure. Further, these identified patients will be followed-up in the immediate postoperative period and their outcome determined.

Whilst cTnI is of interest, the current research regarding preoperative cardiac biomarkers as a marker of outcome is aimed primarily at investigating BNP or NT-proBNP. Although there are numerous papers reporting outcome with regards BNP in major vascular surgery, no research has concentrated on the elective open AAA repair population, where the decision to operate has added importance. The foremost aim of this thesis is to investigate the ability of BNP to predict outcome in the elective open AAA repair population. Outcomes to be measured are major adverse cardiac events (non-fatal MIs and cardiac death), all-cause mortality and postoperative elevated cTnI (with or without a diagnosed cardiac event), measured in the immediate (<30 days), intermediate (30 days - 1 year) and long-term (>1year) postoperative periods.

Non-invasive cardiac testing, such as dobutamine stress echocardiography, is expensive, relatively inaccessible and rarely used in the decision making process with regards elective open AAA repair in the West of Scotland. Therefore decisions are often helped by estimates from current cardiac or all-cause mortality based risk indices devised around AAA surgery. The further aim of this thesis is therefore to compare these risk indices to BNP with an emphasis on predicting MACE and all-cause mortality in the immediate postoperative period.

Finally, EVAR has recently had an increasing but uncertain role in repair of a patients AAA. Currently there are no published papers looking at the use of BNP in decision making when considering EVAR. The final aim of this thesis is to investigate if BNP can predict outcome in patients undergoing elective EVAR, again concentrating on MACE and all-cause mortality in the immediate postoperative period.

Chapter 2

Patients and Methods

2.1 Recruitment

Patients were recruited from within the Glasgow tertiary referral centres specialising in vascular surgery, where distinct geographical borders and minimal migration resulted in a geographically defined prospective cohort with minimal selection bias, and facilitated complete follow-up. The patients were recruited in 2 groups.

In the first group consecutive patients undergoing elective major vascular surgery in Gartnavel General Hospital and the Western Infirmary were prospectively identified using theatre diaries. Patients were included if they were over 40 years of age and undergoing vascular surgery with a >5% estimated cardiac risk including abdominal aortic surgery, infrainguinal bypass surgery and major extremity amputation. All patients were approached the day prior to surgery and informed consent was obtained (appendix 1). Patients were excluded if the surgery could not be delayed by more than 24 hours (due to clinical need), if they were unable to give informed consent or were being included in another study.

In the second group all patient undergoing elective open AAA surgery or endovascular AAA repair were prospectively identified in the 3 major Glasgow vascular units; Gartnavel General Hospital, Glasgow Royal Infirmary and the Southern General Hospital. Patients were prospectively identified using theatre diaries, regular check of theatre lists and weekly contact with surgical secretaries. All patients were approached the day prior to surgery and informed consent was obtained (appendix 2). Patients were excluded if the surgery was required on an emergency basis, if they were unable to give informed consent or were being included in another study.

2.2 Clinical Details

Patients' clinical details were gathered prospectively from case-note review or history taking and were recorded on a common study proforma on the day prior to surgery (appendix 3). These details included basic patient and demographic data including aneurysm size and operative procedure.

2.2.1 Details of Cardiac Risk

Factors relating to cardiac risk of surgery were recorded including age, sex, smoking history, medical diagnoses of angina, myocardial infarction, heart failure, hypertension, hyperlipidaemia, cerebrovascular disease, medically treated diabetes and renal impairment with estimated glomerular filtration rate. In addition to cardiac risk, a history of chronic obstructive airways disease was noted.

2.2.2 Details of Current Cardiac Medications

All patients' current medications were noted with particular attention to the inclusion of those related to cardiac disease and to preoperative cardiac risk intervention including beta-blockers, statins, anti-platelets, diuretics, ACE-inhibitors, calcium-channel antagonists and anti-anginals.

2.3 Preoperative Testing

2.3.1 Basic Measures

Data relating to basic haemodynamic parameters were recorded including pulse and resting blood pressure, oxygen saturations on air, and body temperature to ensure there was no underlying current or acute ill health.

2.3.2 Electrocardiography

All patients underwent 12-lead electrocardiography which was recorded in a standard fashion at a paper speed of 25mm/second by a qualified cardiac technician. All preoperative ECGs were analysed by a cardiologist of consultant or senior registrar grade, to ensure that there was no evidence of acute or unstable ischaemia and to allow postoperative comparison.

2.3.3 Further Cardiac Investigation

Selected patients underwent transthoracic echocardiography with estimate of left ventricular ejection fraction (LVEF) to allow function to be recorded as normal (LVEF >55%), mildly impaired (LVEF 45-54%), moderately impaired (LVEF 30-44%) or severely impaired (LVEF<30%) in accordance with the recommendations of the American Society of Echocardiography and the European Association of Echocardiography.[256]

Additional investigations including DSE, thallium scanning, angiography and pulmonary function tests were performed at the discretion of the surgical, anaesthetic or cardiology staff involved in individual patient care.

2.4 Preoperative Blood Sampling and Analysis

Samples were collected and analysed by collection of an aliquot of venous blood obtained from recumbent patients the evening before surgery.

2.4.1 Cardiac Troponin I

5ml venous blood samples were collected in sterile lithium heparin tubes for serum cTnI measurement using the ARCHITECT *STAT* Troponin I immunoassay (Abbot Diagnostics) which had an assay range of 0.02-50 ng/ml with a sensitivity of ≤0.01 ng/ml. Assay precision was ≤10% of the concentration value (CV) for samples ≥0.20 ng/ml. The lowest assay value exhibiting a 10% CV on the precision profile was 0.032 ng/ml. A positive result was taken as a cTnI >0.02 ng/ml. cTnI results were not initially made available to clinicians. However, as documented in chapter 3, positive results were given to appropriate medical staff towards the end of the study period.

2.4.2 B-type Natriuretic Peptide

2.4.2.1 Sample Handling

A 10 ml sample was collected from patients who had lain supine for 20 mins. This was collected in chilled sterile EDTA and aprotonin (Trasylol®, Bayer, LeverKusen, Germany; 50units/ml) and immediately centrifuged at 3000rpm at $4^{o}C$ for 10 minutes. The serum was then removed from the tube using a pipette, placed in a plain tube and stored in a freezer at $-22^{o}C$.

2.4.2.2 BNP Testing

BNP was batch analysed in lots of 100 samples at the end of the study period using a direct immunoradiometric assay kit (Shinoria BNP kit) supplied by Shinogi & Co, Ltd. (Osaka, Japan). This used two monoclonal antibodies which recognise the carboxyl terminal sequence and the ring structure of human BNP, respectively, measuring BNP concentration between the two antibodies without plasma extraction. The minimum detectable quantity of human BNP was 2 pg/ml and the degree of cross reactivity with human ANP was less than 0.001%. The within-assay and between-assay co-efficient of variation were both <5%.

2.4.3 Biochemistry Analyses

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

2.4.4 Haematological Analyses

A 5ml sample was taken in a sterile EDTA tube for analysis of haemoglobin concentration, white cell count and platelet count. A further 5ml sample was collected in a citrate tube for coagulation screening which included pro-thrombin time, activated partial pro-thromboplastin time and fibrinogen.

2.5 Clinical and Cardiac Risk Scoring

Clinical variables were recorded preoperatively to allow calculation of risk of cardiac events and mortality using established clinical scoring systems.

2.5.1 The Glasgow Aneurysm Score (GAS) [154]

GAS was calculated for all patients undergoing AAA repair. Scores were calculated on the basis of several risk factors, each allocated a weighted value: age (n=age), presence of shock (n=17), history of myocardial disease (n=7), history of cerebrovascular disease (n=10) and a history of renal disease (n=14). Based on the original description for GAS, shock was defined as documented tachycardia, hypotension, pallor and sweating. Myocardial disease included a previous myocardial infarction and/or angina. Cerebrovascular disease referred to all grades of stroke including a transient ischaemic attack. Renal disease included chronic and acute renal failure.

No further categorisation or grouping has been shown of use with GAS and therefore the score represents a point within a linear degree of risk. Increasing scores suggest higher risk of all-cause mortality.

2.5.2 The Vascular Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (V-POSSUM)

V-POSSUM, as previously described, is a vascular surgical modification of POSSUM in which the original developers examined 62 physiological parameters and used multi-variate analysis to identify the most powerful predictors of mortality. This eventually reduced the 62 to 12 physiological and 6 operative parameters. In the preoperative period only the 12 physiological parameters can be collected.

The 12 physiological parameters required include age, evidence of cardiac failure (categorised based on current cardiac medication and on clinical evidence of heart failure), evidence of pulmonary disease (categorised based on severity of dyspnoea or evidence of consolidation), preoperative ECG changes (based on rate, ectopics, Q-waves and ST changes), systolic BP, resting pulse rate, Glasgow Coma Scale scoring, and serum levels of haemoglobin, white cell count, urea, sodium and potassium. These were placed into the online V-POSSUM calculator at www.riskprediction.org.uk to calculate individual scores.

2.5.3 Vascular Biochemical and Haematological Outcome Model (VBHOM) [166]

All patients undergoing open AAA repair were given VBHOM scores based on gender, mode of admission (elective or emergency), age at time of admission, serum urea, sodium, potassium, haemoglobin concentrations and white cell count. These were then placed into the following calculation to give a final VBHOM score:

$$VBHOM = \ln_e(R/1\text{-}R) = -2.257 + (0.1511 \times sex) + (0.9940 \times \text{mode of admission}) + (0.05923 \times \text{age on admission[years]}) + (0.001401 \times urea[mmol/l]) + (-0.01303 \times sodium[mmol/l]) + (-0.03585 \times potassium[mmol/l]) + (-0.2278 \times haemoglobin[g/dl]) + (0.02059 \times \text{white cell count}[\times 10^9/l])$$

R is the risk of death. Sex takes the value 0 for female and 1 for male, and mode of admission takes the value 0 for elective and 1 for non-elective admissions. The VBHOM score was not categorised but expressed as a numerical value, higher values being associated with high estimated risk of mortality.

2.5.4 Lee's Revised Cardiac Risk Index (RCRI) [64]

All patients were given a RCRI score based on six clinical variables: high-risk surgery, history of ischaemic heart disease, history of congestive heart failure, history of cerebrovascular disease, preoperative treatment with insulin, and preoperative creatinine >2.0 mg/dl (>176 μmol/l), with each factor being attributed a value of 1 (maximum score of 6)

Ischaemic heart disease was defined as a previous MI, history of a positive exercise test, current complaint of chest pain considered to be secondary to myocardial ischemia, use of nitrate therapy or ECG with pathological Q waves. Congestive heart failure was defined as a history of congestive heart failure, pulmonary oedema or paroxysmal nocturnal dyspnoea, physical examination showing bilateral rales or S3 gallop, or chest radiography showing pulmonary vascular redistribution. Cerebrovascular disease was defined as a history of transient ischemic attack or stroke.

Patients were categorised on the basis of RCRI into four groups of increasing cardiac risk: 1. patients with 0 risk factors, 2. patients with 1 risk factor, 3. patients with 2 risk factors, and 4. patients with 3+ risk factors. As open AAA surgery was considered high risk, all patients admitted for this procedure had a score of 1 and thus could not be placed in the lowest risk group using RCRI.

2.5.5 Preoperative Risk Score of the Estimation of Physiological Ability and Surgical Stress Score (PRS of E-PASS)[257]

The PRS component of the E-PASS score was calculated for all patients based on the following equation:

$$PRS = -0.0686 + 0.00345(age) + 0.323(cardiac\ score) + 0.205(pulmonary\ score) + 0.153(diabetes\ score) + 0.148(performance\ status\ index) + 0.0666(ASA)$$

Age was expressed in years. Cardiac, pulmonary and diabetes scores were scored 1 for the presence of the disease, or 0 in its absence. Cardiac disease was defined as heart failure (New York Heart Association Class III or IV) or severe arrhythmia requiring mechanical support. Pulmonary disease was defined as any condition with a vital capacity of less than 60% and/or a forced expiratory volume in 1 second of less than 50%. Diabetes mellitus was defined according to the World Health Organization criteria as the presence of either fasting venous plasma glucose levels of 7.0 mmol/L (126 mg/dL) or greater, or 2-hour venous plasma glucose levels of 11.1 mmol/L (200 mg/dL) or greater after a 75 g oral glucose tolerance test. The ASA score was allocated according to table 1.3.

Performance status was based on that of the Japanese Society of Cancer Therapy as follows:

- Grade 0 - conditions without symptoms that do not restrict social activities.

- Grade 1 - conditions with mild symptoms that restrict muscular labour, but do not restrict walking or mild exertion.

- Grade 2 - conditions that require some physical assistance for daily living, but do not restrict walking or mild exertion; grade 2 patients are not in bed for more than half of the day.

- Grade 3 - conditions that require frequent physical assistance for daily living; grade 3 patients are in bed for more than half of the day.

- Grade 4 - conditions that require constant physical assistance; grade 4 patients are in bed all day long.

2.6 Intraoperative Details

Intraoperative details were extracted from anaesthetic charts and operative notes.

2.6.1 Intraoperative Blood Loss

Blood loss was recorded from charted suction volumes and weighed swabs documented in intraoperative anaesthetic records.

2.6.2 Operative Time

Operative time was recorded for all patients from anaesthetic charts using the time from induction to last recorded observation.

2.6.3 Intraoperative Hypotension

Intraoperative hypotension was recorded for all patients from anaesthetic charts. This was defined as systolic blood pressure below 90mmHg for a period of greater than 5 minutes.

2.6.4 Intraoperative Hypothermia

Intraoperative hypothermia was recorded for all patients from anaesthetic charts. Hypothermia was defined as core body temperature below 34.5 $^{\circ}$C.

2.6.5 Cross-clamp Level and Time

In all patients undergoing open AAA repair, the anatomical level of aortic cross-clamp and duration of aortic occlusion was recorded. Cross-clamp level was either infrarenal or suprarenal and was determined from operative notes. Cross-clamp time was calculated from anaesthetic charts.

2.7 Postoperative Testing and Follow-up

2.7.1 Short-term Testing (<30 days post-op)

All patients underwent postoperative screening for cardiac events. This consisted of daily clinical assessment, with serial ECGs and cTnI measurement conducted on the morning of the 2nd and 5th postoperative days. If a patient was due to be discharged prior to the fifth postoperative day, tests were conducted on the morning of discharge. ECG and cTnI were also measured if there was clinical need outside these fixed times. ECGs and cTnI measurements were conducted in the same manner as previously stated. Postoperative ECGs were analysed by consultant or senior registrar grade cardiologist to identify acute myocardial ischaemia, development of a myocardial infarction or new cardiac pathology. Those analysing ECGs were blinded to patient and clinical details.

In addition to cTnI measurement, blood samples were sent for serum creatinine. This was primarily measured to ensure that there was no new acute renal dysfunction that could account for elevations in cTnI. All other postoperative investigations were conducted at the discretion of the treating physician or surgeon.

2.7.2 Intermediate (30 days – 1 year) and Long-term Follow-up (>1 year)

Patients were routinely followed up at a surgical outpatient clinic 6-8 weeks after surgery. Patients who defaulted from their follow-up clinic appointment were identified and recent progress accounted for through hospital records and GP phone-calls.

Three-year follow-up was performed on all patients undergoing elective open AAA repair through GP phone-calls. Information was gathered on mortality and cause of death.

Patient inclusion and follow-up numbers in those identified for elective open AAA repair and EVAR are shown in Figure 2.1.

Figure 2.1 Inclusion and follow-up patient numbers of those included in the multicentre preoperative BNP in elective open AAA repair and EVAR trials.
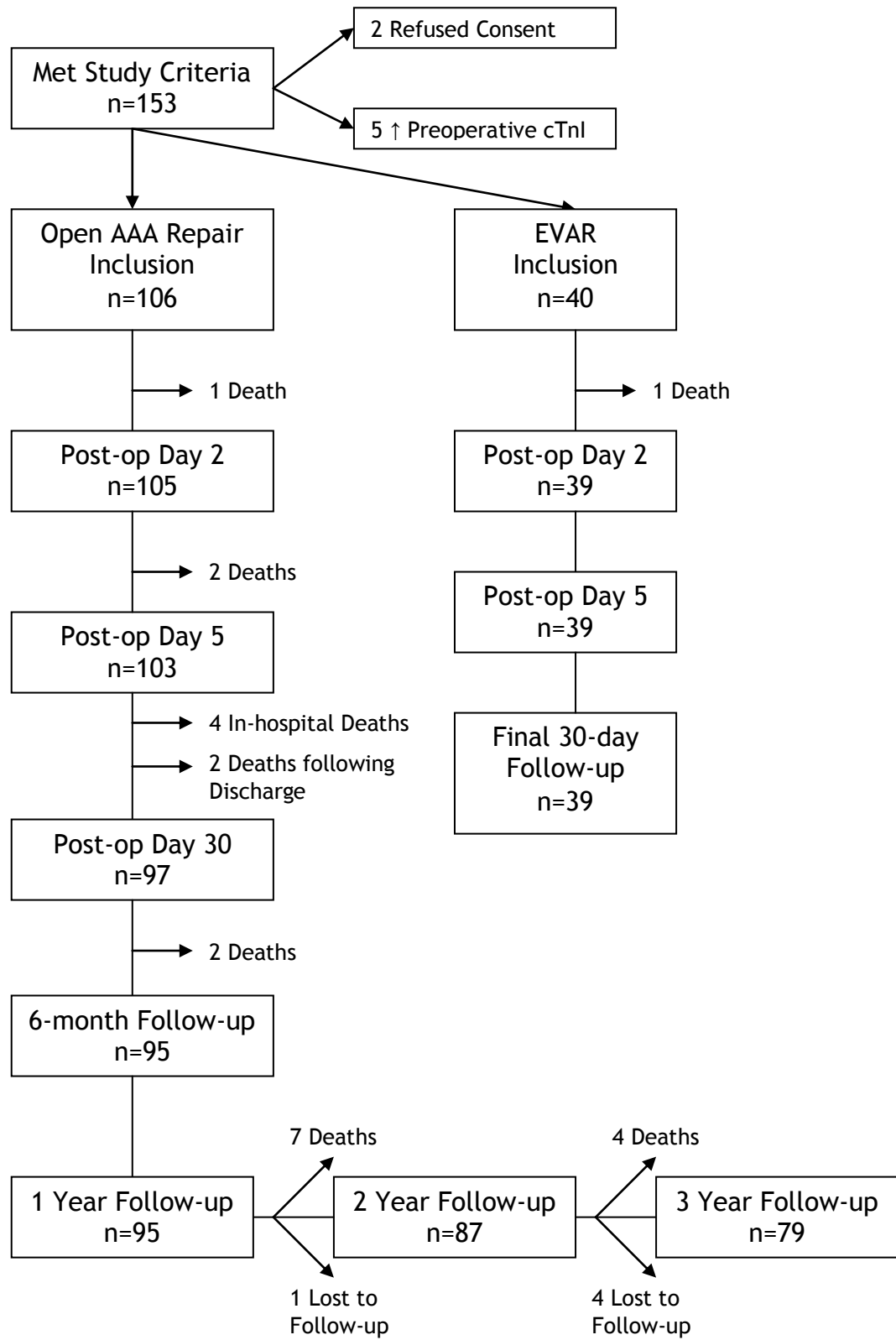
2.8 Study Endpoints

The primary study endpoints were Major Adverse Cardiac Event or MACE (non-fatal myocardial infarction or cardiac death). Secondary endpoints were all-cause mortality and elevated postoperative cTnI with or without a defined cardiac event.

2.8.1 Major Adverse Cardiac Event (MACE)

2.8.1.1 Non-fatal Myocardial Infarction

The definition of a nonfatal myocardial infarction used was that of the Joint European Society of Cardiology/American College of Cardiology Committee. This required a typical rise and gradual fall in cTnI with at least one of: ischaemic symptoms, development of pathological Q-waves on the ECG, ECG changes indicative of ischaemia (ST segment elevation or depression), or coronary artery intervention.

2.8.1.2 Cardiac Death

Cardiac death was defined as death secondary to myocardial infarction, cardiogenic shock or intractable dysrhythmia following review by 2 cardiologists blinded to preoperative BNP levels.

2.8.2 All-cause Mortality

All-cause mortality was simply defined as death due to any cause. The cause of death was recorded for anecdotal interest but was not used as a secondary end-point.

2.8.3 Elevated cTnI

Postoperative cTnI was defined as any postoperative cTnI elevation, independent of clinical outcome and regardless of presence or absence of symptoms, where the level was greater than 0.02 ng/ml.

2.9 Definitions of Preoperatively Recorded Conditions

2.9.1 Myocardial Infarction

Myocardial infarction was defined as the presence of a previous medically confirmed myocardial infarction from hospital or GP records.

2.9.2 Angina Pectoris

Angina pectoris was defined as the presence of a previous medical diagnosis of angina, the presence of symptoms of angina or current medical treatment for angina.

2.9.3 Heart Failure

Heart failure was defined as the presence of a previous medical diagnosis of heart failure, the presence of symptoms or signs of heart failure, previous or current treatment of heart failure, or objective signs of impaired left ventricular function or lung congestion on either echocardiography or plain chest radiography.

2.9.4 Hypertension

Hypertension was defined as the presence of a medical diagnosis of hypertension preoperatively (treated or untreated).

2.9.5 Hyperlipidaemia

Hyperlipidaemia was defined as a preoperative total cholesterol of >5.5mmol/l.

2.9.6 Cerebrovascular Disease

Cerebrovascular disease was defined as a previous medically confirmed transient ischaemic attack (TIA) or stroke.

2.9.7 Diabetes Mellitus

Diabetes was defined as the presence of a medical diagnosis of diabetes mellitus with the current use of insulin or oral hypoglycaemic agents.

2.9.8 Renal Impairment

Renal impairment was defined as a preoperative creatinine of >130 µmol/l or an eGFR of <60. The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) Study equation:

$$\text{GFR (mL/min/1.73 m}^2\text{)} = \mathbf{186} \times (\text{Serum creatinine})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African-American})$$

Patients were then categorised by chronic kidney disease (CKD) stage using eGFR as derived from the NICE, SIGN and Renal Association guidelines 2009.[258-260]

2.9.9 Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) was defined as the presence of a medical diagnosis of COPD or the presence of current active treatment for COPD.

2.10 Classification of Operative Procedures

Procedures were classed urgent if they were conducted on the same admission as a referral from the emergency department or another source, but did not require to be conducted within 24 hours. Procedures were considered elective if patients were admitted from home for treatment.

2.10.1   Vascular Procedures

Vascular procedures included open or endovascular AAA repair, aorto-bifemoral bypass grafting, infra-inguinal vascular reconstruction or major lower extremity amputation due to vascular insufficiency.

2.10.2   Elective Open AAA Repair

The open elective AAA repair patients included those brought in from home by planned admission undergoing AAA tube graft or aortic bifurcation graft repair.

2.10.3   Elective Endovascular AAA Repair

The elective EVAR group included those brought in from home by planned admission for endovascular repair primarily performed due to their AAA. Endovascular techniques were varied but principally involved exclusion of the aneurysm sac by insertion of stent grafts.

2.11 Ethical Approval

Local Research and Development, and Central Ethics Committee approval was obtained for the study (REC reference number 06/S0703/148). All patients were provided with an information sheet and signed a study consent form (Appendices 1+2) prior to inclusion. This study involved no additional risk to patients other than extra blood tests and non-invasive cardiac imaging.

2.12 Statistical Analyses

Statistical analysis was conducted using SPSS® statistical software package (SPSS, Chicago, Illinois, USA). Non-parametric continuous variables were reported as median (interquartile range) and compared using Mann-Whitney U and Kruskall-Wallis analyses. A two tailed Fisher's exact test was used to analyse the differences between independent categorical data. Normally distributed data was reported as mean (+/- standard deviation) and compared using a 2-sample t-test. Regression analysis was performed to assess the association of BNP with MACE and all-cause mortality, adjusting for preoperative and operative variables identified through univariate analysis. ROC analysis was performed to determine the association between BNP and outcome. Kaplin-Meier survival analyses were performed to estimate the survival function allowing for censoring on long-term follow-up. A p-value of less than 0.05 was considered statistically significant.

Chapter 3

The Prognostic Value of Raised Preoperative Cardiac Troponin I in Major Vascular Surgery

3.1 Introduction

Vascular disease is a systemic disorder, with 50-60% of patients undergoing peripheral vascular procedures having co-existent severe coronary artery disease and only 10% having normal coronary arteries.[67, 261] It is predictable therefore that vascular surgery is associated with a substantial risk of major adverse cardiovascular events (MACE) and death.[24, 261]

Cardiac Troponin I (cTnI) is a contractile protein that is released into the circulation after myocardial cell injury. Unlike other cardiac-related enzymes, cTnI is not found in skeletal muscle and it is therefore a highly sensitive and specific marker of myocardial necrosis,[133,262] and a specific marker of myocardial infarction following surgery.[133] Elevated cTnI after major vascular surgery is associated with an increased risk of short-term mortality and morbidity,[140] and is an independent predictor of intermediate and long term outcomes.[140-143, 263-264] It is widely recognised that known preoperative impaired cardiac function correlates with MACE. The impact of adverse cardiac function on postoperative outcome is well established and has been refined since Goldman's first risk stratification.[60] The sophistication of cardiac testing has changed dramatically since then with both functional and stress testing with radioisotope scanning, biochemical tests, ECG, echocardiographic and angiographic studies. However 50% of postoperative cardiac events and 29% in the general population are asymptomatic and detected principally through cTnI analysis.[43] Whilst asymptomatic elevation in cTnI has been widely correlated with angiographic findings and outcome in patients presenting to cardiology,[43] there have been no studies that have systematically addressed the incidence of elevated preoperative cTnI and the impact on MACE postoperatively other than a case-report and a series of amputation patients.[265,266]

The aim of this case series is to report the incidence of asymptomatic elevated preoperative cTnI and it's associated outcome in 213 consecutive patients undergoing major vascular surgery.

3.2 Patients and Methods

3.2.1 Patients

A prospective, observational single centre cohort study was performed over a 2 year period (April 2004 and April 2006) in Glasgow, to assess cardiac risk stratification and novel markers in non-cardiac surgery. Inclusion criteria for participation included an estimated procedure-related cardiac event rate of >5% (lower limb revascularisation, aneurysm repair, major amputation). In addition to preoperative tests done at the discretion of anaesthetic and surgical teams, each patient had a preoperative measurement of cTnI and an electrocardiogram (ECG) performed on the day before surgery. The cTnI level was available to the anaesthetic and surgical teams if requested, but was not routinely sought. Basic demographic data and factors relating to the risk of surgery were prospectively gathered for each patient. Patients were excluded if there was evidence of unstable coronary artery disease preoperatively (cardiac chest pain or ischaemic ECG changes), if the surgery was emergency (<24 hours) or if they were unable to provide informed consent. COREC and local Research and Development committee approval was obtained for the study.

3.2.2 Sample Collection and Analysis

Preoperative venous blood samples were collected the evening before surgery in sterile lithium heparin tubes. Serum cTnI was measured using the ARCHITECT *STAT* Troponin I immunoassay (Abbot Diagnostics) which had an assay range of 0.02-50 ng/ml with a sensitivity of ≤0.01 ng/ml. Assay precision was ≤10% of the concentration value (CV) for samples ≥0.20 ng/ml. The lowest assay value exhibiting a 10% CV on the precision profile was 0.032 ng/ml. A positive result was taken as a cTnI >0.02 ng/ml.

3.2.3 Postoperative Follow-up

Postoperative screening for cardiac events consisted of daily clinical assessment, and serial ECGs and cTnI measurement on postoperative days 2 and 5. These test results were made available to the treating clinicians. Other investigations were performed as indicated. Clinical follow-up continued to 6-weeks post-procedure. A cardiologist blinded to the study data compared the paired pre- and postoperative ECGs at the end of the study. Endpoints were non-fatal myocardial infarction (MI) and cardiac death. MI was defined by the presence of a typical rise and fall of plasma cardiac troponin I with either ischaemic symptoms +/- development of Q-waves on ECG +/- ischaemic changes noted on ECG +/- coronary artery intervention. Cardiac death was determined by review of all postoperative data by two cardiologists blinded to preoperative cTnI levels.

3.2.4 Statistical Analysis

Statistical analysis was conducted using SPSS® statistical software package. All analyses were performed between groups using a two tailed Fisher's exact test.

3.3 Results

3.3.1 Population

During the 2 year study, a total of 222 patients underwent an elective major vascular procedure of which 213 (144 male, 69 female) were included in the study. Nine patients were excluded (5 unable to give informed consent, 3 unstable cardiac disease and 1 missing preoperative cTnI sample). Seventy four (35%) patients underwent a major lower extremity amputation, 72 (34%) abdominal aortic surgery, 37 (17%) infrainguinal bypass and 30 (14%) extra-anatomical bypass. Co-morbidity included 84 (39%) patients with ischaemic heart disease, 44 (21%) with congestive cardiac failure, 23 (11%) with renal impairment and 60 (28%) with diabetes mellitus. Sixty (28%) patients were prescribed a preoperative statin and 28 (13%) a beta-blocker. All patients were on anti-platelet therapy.

Eleven (5.2%) of the 213 patients had an asymptomatic raised preoperative cTnI (median cTnI 0.22 ng/ml [0.08-14.8] ng/ml). All 11 patients had significant co-morbidity: 5 patients had known ischaemic heart disease, 5 had cerebrovascular disease, 4 had diabetes mellitus and 3 had renal impairment. Eight out of the 11 patients had multiple risk factors [Table 3.1].

Table 3.1 Co-morbidity and outcome.

Case	cTnI (ng/ml)	Creatinine (µmol/l)	Cholesterol (mmol/l)	IHD	Diabetes	COPD	CVD	ßblocker	Statin	Urgent (U) Elective (E)	Eagle	RCRI	Outcome
AFB	**0.08**	118	2.7	✓	✓		✓		✓	E	2	3	Cardiac Death
BKA	**0.8**	126	3.6	✓	✓		✓			U	3	4	Cardiac Death
BKA	**0.3**	172	2.7	✓	✓	✓		✓		U	4	3	Cardiac Death
BKA	**14.8**	50	5.4				✓			U	0	1	Non-fatal MI
BKA	**0.11**	70	2.7				✓		✓	U	1	2	Death (sepsis)
BKA	**0.4**	189	1.6	✓				✓	✓	U	2	2	Death (sepsis)
AAA	**0.12**	120	3.7						✓	U	1	0	ARF
AAA	**0.64**	95	3.4	✓				✓	✓	E	3	2	-
TA	**0.22**	483	2.2		✓	✓				U	1	2	-
AKA	**0.09**	68	4.6				✓			E	2	2	-

AFB - axillary-femoral bypass, BKA – below knee amputation, AKA – above knee amputation, AAA – abdominal aortic aneurysm repair, TA – toe amputation, IHD – ischaemic heart disease, COPD – chronic obstructive pulmonary disease, ARF – acute renal failure, RCRI – Revised Cardiac Risk Index, Eagle – cumulative score, scoring 1 for each of: >70 yrs, diabetes mellitus, Angina, Q-waves on ECG, vent. Arrhythmias.

Pre-existing cerebrovascular disease was significantly more prevalent in patients shown to have an elevated preoperative cTnI (p=0.023). Although none of the other risk factors were statistically significantly associated with raised preoperative cTnI, the proportions of elevated asymptomatic cTnI patients with renal impairment (24% vs 12%), who were prescribed beta-blockers (27% vs 12%) or had an urgent procedure (36% vs 13%) were more than double compared to the normal cTnI patients [Table 3.2].

3.3.2 Outcome

Patients with an asymptomatic elevated preoperative cTnI were more likely to be undergoing major lower extremity amputation (7/11 [64%]), with nearly double the proportion compared to the normal cTnI group (67/202 [33%]), although this difference was not significant (p=0.262). Other procedures included 2 for open abdominal aortic aneurysm (AAA) repair and an axillary-femoral bypass. The management of patients with an elevated cTnI varied with initially 8 of the 11 patients having no change in their routine perioperative course. As a consequence of the poor outcome in those with preoperative elevated cTnI, noted early in the study period, preoperative cTnI levels were subsequently made available to both anaesthetist and surgeon. Of the remaining patients with elevated preoperative cTnI one was started on a perioperative beta-blocker, and one of the lower extremity amputations was delayed to remeasure cTnI and was taken to theatre uneventfully with a persistently elevated cTnI. One final patient scheduled to undergo an aorto-bifemoral bypass was delayed for cardiac investigation and subsequently underwent triple coronary artery bypass grafting. This patient consequently had an uncomplicated aorto-bifemoral graft at a later date with a normal preoperative cTnI.

Table 3.2. Preoperative risk factors and outcome by cTnI.

Risk Factor	n	PreOperative cTnI		
		<0.02ng/ml	≥0.02ng/ml	p
Sex (male)	144	135 (67%)	9 (73%)	0.64
IHD	84	79 (40%)	5 (45%)	0.76
DM	60	56 (28%)	4 (36%)	0.52
CVD	29	24 (12%)	5 (45%)	0.023
COPD	44	42 (21%)	2 (18%)	1.0
Renal Impairment	23	20 (10%)	3 (27%)	0.12
Urgent Procedure	30	26 (13%)	4 (36%)	0.079
Beta-Blocker	28	25 (12%)	3 (27%)	0.18
Statin	60	55 (27%)	5 (45%)	0.33
Total	213	202	11	
MACE	31	27 (13%)	4 (40%)	0.087
Cardiac death	15	12 (6%)	3 (30%)	0.044
Mortality	23	18 (9%)	5 (50%)	0.0089

IHD – ischaemic heart disease, DM – diabetes mellitus, CVD – cerebrovascular disease, COPD – chronic obstructive pulmonary disease, MACE – major adverse cardiac event.

The incidence of MACE in the 10 patients that proceeded to theatre with preoperative asymptomatic elevated cTnI was three times more common (4/10 (40%) vs 27/202 (13%), p=0.087), although this was not statistically significant. Of these 10 patients, 4 suffered a postoperative major adverse cardiac event: 3 cardiac deaths (30%) and 1 non-fatal MI (10%). There were a total of 5 deaths (50%), the 2 further deaths occurring secondary to sepsis. The number of postoperative MACE in the 'normal' cTnI group was 27 (13%) with 12 cardiac deaths (6%) and 15 non-fatal MIs (7%). There was a total of 18 deaths (9%) in the 'normal' cTnI group, with the 6 additional deaths due to sepsis (3), respiratory failure (2) and multi-organ failure (1). There was a statistically significant difference in cardiac death (p=0.044) and in all cause mortality (p=0.0089) between those with a normal preoperative cTnI and those with an asymptomatic elevation of cTnI, with poorer outcome in the elevated cTnI group.

3.4 Discussion

This is the first inclusive study to report the incidence of asymptomatic elevated preoperative cTnI and associated clinical outcome. Of the 213 patients included, 5.2% had an asymptomatic elevated cTnI. These patients had a significantly higher risk of cardiac death and all cause mortality, with a trend towards an increased proportion of MACE, the pre-op assay thus predicting poor outcome.

The outcome in these patients was poor with death in 5 of 10 patients. A total of 4 patients had a major adverse cardiac event of which 3 were cardiac death. All of the patients who suffered an event were urgent cases most of whom required a lower extremity amputation for critical ischaemia. The preoperative EAGLE [63] and revised cardiac risk index (RCRI) [64] scores for these patients was ≥2, predictive of poor cardiac outcome in patients undergoing vascular surgery.[64,267] In addition asymptomatic elevations have been shown to identify patients who are at increased risk of first cardiac events and who have increased mortality over 10 years irrespective of surgery, with potential contributing subclinical silent myocardial damage.[268, 269] This implies that preoperative asymptomatic elevations in cTnI could identify a subset of patients from an already high risk population in whom the outcome is likely to be considerably worse.

Evidence for a potential cause of the elevated cTnI was present in the majority of cases such as sepsis in the amputation patients,[268] and renal impairment [269-271] [Table 3.3].[272-274] Co-morbidity was common in patients who had elevated cTnI, with a significantly greater prevalence of cerebrovascular disease in the elevated cTnI group. There was a high prevalence of cardiac risk determinants such as diabetes mellitus, chronic kidney disease and ischaemic heart disease, known to be associated with asymptomatic elevations in cardiac troponin.[274] The most concerning alternative reason for such an elevation, however, include acute coronary syndrome and pulmonary embolism. Further investigation may therefore be of benefit in such cases and could involve investigating the cause of their elevated cTnI and obtaining a cardiology opinion. A pragmatic approach may be to delay operative stress where feasible, and await a fall in levels, such as that seen in a cardiac event. This could allow further patient optimisation or cardiac intervention.[207] Where delay and intervention is not practicable, other

options could involve change in anaesthetic modality, closer perioperative monitoring or modification of surgical procedure.

In summary, this case series presents 11 patients with an elevated preoperative cTnI associated with poor prognosis. Although the numbers are limited, this is the largest case series of patients with a preoperative elevation in cTnI in the literature. This study could be taken forward to commence routine preoperative cTnI measurement in those patients already at high postoperative cardiac risk to further help identify those that might benefit from delay or preoperative cardiac optimisation.

Table 3.3 Conditions associated with elevated cTnI levels.

Myocardial related

    Acute coronary syndrome
      – Myocardial infarction and unstable angina
    Cardiac contusion/amyloidosis
    Cerebrovascular accident
    Coronary vasospasm
    Heart Failure
    Cardioversion
    Left ventricular hypertrophy
    Myocarditis
    Pericarditis
    Pulmonary thromboembolism
    Postoperative – cardiac surgery
    Sepsis/Septic shock
    Sub-arachnoid haemorrhage
    Tachycardia
    Ultraendurance exercise (marathon running)
    Scorpion envenomation
    Chemotherapy

Other

Assay cross-reactivity
    Antibody cross-reactivity
    Heterophile antibody
    Rheumatoid factor positive
Decreased clearance
    Renal failure, acute or chronic
Miscellaneous
    Central nervous system disorder
    Haematological malignancy
    Labour/Delivery
    Pre-eclampsia

Chapter 4

B-type Natriuretic Peptide Predicts Immediate Outcome after Elective Open Abdominal Aortic Aneurysm Repair

4.1 Introduction

About 6000 men die annually from ruptured abdominal aortic aneurysm (AAA) in the UK. Prophylactic surgical repair is associated with a mortality of around 5-6% in the UK.[17,18] The UK Small Aneurysm Trial comparing surgical repair with observation of small AAA demonstrated a greater risk of death from surgery than from rupture in the observation group for the first three years of follow-up.[18] The majority of postoperative deaths in the operative group were related to cardiac complications such as myocardial infarction. This level of postoperative cardiac mortality has led to the development of endovascular aneurysm repair (EVAR). Trials of EVAR have shown that whilst perioperative mortality is lower, there is a constant level of device failure that requires regular surveillance and reintervention with consequent increased cost.[21,22] Greater discrimination of those at risk of perioperative cardiac complications or with poorer short-term survival would improve management. Current strategies for cardiac–risk assessment are limited by subjectivity (clinical assessment) and poor sensitivity and specificity, whilst imaging or functional assessment is limited by availability and expense.

B-type natriuretic peptide (BNP), originally identified in the porcine brain, is one of a family of cardiac peptides secreted almost exclusively by the myocardium in a non-specific response to wall stress.[82] It is a vasodilator and diuretic that serves to counter the renin-angiotensin system.[83] A correlation has been demonstrated between the concentration of BNP and cardiac risk factors in the general population in the West of Scotland, as well as with short-term survival.[275] It has proven predictive value in the clinical assessment of heart failure, ventricular dysfunction and risk stratification of patients with acute coronary syndrome.[101, 276] A number of studies have evaluated preoperative concentrations of BNP in non-cardiac surgery as a method of predicting cardiac complications and it is now clear that there is a direct association between increasing levels of BNP and risk of postoperative cardiac events in both the elective and emergency settings.[111-120] To date however there have been no adequately powered studies of preoperative BNP in the elective open AAA surgical population.

The aim of the present study is to determine if a single preoperative BNP value can predict cardiac complications and thus be of help in the selection of patients for elective open AAA repair.

4.2 Methods

4.2.1 Study Population and Power

A prospective, observational, multi-centre cohort study was performed involving the 3 major vascular units within Glasgow (Gartnavel General Hospital, Glasgow Royal Infirmary and the Southern General Hospital). Consecutive patients admitted for elective open AAA surgery between August 2005 and September 2007 were prospectively included in the study with the aim of recruiting a minimum of 100 patients based on a power calculation using a cardiac event rate of 15-20% and a spread of BNP concentration with a cut-off level at 100 pg/ml (selected through BNPs diagnostic capability for heart failure with values above this threshold, and through its ability to predict MACE with higher BNP levels in non-cardiac surgery, as identified through previous derivation and validation studies in Glasgow).[101, 116] There was no uniform criterion with regards patient selection for surgery. Inclusion was based on consultant selection taking into account individual patient factors such as AAA size, co-morbidity, pre-operative testing (see section 1.5.7) and patient preference, and was in line with current practice at that time. All patients were approached the evening prior to surgery and informed consent obtained. Patients were excluded if their surgery required to be undertaken within less than 24 hours of admission on clinical grounds or if they were unable to give informed consent.

4.2.2 Patients

Basic demographic data and factors relating to the cardiac risk of surgery were gathered for each patient by a combination of history taking and case-note review. This included age, sex, smoking and medical history. Patients requiring either insulin or oral hypoglycaemics were considered diabetic. Angina, congestive cardiac failure, cerebrovascular disease and renal impairment were all recorded using the definitions in chapter 2. All patients' medication were noted with particular attention to the prescription of anti-platelets, statins, beta-blockers, diuretics, anti-hypertensives and anti-anginals. Preoperative pulse, blood pressure and oxygen saturation of haemoglobin by pulse oximetry on air were noted. Weight and height were recorded to allow calculation of BMI.

Chronic renal impairment (defined as preoperative serum creatinine of >130 µmol/l or an eGFR of <60 ml/min) was recorded. Estimated Glomerular Filtration Rate (eGFR) was calculated from serum creatinine using the Modification of Diet in Renal Disease (MDRD) Study equation:

$$\text{GFR (mL/min/1.73 m}^2) = \mathbf{186} \times (\text{Serum creatinine})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African-American})$$

This also allowed patient categorisation by Chronic Kidney Disease (CKD) stage as derived from the NICE, SIGN and Renal Association guidelines 2009.[258-260] Factors required for the Revised Cardiac Risk Index (RCRI) were also recorded and each patient scored accordingly (see section 2.5.4).

4.2.3 Preoperative Assessment

Preoperative assessment and investigation was largely at the discretion of the surgical and anaesthetic teams; however preoperative venous blood samples were sent for all patients for urea and electrolytes, lipid screen, C-reactive protein, magnesium, full blood count and coagulation screen, as well as for serum cTnI which was measured using the ARCHITECT *STAT* Troponin I immunoassay (Abbot Diagnostics, assay range of 0.02-50 ng/ml, sensitivity of ≤0.01 ng/ml). This ensured that patients with evidence of preoperative unstable cardiac disease were excluded from the study. All patients also underwent preoperative electrocardiography (ECG) performed by a cardiac technician. Information on further preoperative testing such as echocardiography, pulmonary function tests or coronary angiography was collected if available, but was not routinely performed on all patients.

Preoperative BNP samples were collected and analysed in a standard fashion. An aliquot of venous blood was obtained from recumbent patients the evening before surgery. This was collected in chilled EDTA and aprotonin (Trasylol®, Bayer, Leverkusen, Germany; 50units/ml) and immediately centrifuged at 3000rpm for 10 minutes. The serum was then removed from the tube using a pipette, placed in a plain tube and stored in a freezer at -22°C. BNP concentrations were analysed in batches at the end of the study using a standard radioimmunoassay.

4.2.4 Intraoperative Details

Intraoperative details were obtained from the anaesthetic records postoperatively. Hypotension was recorded if systolic blood pressure remained below 90 mmHg for a period of 5 minutes or more. Hypothermia was recorded if temperature dropped below 34.5 $^{\circ}$C. Aortic cross clamp times and length of operation were recorded. Blood loss was collected from intraoperative anaesthetic records. Immediate postoperative blood gasses were performed and analyses included hydrogen ion, bicarbonate and lactate concentrations, and base excess calculations where facilities allowed.

4.2.5 Postoperative Testing

Postoperative investigations were mainly conducted at the discretion of the treating physician or surgeon. In addition postoperative screening for cardiac events was performed. This consisted of daily clinical assessment, with serial ECGs and cTnI measurement on the morning of the 2nd and 5th postoperative days. If a patient was due to be discharged prior to the fifth postoperative day, tests were conducted on the morning of discharge instead of day 5. Patients were then reviewed at an outpatient clinic 6 to 8 weeks post-procedure. All ECGs were interpreted by two cardiologists of consultant or senior registrar grade who were blinded to all other data and patient details. Cardiology comments included the presence of any abnormal findings on the preoperative ECG and of ECG evidence of myocardial infarction.

4.2.6 Endpoints

Endpoints for the study were non-fatal myocardial infarction (MI) and cardiac death. The definition of a nonfatal myocardial infarction used was that of the Joint European Society of Cardiology/American College of Cardiology Committee requiring a typical rise and gradual fall in cTnI with at least one of: 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 myocardial infarction, cardiogenic shock or intractable dysrhythmia, and was determined by a review of postoperative data by two cardiologists blinded to preoperative BNP levels.

4.2.7 Statistical Analysis

Statistical analysis was performed using the SPSS® statistical software package (SPSS, Chicago, Illinois, USA). BNP values were reported as median (interquartile range) with continuous variables compared using Mann-Whitney U and Kruskall-Wallis analyses. Fisher's exact test was used to analyse the differences between independent categorical data. Receiver operating characteristics (ROC) curves were plotted and the area under the curve estimated. Multivariate logistic regression analysis was performed to determine independent factors associated with cardiac complications. A p-value <0.05 was considered significant.

4.2.8 Ethical Approval

Local Research and Development, and Central Ethics Committee approval was obtained for the study. All patients were provided with an information sheet and signed a study consent form. This study involved no additional risk to patients other than extra blood tests and non-invasive cardiac imaging.

4.3 Results

4.3.1 Patient Characteristics and BNP Levels

During the study period 111 patients met the inclusion criteria and were invited to participate. Two refused consent and a further 3 were found to have elevated preoperative cTnI and were not included, resulting in 95% inclusion. None of the 5 excluded patients developed a cardiac complication on follow-up. The median age of the remaining 106 patients was 73 (66-77) years. The median preoperative BNP level was 39.5 (18.8-97.2) pg/ml. Further baseline characteristics are shown in table 4.1. The male to female ratio shows a male predominance of 5:1. The majority of patients had smoked at some point in their life (85%). One fifth of patients had suffered a previous MI with similar numbers having suffered from cerebrovascular disease. In addition 13 patients (12%) suffered from congestive cardiac failure (CCF). As shown in table 4.2, despite the known pathology of a AAA only 59% patients were on an anti-platelet agent and 62% on a statin.

The median AAA size was 6.4 (5.7-7.2) cm. The largest AAA repaired was 9.8cm with the smallest 4.7cm. Only 8 patients had an AAA under 5.5cm whilst a further 47 patients had an AAA measuring between 5.5 and 6cm. There was no significant difference in median BNP in those with a small AAA compared to those with an AAA >5.5cm (median BNP in those with small AAA 51 [14-179] vs 40 [19-98] pg/ml, p=0.914).

BNP levels were found to be significantly higher in those that had suffered a previous MI (median BNP 70 [31-175] vs 35 [17-85] pg/ml, p=0.031) or suffered angina (median BNP 63 [31-154] vs 35 [17-81], p=0.007). Levels were also significantly higher in those that had CCF (median BNP 184.5 [72-392] vs 35 [17-60] pg/ml, p=0.002). Although not significant, BNP levels were noted to be lower in those patients prescribed a preoperative beta-blocker (median BNP 34 [14-61] vs 60 [25-129] pg/ml, p=0.050). BNP levels were also lower in those patients on antiplatelet, diuretic and anti-anginal therapy and those found to have a preoperative CRP<6, although in each case this was not significant.

Table 4.1 Clinical details and BNP levels in elective open AAA patients.

	Patient Characteristic n=106	BNP level (pg/ml)	p value
Sex			
Male	88 (83%)	42 (26-74)	
Female	18 (17%)	38.5 (17-99)	0.433
Angina			
Present	25 (24%)	63 (31-154)	
Absent	81 (76%)	35 (17-81)	0.007
Previous MI			
Present	23 (22%)	70 (31-175)	
Absent	83 (78%)	35 (17-85)	0.031
Hypertension			
Present	72 (67%)	14 (17-75)	
Absent	34 (33%)	39 (19-100)	0.915
Hyperlipidaemia			
Present	15 (14%)	30 (17-82)	
Absent	91 (86%)	40 (19-98)	1.0
Diabetes			
Present	9 (8%)	40 (18-93)	
Absent	97 (92%)	39 (32-105)	0.139
Current smoker			
Present	35 (33%)	37 (18-85)	
Absent	71 (67%)	56 (21-98)	0.713
Smoked ever			
Present	90 (85%)	62 (14-212)	
Absent	16 (15%)	40 (19-83)	0.093
CVD			
Present	22 (21%)	47 (21-100)	
Absent	84 (79%)	30 (12-55)	0.289
CCF			
Present	13 (12%)	184.5 (72-392)	
Absent	93 (88%)	35 (17-60)	0.002
COPD			
Present	25 (24%)	38 (17-100)	
Absent	81 (76%)	52 (23-75)	0.609
CRF			
Present	8 (8%)	39 (17-91)	
Absent	98 (92%)	50 (36-114)	0.634

Patient characteristics by BNP reveal significant differences in BNP levels in patients that had angina, suffered a previous MI or had CCF (p=0.007, p=0.031 and p=0.002 respectively) when analysed using Mann-Whitney U test. MI – myocardial infarction, CVD – cerebrovascular disease, CCF – congestive cardiac failure, COPD – chronic obstructive pulmonary disease, CRF - chronic renal failure.

Table 4.2 Selected other patient details and BNP.

	Patient Characteristic n=106	BNP level (pg/ml)	p value
Anti-platelet			
Present	63 (59%)	35 (17-64)	
Absent	43 (41%)	52 (20-99)	0.151
Statin			
Present	66 (62%)	37 (14-85)	
Absent	40 (38%)	43 (22-98)	0.444
Beta-blocker			
Present	43 (41%)	34 (14-61)	
Absent	63 (59%)	60 (25-129)	0.050
Antianginal			
Present	23 (22%)	39 (17-98)	
Absent	83 (78%)	61 (22-85)	0.186
Diuretic			
Present	35 (33%)	35 (17-73)	
Absent	71 (67%)	44 (21-110)	0.213
RCRI			
1	31 (29%)	32 (15-98)	
2	35 (33%)	40 (22-73)	
≥3	40 (38%)	56 (23-100)	0.193
eGFR			
>60	42 (40%)	35 (17-81)	
≥60	64 (60%)	55 (27-100)	0.461
CKD			
1	9 (8%)	21 (11-108)	
2	55 (52%)	35 (17-82)	
3	40 (38%)	55 (26-100)	
4	1 (1%)	545	
5	1 (1%)	37	0.386
CRP			
<6	62 (58%)	35 (15-60)	
≥6	44 (42%)	55 (20-100)	0.078

Although not significant, BNP levels were lower in those on antiplatelets, antianginals, diuretics and in those with a preoperative CRP<6. BNP levels were also lower in those on preoperative beta-blockers, although this did not quite reach statistical significance with p=0.050. Analyses were determined using Mann-Whitney and Kruskall-Wallis for RCRI and CKD. RCRI – revised cardiac risk index, eGFR – estimated glomerular filtration rate, CKD – chronic kidney disease, CRP – C-reactive protein.

Renal failure by chronic kidney disease stage did not show variation in BNP levels. Two patients had an eGFR <30 ml/min, one of whom had a BNP of 37 pg/ml and had an uncomplicated postoperative recovery, and the second patient had a BNP of 545pg/ml and suffered cardiac death. As a further potential confounder body mass index was calculated in all. No patient was found to have a BMI of either <20 kg/m^2 or ≥35 kg/m^2. The median BMI was 28(24-31) kg/m^2.

4.3.2 Primary Outcome and BNP

Sixteen patients (15%) suffered MACE within 30 days of their open AAA repair, of whom 5 suffered a cardiac death and 11 had a non-fatal MI. Of those suffering a non-fatal MI, 3 were of the non-ST elevation type, with 3 of the remaining 8 patients suffering asymptomatic ST-elevation MIs. As detailed in Table 4.3, patients with preoperative CCF were significantly more likely to suffer MACE (p=0.026). Patients were more likely to suffer MACE if they had preoperative hypertension, diabetes mellitus or increasing grades of CKD, although this was not statistically significant. The median estimated GFR was 54 (49-75) ml/min in those with MACE compared to 63 (51-77) ml/min in those without (p=0.283). As detailed in table 4.4 no preoperative cardiac medication appeared to be protective. Although not statistically significant, there was a greater proportion of patients suffering MACE in those taking a preoperative beta-blocker (p=0.180), and in longer operating times (median time 200 [183-240] vs 180 [150-210] mins; p=0.055) [Table 4.4].

Table 4.3 Case mix and Major Adverse Cardiac Events (MACE).

	Total Cohort (n=106)	MACE (%)	p value
Sex			
Male	88 (83%)	13/88 (15%)	
Female	18 (17%)	3/18 (17%)	0.733
Angina			
Present	25 (24%)	4/25 (16%)	
Absent	81 (76%)	12/81 (15%)	1.0
Previous MI			
Present	23 (22%)	5/23 (22%)	
Absent	83 (78%)	11/83 (13%)	0.332
Hypertension			
Present	72 (67%)	14/72 (19%)	
Absent	34 (33%)	2/34 (6%)	0.085
Hyperlipidaemia			
Present	15 (14%)	3/15 (20%)	
Absent	91 (86%)	13/91 (13%)	0.416
Diabetes			
Present	9 (8%)	3/9 (33%)	
Absent	97 (92%)	13/97 (13%)	0.134
Current smoker			
Present	35 (33%)	5/35 (14%)	
Absent	71 (67%)	11/71 (15%)	1.0
Smoked ever			
Present	90 (85%)	12/90 (13%)	
Absent	16 (15%)	4/16 (25%)	0.258
CVD			
Present	22 (21%)	2/22 (9%)	
Absent	84 (79%)	14/84 (17%)	0.515
CCF			
Present	13 (12%)	5/13 (38%)	
Absent	93 (88%)	11/86 (12%)	0.026
CRF			
Present	8 (8%)	0/8 (0%)	
Absent	98 (92%)	16/98 (16%)	0.604
CKD			
1	9 (8%)	1/9 (11%)	
2	55 (52%)	6/55 (11%)	
3	40 (38%)	8/40 (20%)	
4	1 (1%)	1/1 (100%)	
5	1 (1%)	0/1 (0%)	0.184
eGFR			
<60	42 (40%)	9/42 (21%)	
≥60	64 (60%)	7/64 (11%)	0.294

The likelihood of MACE was significantly higher in those with CCF (p=0.026). MACE was also more likely in the presence of preoperative hypertension, diabetes mellitus and increasing CKD, although this was not significant. Analyses were determined using Fisher's Exact Test. MI – myocardial infarction, CVD – cerebrovascular disease, CCF – congestive cardiac failure, CKD – chronic kidney disease, eGFR – estimated glomerular filtration rate.

Table 4.4 Other selected characteristics and Major Adverse Cardiac Events (MACE).

	Total Cohort (n=106)	MACE (%)	p value
Anti-platelet			
Present	63 (59%)	11/63 (17%)	
Absent	43 (41%)	5/43 (12%)	0.582
Statin			
Present	66 (62%)	8/66 (12%)	
Absent	40 (38%)	8/40 (20%)	0.280
Beta-blocker			
Present	43 (41%)	9/43 (21%)	
Absent	63 (59%)	7/63 (11%)	0.180
Antianginal			
Present	23 (22%)	3/23 (13%)	
Absent	83 (78%)	13/83 (16%)	1.0
Diuretic			
Present	35 (33%)	7/35 (20%)	
Absent	71 (67%)	9/71 (13%)	0.390
RCRI			
1	31 (29%)	6/31 (19%)	
2	35 (33%)	4/35 (11%)	
≥3	40 (38%)	6/40 (15%)	0.943
Hypotension			
Present	48 (45%)	7/48 (15%)	
Absent	58 (55%)	9/58 (16%)	1.0
Hypothermia			
Present	4 (4%)	1/4 (25%)	
Absent	102 (96%)	15/102(15%)	0.486
Blood Loss			
≤750ml	39 (37%)	6/39 (15%)	
>750ml	67 (63%)	10/67 (15%)	0.512
Cross Clamp time			
≤60 mins	71 (67%)	9/71 (13%)	
>60 mins	35 (33%)	7/35 (20%)	0.430
Operating times			
≤ 3 hours	58 (55%)	4/58 (7%)	
> 3 hours	48 (45%)	12/48 (25%)	0.098
CRP			
<6	62 (58%)	8/62 (13%)	
≥6	44 (42%)	8/44 (18%)	0.121

Although not significant, shorter operating and cross clamp times made MACE less likely. The use of a preoperative beta-blocker did not appear to protect against MACE and infact there was a suggestion that MACE was more likely with its use. Analyses were determined using Fisher's Exact Test. RCRI – revised cardiac risk index, CRP – C-reactive protein.

The median preoperative BNP concentration was significantly higher in patients who had MACE than in those who did not (median BNP 206 [118-454] vs 35 [17-61] pg/ml, p=0.001) [Figure 4.1]. The BNP in patients with cardiac death alone was significantly higher than in those that did not (median BNP 496 [280-881] vs 38 [18-84] pg/ml, p=0.043) [Figure 4.2]. To allow logistic regression modelling, BNP was found to best fit a base-e logarithmic transformation [Figure 4.3]. Logistic regression analysis, using eLogBNP as the covariate revealed a highly significant relationship between eLogBNP and MACE (p<0.001) with an odds ratio of 11.24 (95% CI 3.61-34.95). In a logistic regression model adjusting for hypertension, CCF, diabetes mellitus and operating time, BNP remained a highly significant predictor of MACE (p<0.001) [Table 4.5a]. The odds ratio for eLogBNP in this multivariate analysis was very large with a wide confidence interval (OR 155.03, 95% CI 6.46-3717.62; p=0.002), partly as a function of size of the ratio, but also due to the small size of the dataset. Further, the use of factors which are highly correlated with one and other (eLogBNP and CCF) has resulted in collinearity with a very low odds ratio for CCF. Logistic regression adjusting for CCF and operating time alone still revealed a large odds ratio for eLogBNP with again a wide confidence interval (OR 81.94, 95% CI 7.07-949.16; p<0.001) [Table 4.5b]. It should, however, be borne in mind that the sample size here is generally considered too small for a multivariate analysis. A univariate analysis is also significant for eLogBNP [Table 4.5c], and although the confidence intervals for the odds ratio are still wide, the lower end of it is large enough to show that BNP values are an important predictor of MACE.

4.3.3 ROC Curve Analyses and BNP

To find the BNP concentration that would best predict MACE, a receiver-operator characteristic (ROC) curve analysis was performed [Figure 4.4]. This revealed a cut-off value of 99.5 pg/ml and an area under the curve (AUC) of 0.927. With this cut-off value, sensitivity was 88% and specificity 89%. The positive predictive value (PPV) was 61% and the negative predictive value (NPV) 98%. ROC analysis was also used to predict a BNP concentration that would predict cardiac death [Figure 4.5]. A cut-off value of 448 pg/ml was identified with an AUC of 0.963. Sensitivity was 80% and specificity 100%. The PPV was 100% and NPV 99%.

Figure 4.1 BNP concentration and Major Adverse Cardiac Event (MACE).
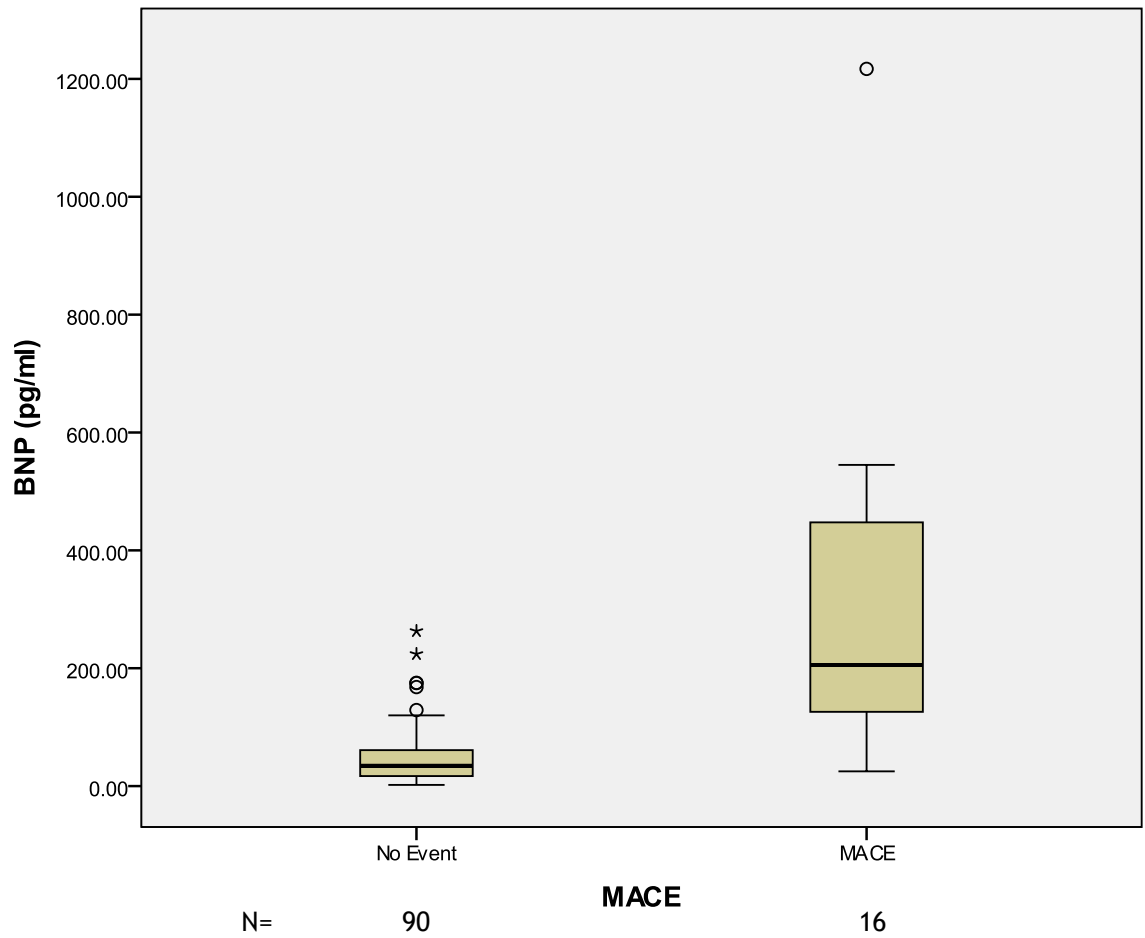
The median preoperative BNP concentration was significantly higher in those that had MACE than those that did not (median BNP 206 [118-454] vs 35 [17-61] pg/ml, p=0.001) as analysed by Mann-Whitney U test. The dots represent outliers. The asterisks/stars represent extreme outliers where the level marked is >3 times the height of the boxes. N is number of patients.

Figure 4.2 BNP concentration and cardiac death.
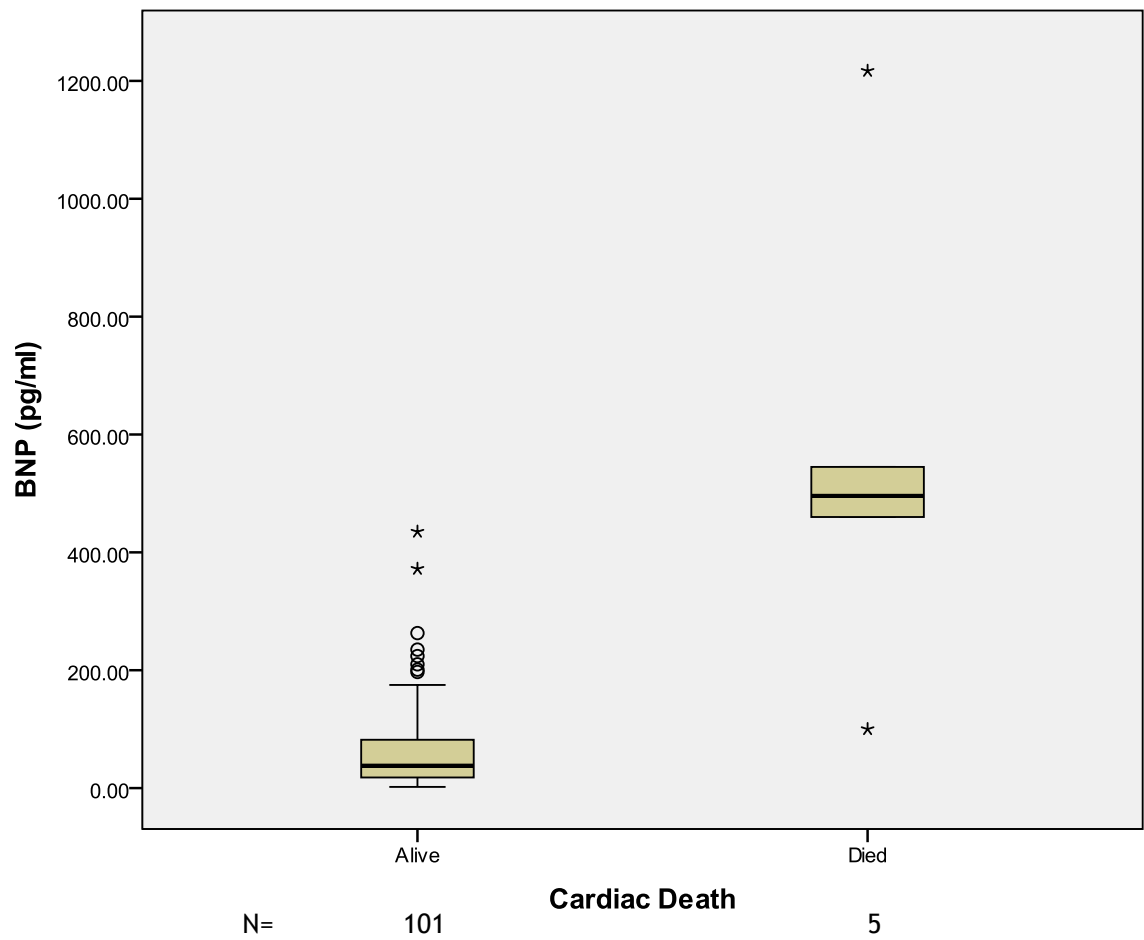
The median BNP was significantly higher in those that died of a cardiac origin compared to those that did not (median BNP 496 [280-881] vs 38 [18-84] pg/ml, p=0.043) as analysed by Mann-Whitney U test. The dots represent outliers. The asterisks/stars represent extreme outliers where the level marked is >3 times the height of the boxes. N is number of patients.

Figure 4.3 Histogram of eLogBNP.
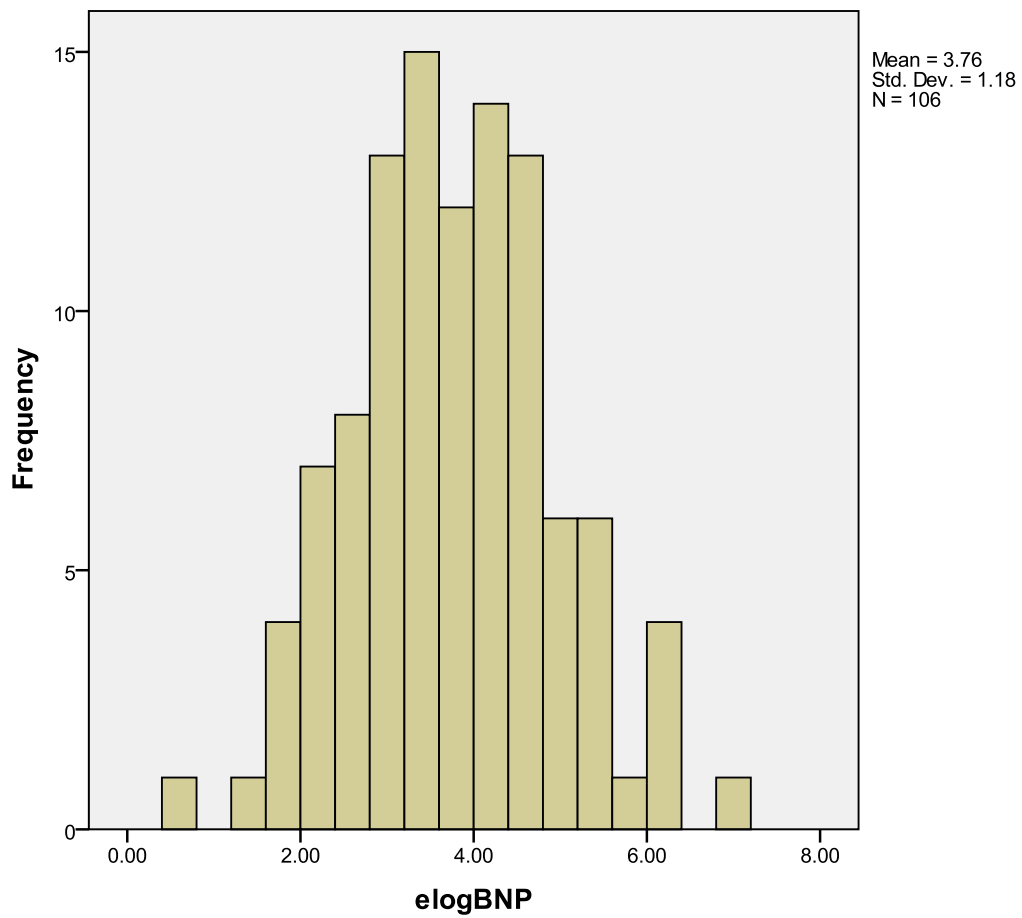
Table 4.5 Logistic regression model of eLogBNP and MACE.

a. Correcting for hypertension, diabetes mellitus (DM), congestive cardiac failure (CCF), length of operation (Op-time) and beta-blocker use – multivariate analysis.

Variable	Coef	SE Coef	Significance	Odds Ratio	95% CI Lower	95% CI Upper
Constant	-32.877	10.649	0.002			
eLogBNP	5.043	1.621	0.002	155.034	6.463	3717.626
Hypertension	1.712	1.368	0.211	5.542	0.380	80.898
DM	-0.083	1.534	0.957	0.921	0.046	18.603
CCF	-4.525	2.248	0.004	0.011	0.000	0.888
Op-time	0.034	0.016	0.030	1.035	1.003	1.067
Beta-Blocker	-0.162	1.048	0.878	0.851	0.109	6.637

b. Correcting for CCF and length of operation alone – multivariate analysis.

Variable	Coef	SE Coef	Significance	Odds Ratio	95% CI Lower	95% CI Upper
eLogBNP	4.406	1.250	0.000	81.944	7.075	949.161
CCF	-3.477	1.632	0.033	0.031	0.001	0.758
Operating time	0.031	0.011	0.007	1.032	1.009	1.054

c. Univariate analysis for eLogBNP, CCF and length of operation.

Variable	Coef	SE Coef	Significance	Odds Ratio	95% CI Lower	95% CI Upper
eLogBNP	3.260	0.841	0.000	26.045	5.009	135.424
CCF	1.397	1.560	0.026	1.601	1.104	1.934
Operating time	0.020	0.009	0.089	1.021	1.003	1.039

Figure 4.4 ROC curve: BNP concentration and Major Adverse Cardiac Event (MACE).
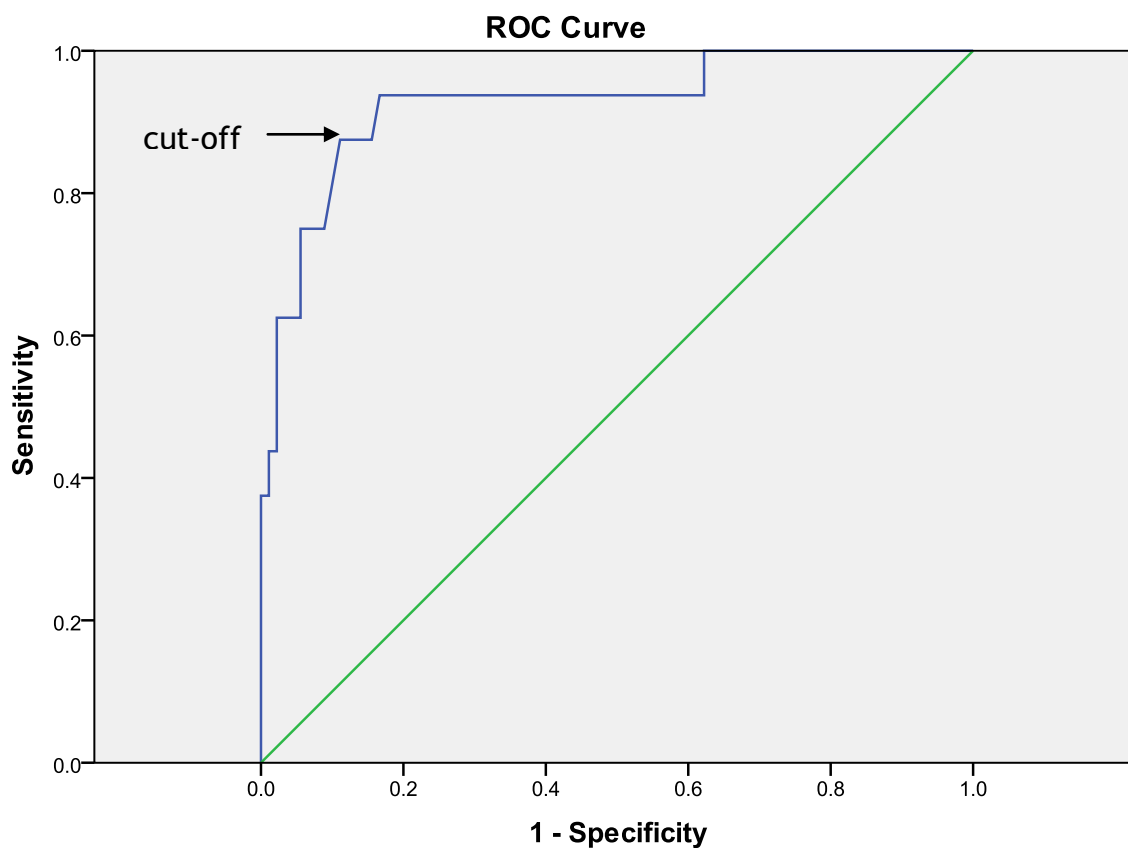
ROC analysis revealed a cut-off value of 99.5 pg/ml and an area under the curve (AUC) of 0.927, with a sensitivity of 88% and specificity 89% (SE 0.039, 95% CI 0.850-1.004; p<0.001).

Figure 4.5 ROC curve: BNP concentration and Cardiac Death.
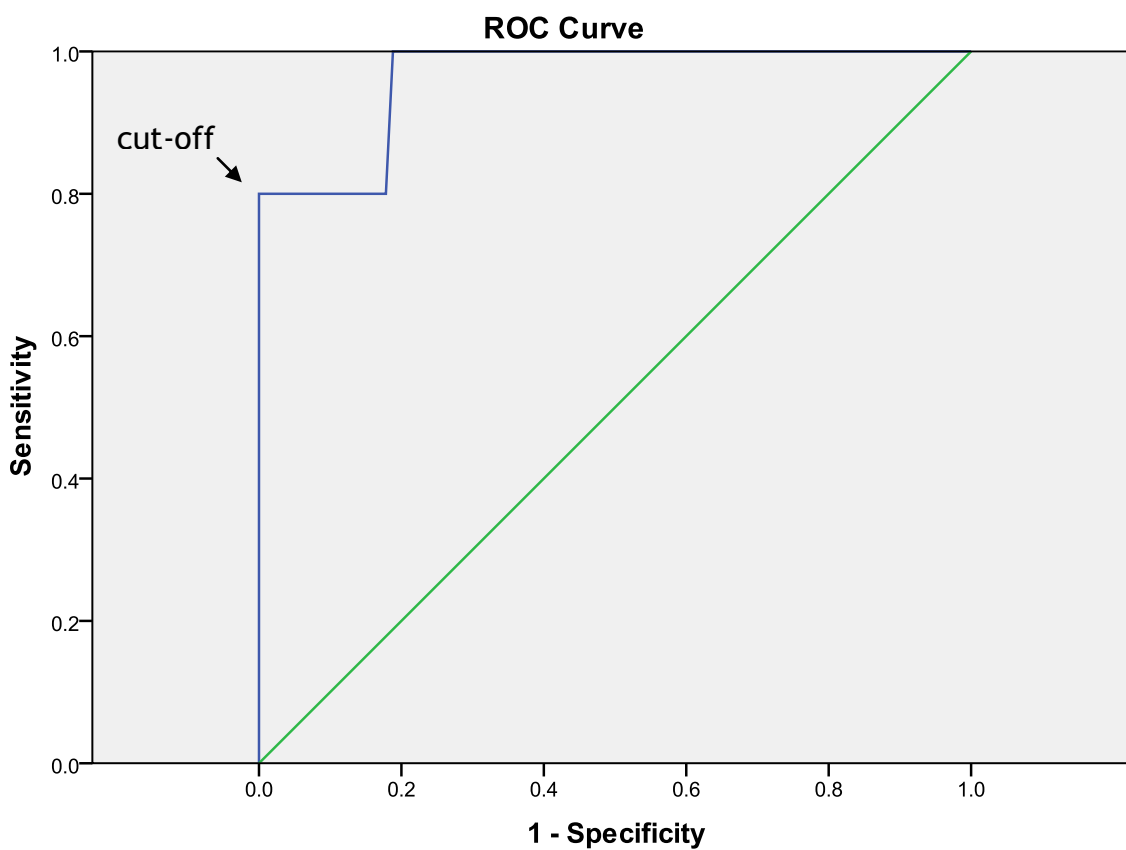
ROC analysis revealed a cut-off value of 448 pg/ml with an AUC of 0.963. Sensitivity was 80% with a specificity of 100% (SE 0.034, 95% CI 0.896-1.031; p<0.001).

4.3.4 Best Performing BNP for Prediction of MACE

Using a threshold level of 99.5 pg/ml as identified from ROC curve analyses, BNP predicted outcome independently of almost all preoperative risk factors or intraoperative factors. Only in the presence of a previous MI, diabetes mellitus or current use of a diuretic did this BNP level not predict MACE [Table 4.6]. There were no episodes of MACE in the presence of a BNP <99.5 pg/ml with both a CRP <6 and eGFR ≥60.

4.3.5 Secondary Outcome Measures and BNP

The 30-day all-cause postoperative mortality was 8.5% (9 deaths), of which 7 deaths occurred prior to hospital discharge (6.6% in-hospital mortality). As previously described 5 of these deaths were cardiac in origin. Others were:

1. Respiratory failure secondary to pneumonia on background of COPD.

2. Pulmonary thromboembolism.

3. Postoperative major haemorrhage secondary to operative complications resulting in multiorgan failure.

4. Acute mesenteric ischaemia.

The median preoperative BNP concentration was significantly higher in those that died than in those that survived the immediate postoperative period (median BNP 100 [84-521] vs 35 [17-81] pg/ml, p=0.028) [Figure 4.6]. ROC analysis revealed a cut-off of 93 pg/ml to predict 30-day all-cause mortality [Figure 4.7]. The AUC was 0.860 with associated sensitivity of 78% and specificity of 79%. Although the PPV was 30% the NPV for this value was 99%. In univariate analysis CCF was also a significant predictor of postoperative all-cause mortality (p=0.042), whereas in multivariate analysis BNP was the only significant predictor of 30-day all-cause mortality (p<0.001). However, the very low number of events (n=9) means even univariate analysis is not appropriate.

Postoperative elevations of cTnI were observed in 24 patients (23%). Of these, 8 patients (33%) had neither chest pain nor ECG changes. The median preoperative BNP concentration was significantly higher in those that had postoperative elevations of serum cTnI compared to those that did not (median BNP 75 [34-200] vs 35 [17-75], p=0.002) [Figure 4.8]. ROC analysis was less convincing with a cut-off of 54 pg/ml and an AUC of 0.704, and associated sensitivity of 64% and specificity 63% [Figure 4.9]. In univariate analysis both operative time and the presence of CCF were significant predictors of postoperative elevations of cTnI (p=0.007 and p=0.023 respectively). This was also true in multivariate analyses.

Table 4.6 MACE by a BNP cut-off of 99.5 pg/ml and by risk factors.

Patient Characteristic	BNP level (pg/ml)	MACE		p-value
Previous MI				
Present	<99.5	1/14	(7%)	
	≥99.5	4/9	(44%)	
				0.056
Absent	<99.5	1/68	(1%)	
	≥99.5	10/15	(67%)	
				<0.001
Diabetes				
Present	<99.5	1/6	(17%)	
	≥99.5	2/3	(67%)	
				0.226
Absent	<99.5	1/76	(1%)	
	≥99.5	12/21	(57%)	
				<0.001
Diuretic				
Present	<99.5	1/18	(6%)	
	≥99.5	2/5	(40%)	
				0.107
Absent	<99.5	1/64	(2%)	
	≥99.5	12/19	(63%)	
				<0.001
CRP				
<6	<99.5	0/49	(0%)	
	≥99.5	8/16	(50%)	
				<0.001
≥6	<99.5	2/33	(6%)	
	≥99.5	6/8	(75%)	
				0.002
eGFR				
≥60	<99.5	0/51	(0%)	
	≥99.5	7/13	(54%)	
				<0.001
<60	<99.5	2/31	(6%)	
	≥99.5	7/11	(64%)	
				0.004

Only in the presence of a previous MI, diabetes mellitus or current use of a diuretic BNP did not predict MACE. There were no episodes of MACE in the presence of a BNP <99.5 pg/ml with both a CRP <6 and eGFR ≥60. Analyses were performed using Fisher's Exact Test.

Figure 4.6 BNP concentration and all-cause mortality.
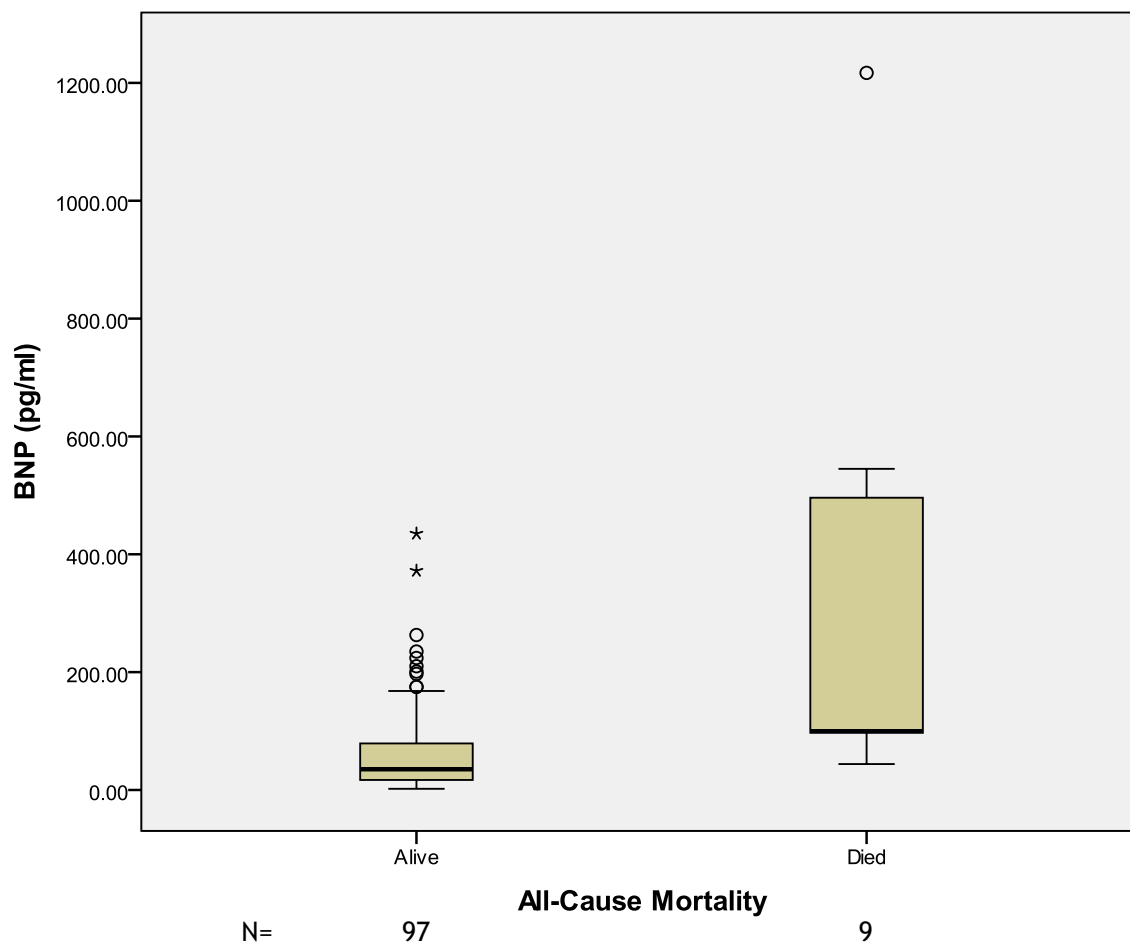
The median preoperative BNP concentration was significantly higher in those that died compared to those that survived the immediate perioperative period (median BNP 100 [84-521] vs 35 [17-81] pg/ml, p=0.028) when analysed with Mann-Whitney U test. The dots represent outliers. The asterisks/stars represent extreme outliers where the level marked is >3 times the height of the boxes. N is number of patients.

Figure 4.7 ROC curve: BNP concentration and all-cause mortality.
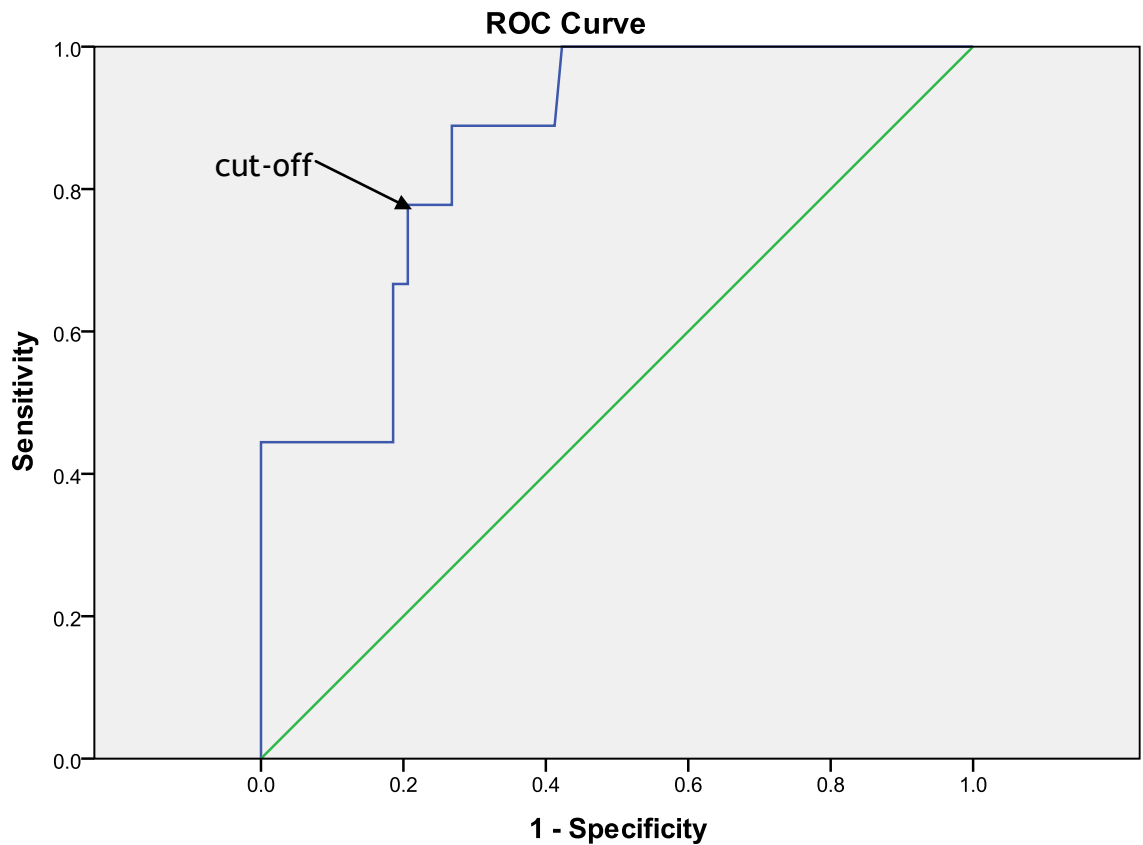
ROC Curve

Diagonal segments are produced by ties.

ROC analysis revealed a cut-off of 93 pg/ml to predict all-cause mortality with an AUC of 0.860 and associated sensitivity of 78% and specificity of 79% (SE 0.052, 95% CI 0.757-0.962; p<0.001).

Figure 4.8 BNP concentration and elevated cTnI.
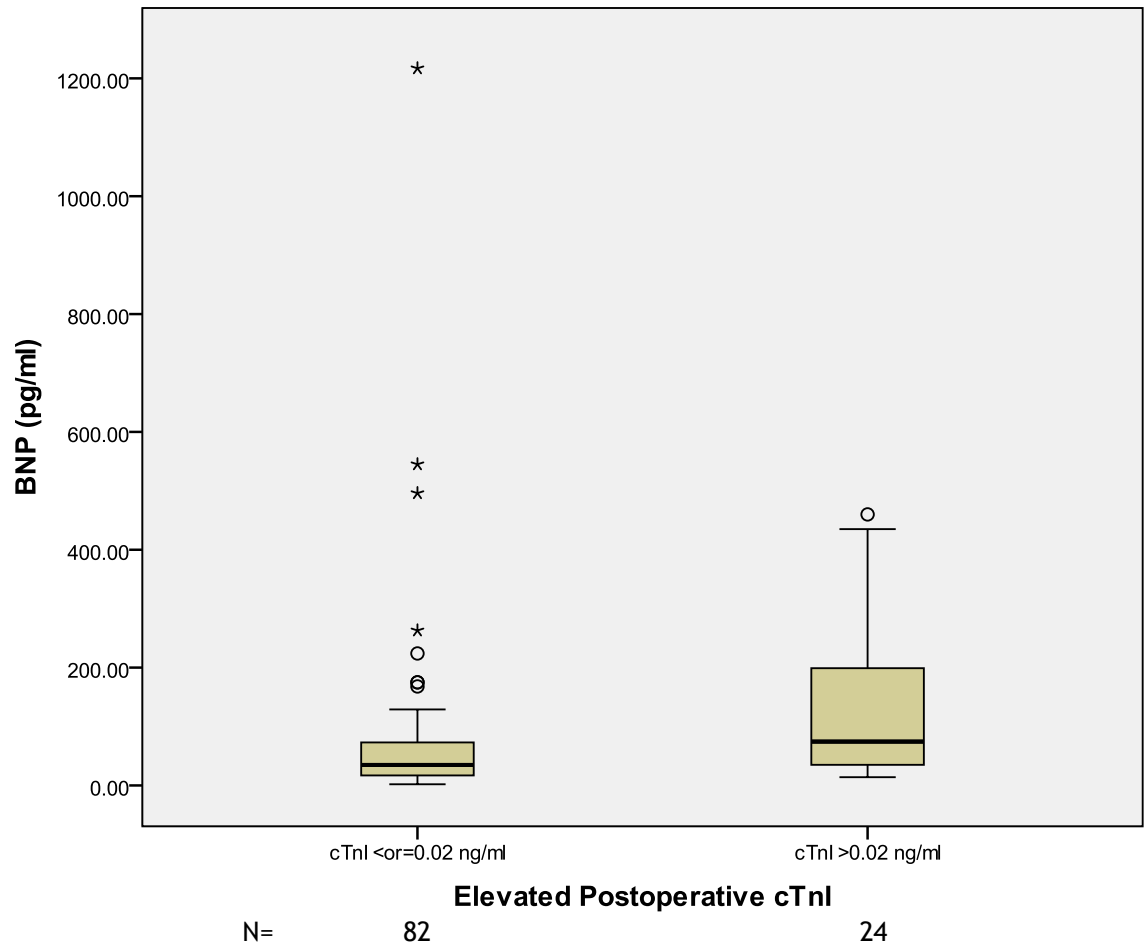
The median preoperative BNP concentration was significantly higher in those that had postoperative elevations of serum cTnI compared to those that did not (median BNP 75 [34-200] vs 35 [17-75] pg/ml, p=0.002) when tested using Mann-Whitney U analyses. The dots represent outliers. The asterisks/stars represent extreme outliers where the level marked is >3 times the height of the boxes. N is number of patients.

Figure 4.9 ROC curve: BNP concentration and elevations in cTnI.
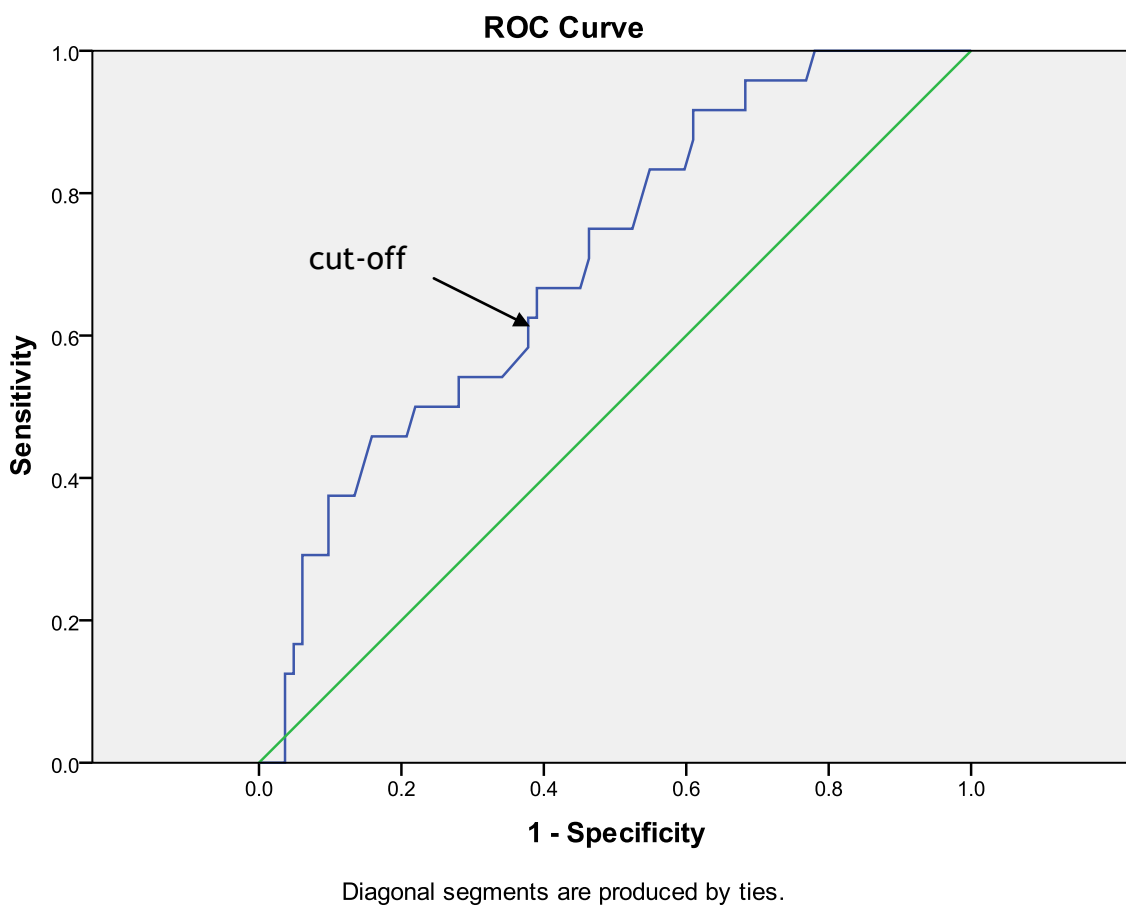
ROC analysis revealed a cut-off of 54 pg/ml with an AUC of 0.704, and associated sensitivity of 64% and specificity 63% (SE 0.057, 95% CI 0.591-0.816; p=0.002).

4.3.6 Preoperative Echocardiography

Preoperative transthoracic echocardiography was performed in 75 patients (71%). This showed moderate left ventricular (LV) dysfunction in 7, mild LV dysfunction in 8 and normal function in 60. No patient was noted to have severe LV dysfunction in the preoperative period. Median BNP levels correlated with recorded LV ejection fraction [Table 4.7]. MACE however did not correlate well with the presence of LV dysfunction or with grade of dysfunction according to transthoracic echocardiography.

Table 4.7. Left ventricular function, BNP levels and Major Adverse Cardiac Events (MACE).

	Patients (n=75)	BNP (pg/ml)	MACE
LV Function			
Normal	60 (80%)	39 (20-89)	11/60 (18%)
Mild dysfunction	8 (11%)	42 (13-150)	0/8 (0%)
Mod dysfunction	7 (9%)	79 (10-496)	2/7 (28%)
			p=0.305

4.3.7 Immediate Postoperative Arterial Blood Gas and Lactate Concentrations

Immediate postoperative arterial blood gas (ABG) analysis was performed in 66 cases. The median hydrogen ion concentration was 44.5 (40.9-48.7) nmol/l. Of the 66 patients who had available ABG analyses, 7 suffered MACE. Immediate postoperative hydrogen ion concentration did not predict MACE (median concentration in MACE of 45.1 [42.7-58] nmol/l vs 44.6 [40.6-48.5] nmol/l without, p=0.808) or all-cause mortality (median concentration in those that died 47.3 [43.9-61.0] nmol/l vs 42.3 [40.2 -48.2] nmol/l in those that survived, p=0.207). Base excess calculations had similarly poor predictive capabilities for both MACE and all-cause mortality.

Despite postoperative arterial blood gas analysis being performed in 66 patients, serum lactate concentrations were only available in 19 of these cases. Median lactate concentration was 1.7 (0.8-2.3) mmol/l. Two patients in this subgroup suffered MACE. There were no cardiac deaths in this group. Immediate postoperative serum lactate levels did not predict either MACE or all cause mortality in the 3 patients that died of a non-cardiac cause (p=0.387 and p=0.781 respectively).

4.4 Discussion

The prospective data from the elective open AAA cohort demonstrates that preoperative BNP levels predict both non-fatal MI and cardiac death in the 30-day postoperative period. Using a cut-off point of 99.5 pg/ml, similar to that seen in the diagnosis of heart failure[277], there is a 7-fold increased risk of MACE. With a sensitivity of 88% and specificity of 89%, preoperative BNP appears to outperform currently available non-invasive testing and supersedes the current gold standard of either Dipyridamole Stress Echocardiography (sensitivity ~ 74%, specificity ~ 86%) or Dobutamine Stress Echocardiography (sensitivity ~ 85%, specificity ~ 70%) as the objective cardiac risk stratification tool of choice.[72] Around 78% (83 of 106) of patients had a serum BNP level <99.5 pg/ml. Of those only 2 suffered MACE, both of which were non-fatal MIs. No cardiac deaths occurred with a serum BNP level below this cut-off. There were 3 deaths from other causes which were pulmonary thromboembolism, major postoperative haemorrhage and acute mesenteric ischaemia.

At present in the West of Scotland, there is no single cardiac risk stratification method for assessing elective open AAA patients and often the decision to operate or not is based on a balance of subjective and objective markers. This study however revealed that many current methods of identifying patients at risk of MACE are not accurate. The RCRI did not predict MACE; indeed the highest proportion of MACE was seen in the lowest risk group according to this index. The only other risk factor that significantly predicted MACE was CCF. However this is often inaccurately recorded or subjectively identified. Decisions based on this factor alone are therefore imprecise. LV function as measured by ejection fraction on preoperative echocardiography was also poor at identifying those at risk of MACE. As LV function is a marker of heart failure and therefore impacts on the serum level of BNP [101] it is not clear why this did not predict MACE, although BNP levels did correlate with the degree of heart failure.

Using an upper limit of 99.5 pg/ml for BNP in combination with both a CRP<6 mg/l and eGFR ≥60 ml/min, it is possible to identify a group of patients who are very likely to have an uncomplicated perioperative period given that in these patients no events were identified. Conversely it appears that identifying patients at high risk of cardiac death can be done by BNP level alone where this is found to exceed 448 pg/ml, with an AUC of 0.963 and combined sensitivity of 80% and specificity of 100%. Given the 100% PPV for cardiac death with a BNP over this cut-off, it would seem delaying a prophylactic procedure would be preferable to risking the considerable risk of cardiac death. Indeed one could argue that delaying or cancelling AAA repair in this group would be preferable to facing the apparent near-certainty of cardiac death.

The predictive value of BNP for 30-day all-cause mortality was unexpectedly high. Despite the fact that only 5 of the 9 deaths were cardiac in origin ROC curve analysis revealed a cut-off value of 93 pg/ml with a NPV of 99%. Given the significant perioperative mortality seen in the Small Aneurysm Trial[18] BNP may help to identify a group of patients who would yet benefit from having their small aneurysms repaired. This is further supported by the fact that in open AAA surgery cardiac death is the leading cause of death.[18, 19] Given the ability of BNP to predict cardiac events in this particular scenario, further identification of the candidates most at risk should be possible. The full conclusions regarding postoperative all-cause mortality are in long term follow-up which is explored in more detail in Chapter 5.

As described in chapter 3, numerous studies have demonstrated that postoperative elevations in cTnI, whether as a defined cardiac event or asymptomatic and without evidence of a cardiac event, are a poor prognostic marker and are associated with increased short-, intermediate- and long-term mortality.[140-143, 263, 264] This chapter demonstrates that BNP has the ability to select patients who had postoperative elevations of cTnI. The ROC curve analysis was less convincing with poor sensitivity and specificity. Of interest was that longer operating time was a significant factor in postoperative elevation in cTnI, possibly due to the excessive cardiac strain as a result of prolonged surgical stress causing myocardial ischaemia. Prolonged operating times were also more likely in those patients who suffered MACE, although this was not statistically significant.

In most patients who have very high serum BNP levels it would seem advisable to cancel their elective open AAA surgery, especially if the aneurysm is small and the risk of repair is deemed to outweigh the risk of observation. If the AAA is large and the risk of rupture considerable, other options might include consideration for EVAR or preoperative medical cardiac optimisation. A few patients with a high BNP may be deemed not suitable for EVAR. In those cases the decision to proceed with elective open surgery would be difficult and medical optimisation would be the only avenue currently left open. As discussed in the introduction, the use of statins has been explored; however in this study, although the proportion of patients who suffered MACE was lower in those on statins, this did not reach statistical significance. Preoperative beta-blockade has also been widely researched. Papers differ in their conclusions with many suggesting a benefit from beta-blockade and many not identifying any difference in outcome. In this study there were a greater proportion of events in those on beta-blockade therapy. The reason for this is unclear but may be due to collation of data, as while the use of preoperative beta-blockade was noted, whether it was given on the days (or indeed hours) directly before surgery was not, and no consideration was given to the type of beta-blockade. Some recent research has suggested that epidural anaesthesia in addition to general anaesthesia can reduce BNP levels and potentially cardiac risk.[278]

There is also evidence that aggressive medical management, in a similar manner to treating heart failure, can reduce a patients BNP level[105, 279], but whether this would then change perioperative outcome is unknown. There is no evidence to date looking at the impact of preoperative lowering of BNP on perioperative outcome in the elective AAA population.

There are some limitations in the present study. The small sample size often made statistical analysis difficult with only the most striking differences reaching statistical significance. This was also seen in ROC analysis where, with small numbers, the results at times appear unsatisfactory, for example in ROC analysis with cTnI elevations. However, a larger cohort study for this type of surgery would require at least region-wide if not national data collection to make the results meaningful. The other concern lies with the applicability of these results with populations outside Glasgow. This is clearly a limitation of this and other studies that look into perioperative BNP and this particular issue is discussed further in the final chapter.

This chapter describes a suitably powered, prospective cohort study that takes into account confounding biochemical issues, where BNP has been shown to hold important prognostic information. It outperforms all previous cardiac risk stratification tools and is both simple and objective. The use of this blood test in an outpatient clinic could prove vital in helping make the correct decision regarding the need for elective open AAA repair.

Chapter 5

B-type Natriuretic Peptide Predicts Intermediate and Long-term Outcome after Elective Open Abdominal Aortic Aneurysm Repair

5.1 Introduction

The decision to proceed to elective open repair of an AAA requires careful assessment of factors that influence rupture risk, operative mortality and life expectancy. In the case of asymptomatic AAAs management depends on the size of the aneurysm, as no medical therapy has been shown to reduce the risk of aneurysmal rupture.[17,280] Based upon the best available current evidence, 5.5cm is the best threshold for consideration of repair in the "average" patient, as it is generally accepted that the risk of rupture outweighs the operative risk at aneurysmal diameters above this. However, subsets of younger, low-risk patients or aneurysms at higher rupture risk may be identified in whom repair at smaller sizes could be justified.[281] Despite this statement, published by the vascular surgical societies of America in 2003, the management of small AAAs remain a grey area in clinical practice.

To address the issue of management of the small (4-5.5cm) asymptomatic AAA a number of randomised controlled trials have been published.[20,282-285] The two studies that come closest to answering this question are the UK Small Aneurysm Trial Participants (UKSAT) and the Aneurysm Detection and Management study screening programme (ADAM). These large and well-conducted studies randomised patients with small asymptomatic AAAs to either immediate surgery or ultrasound surveillance and have published results progressively in journals over the last 15 years. In both studies the 30-day operative mortality in the immediate surgery group (5.8% UKSAT [Figure 5.1] and 2.1% ADAM) led to an early disadvantage in terms of survival.[18,286] Long-term mortality results however revealed that there was no survival advantage in either group (surgery vs surveillance; 63.9% vs 67.3% UKSAT; 25.1% vs 21.5% ADAM).[20,285] It is therefore important that when considering risk stratification in elective AAA surgery that not only do we consider perioperative survival, but that we also look to predict long-term outcome.

Figure 5.1 Overall survival by treatment group in the UK Small Aneurysm Trial.
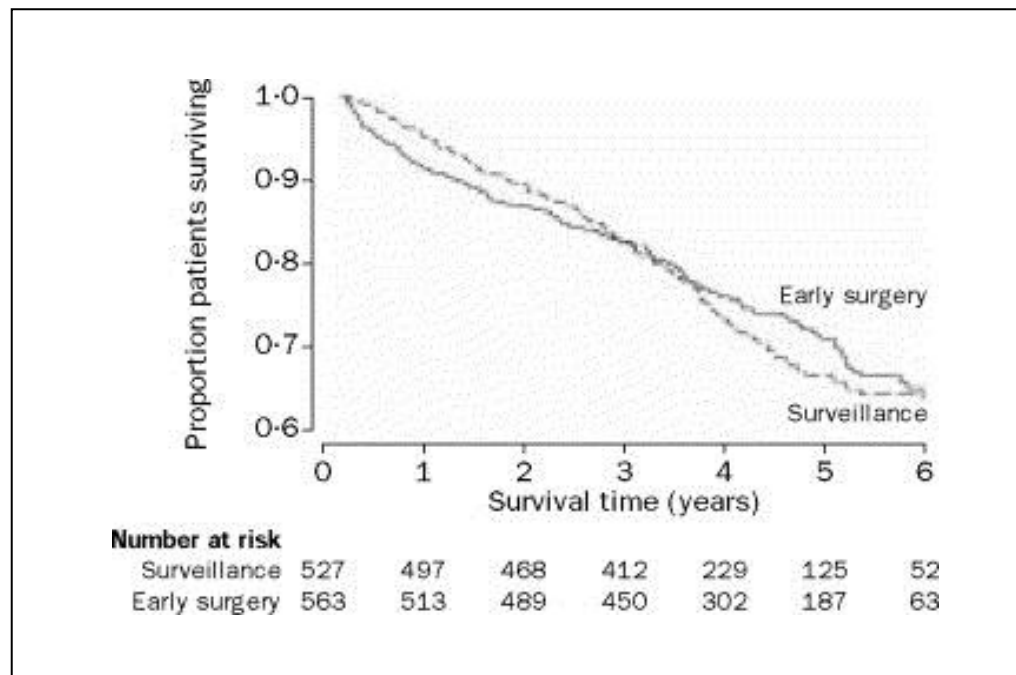
Due to the perioperative mortality rate of 5.8% survival was worse initially in the early surgery group. Survival was subsequently worse in the surveillance group so that the survival curves crossed at approximately 3 years. There were however no significant differences in mortality at 2 years, 4 years or 6 years. Kaplan-Meier estimates, log-rank test p=0·56. Adapted from [18].

As described, cardiovascular complications have been shown to be the leading cause of perioperative death in the elective open AAA repair population. This finding is also seen to hold on long-term follow-up [Table 5.1].[18] Impaired left ventricular function and inducible myocardial ischaemia are strong predictors of perioperative cardiovascular complications. Preoperative elevations in BNP have been shown to correlate with postoperative MACE in the short term.[111-120] Furthermore, a number of studies have demonstrated a greater risk of long-term MACE and all-cause mortality after major non-cardiac surgery in the presence of elevation of preoperative BNP.[114, 117, 120, 122] This has also been shown to be the case locally where preoperative BNP predicts long term survival following major non-cardiac surgery, independent of other prognostic characteristics.[287]

The study in chapter 4 has shown that preoperative elevation of BNP is associated not only with perioperative MACE, but with perioperative cardiac death and all-cause mortality. This could aid the identification of those suitable for repair of their asymptomatic small aneurysm. Whether this prognostic value remains in the long-term, in this cohort, is unknown. This chapter aims to answer the question of whether preoperative elevation in BNP can predict both all-cause mortality in the intermediate and long-term, and whether, when considering data from the UKSAT, BNP can help select suitable patients for repair of their small asymptomatic AAA.

Table 5.1 Numbers of deaths according to reported underlying cause on the death certificate by treatment group from the UKSAT.

	Deaths in surveillance group (n=150)	Deaths in early surgery group (n=159)
Cardiovascular deaths		
Total	105	94
Stroke	7	5
Ruptured thoracic aneurysm	6	2
Ruptured AAA*	17	6
After AAA repair†	18	26
Other cardiovascular deaths	27	31
Cancer deaths		
Total	27	40
Lung cancer	10	14
Other cancer deaths	17	26
Other	17	23
Unknown‡	1	2

* - ten (43%) of 23 ruptured AAA had diameter >5.5 cm, † - underlying cause of death, within 14 days of operative repair, ‡ - patient died abroad, cause of death not known, AAA – abdominal aortic aneurysm. Adapted from [18].

5.2 Methods

5.2.1 Study Population and Power

The study population was recruited as in chapter 4, and therefore comprised a prospective observational multi-centre cohort from the 3 major vascular units within Glasgow. Patients were identified from August 2005 until September 2007 and followed up for 3 years, with final follow-up data collected in September 2010. With expected all-cause mortality rate of 15-20% at 3 years[18] a minimum of 100 patients would need to be recruited and followed-up to 3 years.

5.2.2 Patients and Preoperative Assessment

Collection of patient data was identical to that described in chapter 4. Preoperative BNP samples were collected in the manner previously described.

5.2.3 Postoperative Follow-up

Immediate postoperative testing is described in detail in chapter 4. All patients were initially followed through an area wide interhospital computer database. If a patient had died, the date and cause of death were noted. If no cause of death was noted, then a death certificate review was performed. Where no recent contact was recorded, the patient's General Practice (GP) was contacted again, in the case of death, date and cause of death were noted and death certificates reviewed if necessary.

5.2.4 Endpoints

Endpoints for the study were MACE and all-cause mortality. Individual cause of death was noted but not considered separately. Due to the wide regional and national spread, case notes were not individually reviewed.

5.2.5 Statistical Analysis

Statistical analysis was performed using the SPSS® statistical software package (SPSS, Chicago, Illinois, USA). BNP values were reported as median (interquartile range) with continuous variables compared using Mann-Whitney U Test. Fisher's Exact Test was used to analyse the differences between independent categorical data. Receiver operating characteristics were plotted and the area under the curve estimated. Kaplan-Meier estimates were performed with a log rank test when comparing survival.

5.2.6 Ethical Approval

Local Research and Development, and Central Ethics Committee approval were obtained for the study. All patients were provided with an information sheet and had signed a study consent form. GPs were sent individual letters to inform them of their patients' inclusion in the study.

5.3 Results

5.3.1 Patients Characteristics and Long-term Outcome

All basic patient characteristics are described in chapter 4 and in table 5.4 and table 5.5. Of the 106 patients that underwent elective open AAA repair 97 survived the 30-day postoperative period. All patients were followed-up to a minimum of 3 years after their AAA repair. In 5 cases there had been no recent contact with the hospital or GP at 3 year follow-up. The last point of patient contact in these individual cases was at follow-up day 481, 780, 847, 996 and 1052. Median BNP in this group (n=5) was 58 (16-139) pg/ml. In none of these cases had either GP or hospital been notified of the patients' death, or had the GP been advised of geographical change in medical practice. The 3-year all-cause mortality rate was 21% (n=22) with a total of 79 patients confirmed still alive at 3 years. In the 13 deaths that occurred between 30-days and 3 years, the leading cause of death was cardiac in origin (n=3) [Table 5.2]. Other causes included respiratory disease (n=3), cerebrovascular disease (n=2), renal failure (n=2) and cancer of different primary origins (n=3).

The survival rates at 6 months, 1 year, 2 years and 3 years were 89.6%, 89.6%, 83% and 79.2% respectively. The median BNP level in those that died compared to those that survived for each time interval is shown in table 5.3. The median preoperative BNP in those who survived beyond 30 days was significantly higher in those who died in the first year (late mortality) than in those who survived over that time (median BNP 201 [97-496] vs 35 [17-73] pg/ml, p<0.001) [Figure 5.2]. The median preoperative BNP was significantly higher in those who died during the 3 year follow-up than in those who survived the study period (median BNP 98.5 [58-285] vs 32 [17-71.5] pg/ml, p<0.001) [Figure 5.3].

Despite the fact that death was attributed to a cardiac cause in only 3 cases, those that did suffer a cardiac death between 30 days and 3 years had a significantly higher preoperative BNP level compared to those that did not (median BNP 112[46-435] vs 35[17-75] pg/ml, p=0.049) on Mann-Whitney U analysis.

Table 5.2 Cause of death in 13 of the 97 patients that died within 3 years of elective open AAA repair.

	No.
Fatal myocardial infarction	2
Ventricular rupture	1
Respiratory disease	3
Cerebrovascular accident	2
End-stage renal failure	1
Acute renal failure 2e to sepsis	1
Oesophagogastric carcinoma	1
Colonic carcinoma	1
Bronchial carcinoma	1

Causes of death between postoperative day 30 and 3 years reveal cardiac and respiratory causes as the most frequent cause. Cancer compromised 23% of deaths, similar to that seen in both UKSAT and ADAM.

Table 5.3 Long-term outcomes by median BNP level.

		n (%)	BNP*	p value
Perioperative	Yes	9/106 (8.4%)	100 (84-521)	
All-cause mortality	No	97/106 (91.6%)	35 (17-81)	*0.028*
Late Mortality	Yes	11/106 (10.4%)	201 (97-496)	
(30-days to 1 year)	No	95/106 (89.6%)	35 (17-73)	*<0.001*
Mortality at 1 year	Yes	11/106 (10.4%)	201 (97-496)	
	No	95/106 (89.6%)	35 (17-73)	*<0.001*
Mortality at 2 years	Yes	18/106 (17%)	98.5 (42.25-291.25)	
	No	88/106 (83%)	34.5 (17-77.5)	*0.002*
Mortality at 3 years	Yes	22/106 (20.8%)	98.5 (58-285)	
	No	84/106 (79.2%)	32 (17-71.5)	*<0.001*

Univariate analyses reveal a significant difference in median BNP levels between those that died and those that survived at all stages of follow up with higher levels in those that died. Analyses were performed using Mann-Whitney U test.

Figure 5.2 BNP concentration and late mortality (30 day-1 year).
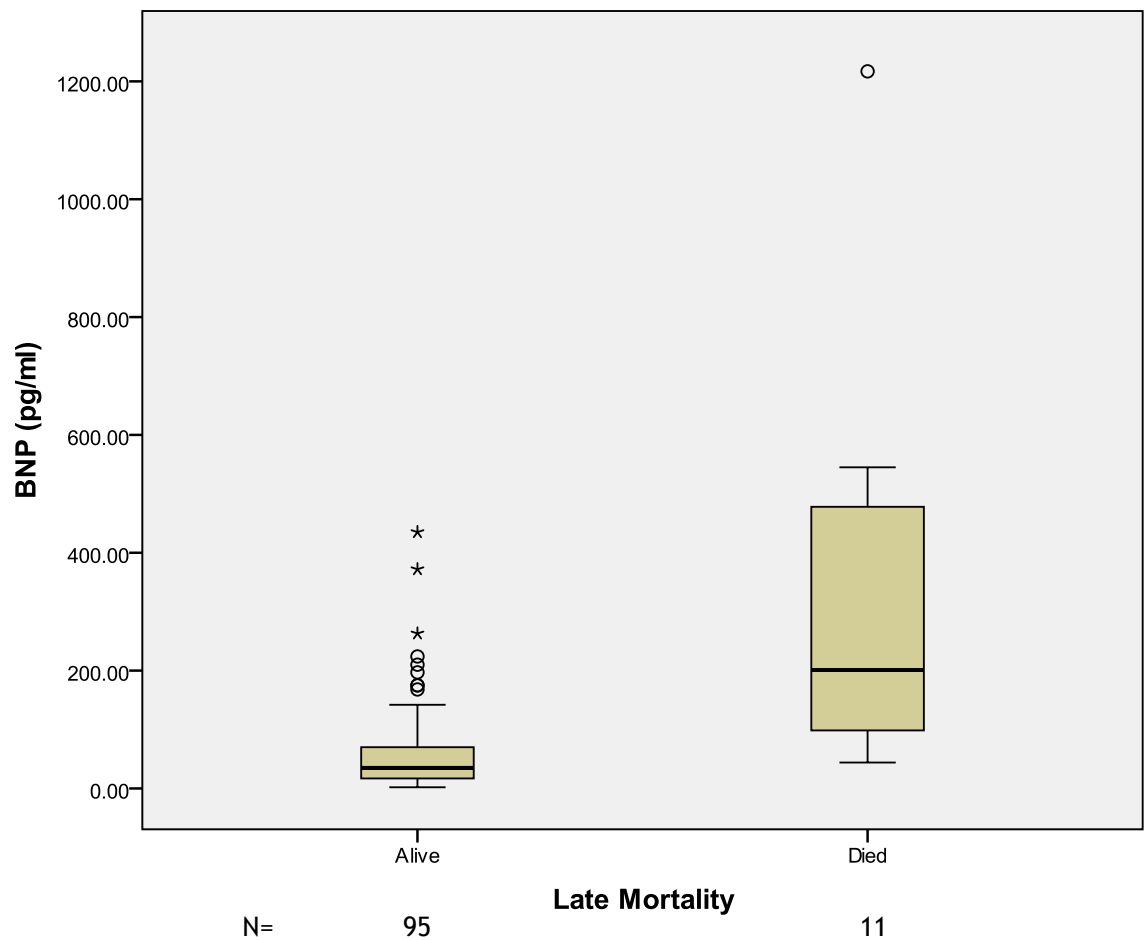
The median BNP was significantly higher in those that died between 30 postoperative days and 1 year, compared to those that did not (median BNP 201 [97-496] vs 35 [17-73] pg/ml, p<0.001) as calculated by Mann-Whitney U test. The dots represent outliers. The asterisks/stars represent extreme outliers where the level marked is >3 times the height of the boxes. N is number of patients.

Figure 5.3 BNP concentration and 3-year mortality.
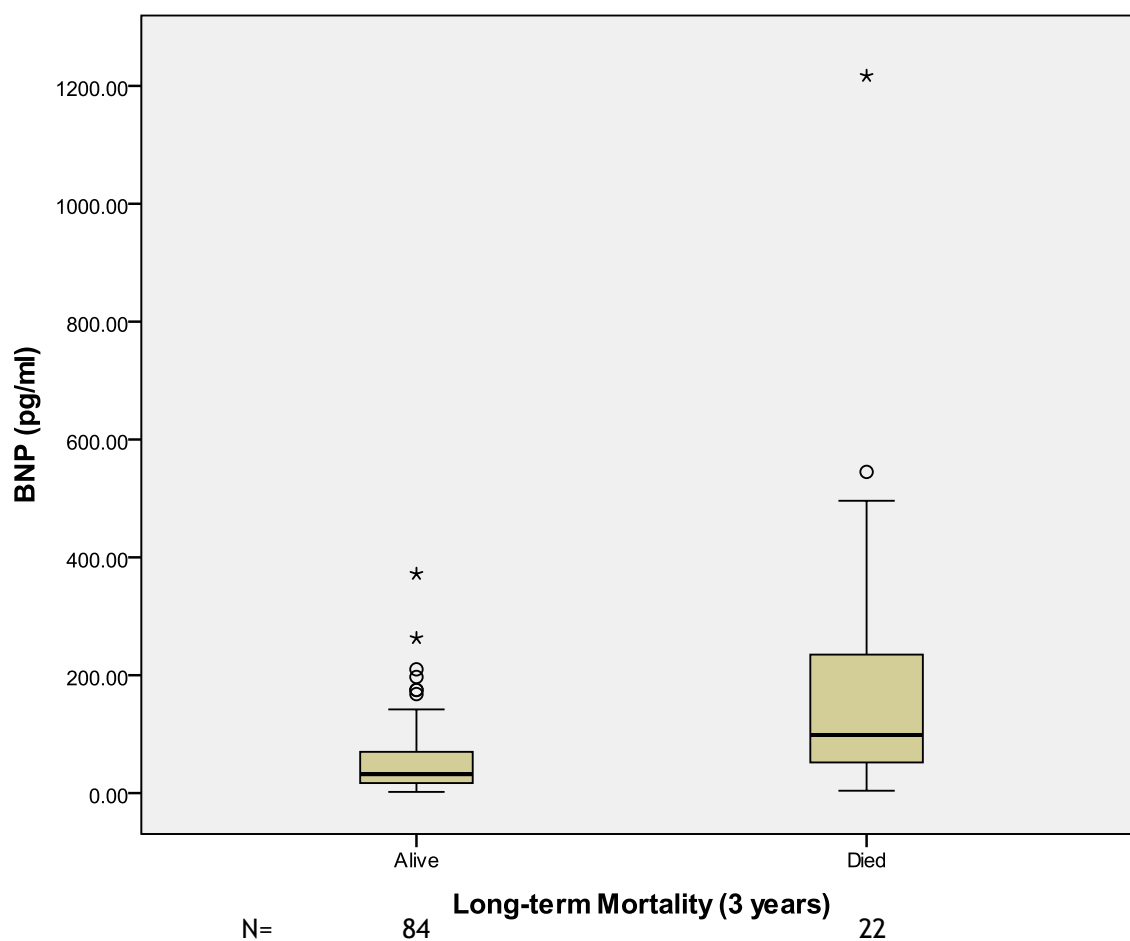
The median BNP was significantly higher in those that died by 3 postoperative years compared to those that did not (median BNP 98.5 [58-285] vs 32 [17-71.5] pg/ml, p<0.001) as calculated by Mann-Whitney U test. The dots represent outliers. The asterisks/stars represent extreme outliers where the level marked is >3 times the height of the boxes. N is number of patients.

The median age in those that died after 30 days but in the first year was 74 (67-77) years compared to 72 (66-77) years in those that survived (p=0.324). The median age in those that died by 3 postoperative years was 74 (67-78) years compared to 72 (65-76) years in those that survived. Univariate analysis of other patient characteristics at all stages of follow up reveal that the presence of CCF was a significant predictor of outcome with death more likely (late mortality p<0.001, 3 year mortality p<0.001). The presence of worsening renal function in relation to CKD stage also made death more likely at 3 years (p=0.031) [Table 5.4]. Although not significant, a longer operating time made late mortality more likely (p=0.081). The presence of a previous MI made 3 year mortality more likely, but not significantly so (p=0.063). None of these studied intraoperative factors or preoperative medication was found to predict outcome at any stage on univariate analyses [Table 5.5].

Multivariate analysis for factors with a p<0.100 in univariate analysis included preoperative MI, CCF, CKD and BNP. In this model only BNP was an independent predictor of both late and 3 year mortality although the odds ratio was low (OR 0.992, 95% CI 0.986-0.999, p=0.017 for late mortality; OR 0.991, 95% CI 0.985-0.995, p=0.012 for 3-year mortality).

Table 5.4 Case mix and outcome.

		Total Cohort (n=106)	Periop Mortality n (%)	Late Mortality n (%)	3-year Mortality n (%)
Sex					
	Male	88 (83%)	7/88 (8%)	9/88 (10%)	19/88 (22%)
	Female	18 (17%)	2/18 (11%)	2/18 (11%)	3/18 (17%)
Previous MI					
	Present	23 (22%)	3/23 (13%)	4/23 (17%)	8/23 (35%)
	Absent	83 (78%)	6/83 (7%)	7/83 (8%)	14/83 (17%)
Hypertension					
	Present	72 (67%)	7/72 (10%)	8/72 (11%)	15/72 (21%)
	Absent	34 (33%)	2/34 (6%)	3/34 (9%)	7/34 (21%)
Hyperlipidaemia					
	Present	15 (14%)	0/15 (0%)	1/15 (7%)	3/15 (20%)
	Absent	91 (86%)	9/91 (10%)	10/91 (11%)	19/91 (21%)
Diabetes					
	Present	9 (8%)	2/9 (22%)	2/9 (22%)	2/9 (22%)
	Absent	97 (92%)	7/97 (7%)	9/97 (9%)	20/97 (21%)
Current smoker					
	Present	35 (33%)	4/35 (11%)	5/35 (14%)	8/35 (23%)
	Absent	71 (67%)	5/71 (7%)	6/71 (8%)	14/71 (20%)
Smoked ever					
	Present	90 (85%)	8/90 (9%)	9/90 (10%)	19/90 (21%)
	Absent	16 (15%)	1/16 (6%)	2/16 (13%)	3/16 (19%)
CVD					
	Present	22 (21%)	4/22 (18%)	4/22 (18%)	6/22 (27%)
	Absent	84 (79%)	5/84 (6%)	7/84 (8%)	16/84 (19%)
CCF					
	Present	13 (12%)	5/13 (38%)‡	7/13 (54%)§	9/13 (69%)§
	Absent	93 (88%)	4/86 (5%)	4/86 (5%)	13/86 (15%)
CRF					
	Present	8 (8%)	1/8 (13%)	1/8 (13%)	1/8 (13%)
	Absent	98 (92%)	8/98 (8%)	10/98 (10%)	21/98 (21%)
CKD					
	1	9 (8%)	0/9 (0%)†	0/9 (0%)	0/9 (0%)†
	2	55 (52%)	2/55 (4%)	4/55 (7%)	10/55 (18%)
	3	40 (38%)	6/40 (15%)	6/40 (15%)	10/40 (25%)
	4	1 (1%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
	5	1 (1%)	0/1 (0%)	0/1 (0%)	1/1 (100%)
eGFR					
	<60	42 (40%)	7/42 (17%)†	7/42 (17%)	12/42 (29%)
	≥60	64 (60%)	2/64 (3%)	4/64 (6%)	10/64 (16%)

The likelihood of perioperative death was significantly higher in those with CCF, CKD and a lower eGFR ($p=0.002$, $p=0.010$ and $p=0.027$). Only in CCF was late mortality more likely ($p<0.001$). The likelihood of 3 year mortality was significantly higher in those with CCF and CKD ($p<0.001$ and $p=0.031$). Analyses were determined using Fisher's Exact Test. MI – myocardial infarction, CVD – cerebrovascular disease, CCF – congestive cardiac failure, CKD – chronic kidney disease, eGFR – estimated glomerular filtration rate. †$p<0.050$, ‡$p<0.010$, §$p<0.001$.

Table 5.5 Other selected characteristics and outcome.

	Total Cohort (n=106)	Periop Mortality n (%)	Late Mortality n (%)	3-year Mortality n (%)
Anti-platelet				
Present	63 (59%)	6/63 (10%)	7/63 (11%)	11/63 (17%)
Absent	43 (41%)	3/43 (7%)	4/43 (9%)	11/43 (26%)
Statin				
Present	66 (62%)	5/66 (8%)	5/66 (8%)	13/66 (20%)
Absent	40 (38%)	3/40 (8%)	6/40 (15%)	9/40 (23%)
Beta-blocker				
Present	43 (41%)	3/43 (7%)	5/43 (12%)	8/43 (19%)
Absent	63 (59%)	6/63 (10%)	6/63 (10%)	14/63 (22%)
Antianginal				
Present	23 (22%)	2/23 (9%)	2/23 (9%)	3/23 (13%)
Absent	83 (78%)	7/83 (8%)	9/83 (11%)	19/83 (23%)
Diuretic				
Present	35 (33%)	2/35 (6%)	2/35 (6%)	5/35 (14%)
Absent	71 (67%)	7/71 (10%)	9/71 (13%)	17/71 (24%)
Hypotension				
Present	48 (45%)	4/48 (8%)	6/48 (13%)	11/48 (23%)
Absent	58 (55%)	5/58 (9%)	5/58 (9%)	11/58 (19%)
Hypothermia				
Present	4 (4%)	0/4 (0%)	0/4 (0%)	1/4 (25%)
Absent	102 (96%)	9/102 (9%)	11/102 (11%)	21/102 (21%)
Blood Loss				
≤750ml	39 (37%)	4/39 (10%)	4/39 (10%)	8/39 (21%)
>750ml	67 (63%)	5/67 (7%)	7/67 (10%)	14/67 (21%)
Cross Clamp time				
≤60 mins	71 (67%)	7/71 (10%)	7/71 (10%)	16/71 (23%)
>60 mins	35 (33%)	2/35 (6%)	4/35 (11%)	6/35 (17%)
Operating times				
≤ 3 hours	58 (55%)	3/58 (5%)	3/58 (5%)	10/58 (17%)
> 3 hours	48 (45%)	6/48 (13%)	8/48 (17%)	12/48 (25%)
CRP				
<6	62 (58%)	7/62 (11%)	8/62 (13%)	14/62 (23%)
≥6	44 (42%)	2/44 (5%)	3/44 (7%)	8/44 (18%)

Although not significant, shorter operating time made late mortality less likely (p=0.063). There were no other factors that made death at any stage more likely. Analyses were performed using Fisher's Exact Test. CRP – C-reactive protein.

5.3.2 ROC Analysis and Outcome

The receiver operating characteristic (ROC) curve analysis was performed to identify the BNP concentration threshold that best predicted late and long term mortality [Table 5.6]. With regards to late mortality, a BNP concentration of 93.0 pg/ml had the best combined sensitivity (81%) and specificity (82%), and the area under the curve (AUC) was 0.885 (SE 0.043, 95% CI 0.80-0.97, $p < 0.001$) [Figure 5.4]. When analysing preoperative BNP concentration with regards to 3 year mortality a cut-off of 60.5 pg/ml had the best combined sensitivity (68%) and specificity (73%) with an AUC of 0.761 (SE 0.060, 95% CI 0.645-0.878, $p < 0.001$) [Figure 5.5].

5.3.3 Postoperative MACE, Elevations in cTnI and Long-term Outcome

Postoperative MACE, without death, was significantly associated with 1 year mortality (2/11 [18%] vs 0/86 [0%], $p < 0.001$). While mortality at 2 years (2/11 [18%] vs 8/86 [9%], $p = 0.285$) and 3 years (3/11 [27%] vs 10/86 [12%], $p = 0.155$) was more common in those with postoperative MACE, this was not statistically significant.

Immediate postoperative elevation in cTnI, regardless of clinical outcome or the presence of a defined event, was associated with increased long-term mortality, although this was not statistically significant. All-cause mortality rates were higher in this group of patients at all studied time intervals (1 year 4/26 [15%] vs 7/80 [9%], $p = 0.066$; 2 years 6/26 [23%] vs 12/80 [15%], $p = 0.076$; 3 years 7/26 [27%] vs 15/80 [19%], $p = 0.100$).

Table 5.6 Results of receiver operating characteristic curve analysis for BNP according to outcome.

	AUC	95% CI	SE	p-value	cut-off	Sens.	Spec.	PPV	NPV
Perioperative Death	0.860	0.757-0.962	0.057	<0.001	93.0 pg/ml	78%	79%	30%	99%
Late Mortality (30 days-1 year)	0.885	0.80-0.97	0.043	<0.001	93.0 pg/ml	81%	82%	35%	97%
2-year Mortality	0.733	0.597-0.896	0.069	0.002	68.5 pg/ml	61%	74%	33%	90%
3-year Mortality	0.761	0.645-0.878	0.060	<0.001	60.5 pg/ml	68%	73%	41%	90%

ROC curve analysis of BNP in relation to outcome reveals that BNP performs well when predicting death at all stages of follow-up. The cut-off value is seen to decrease as follow-up time increases however degree of significance stays similarly low throughout. As follow-up time increases the PPV improves and the NPV diminishes. AUC – area under the curve, CI – confidence interval, SE- standard error, Sens. – Sensitivity, Spec. – Specificity, PPV – positive predictive value, NPV – negative predictive value.

Figure 5.4 ROC curve: BNP concentration and late mortality (30 days – 1 year).
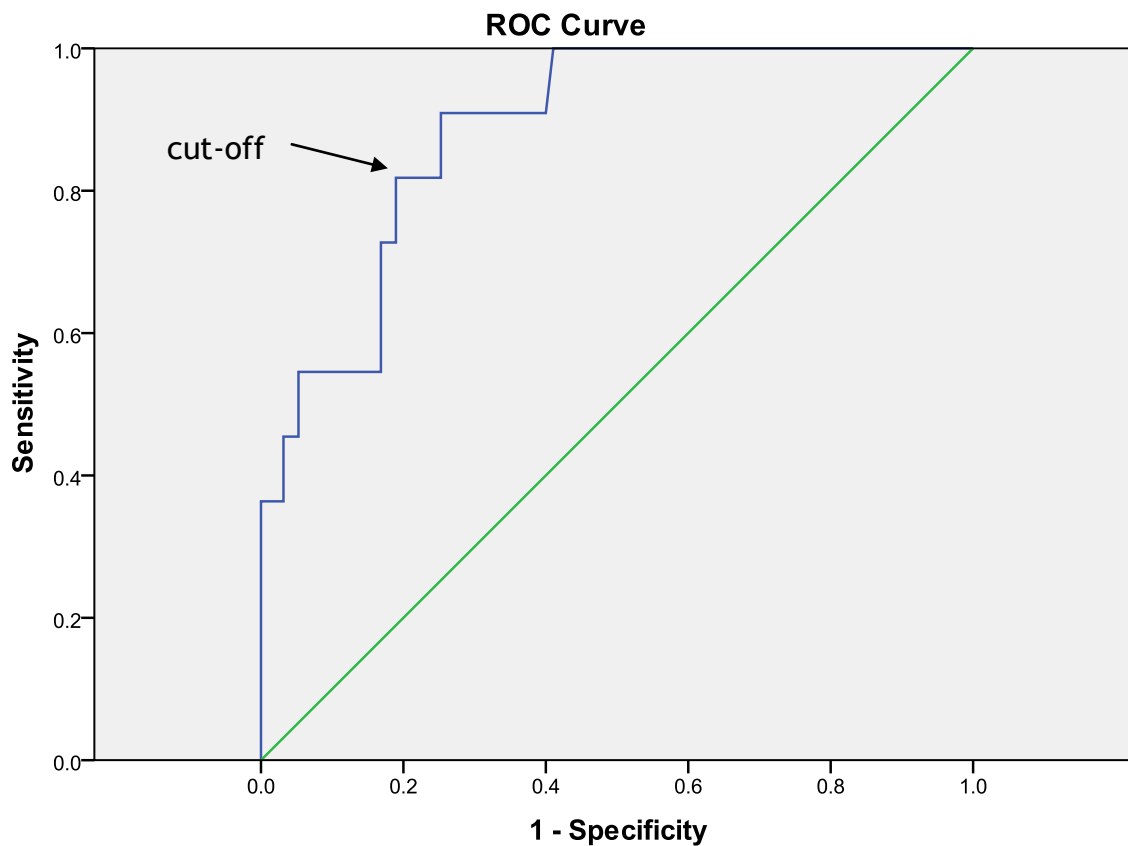
Diagonal segments are produced by ties.

ROC analysis revealed a cut-off value of 93.0 pg/ml and an area under the curve (AUC) of 0.885, with a sensitivity of 81% and specificity 82% (SE 0.043, 95% CI 0.80-0.97; p<0.001).

Figure 5.5 ROC curve: BNP concentration and 3-year mortality.

ROC Curve
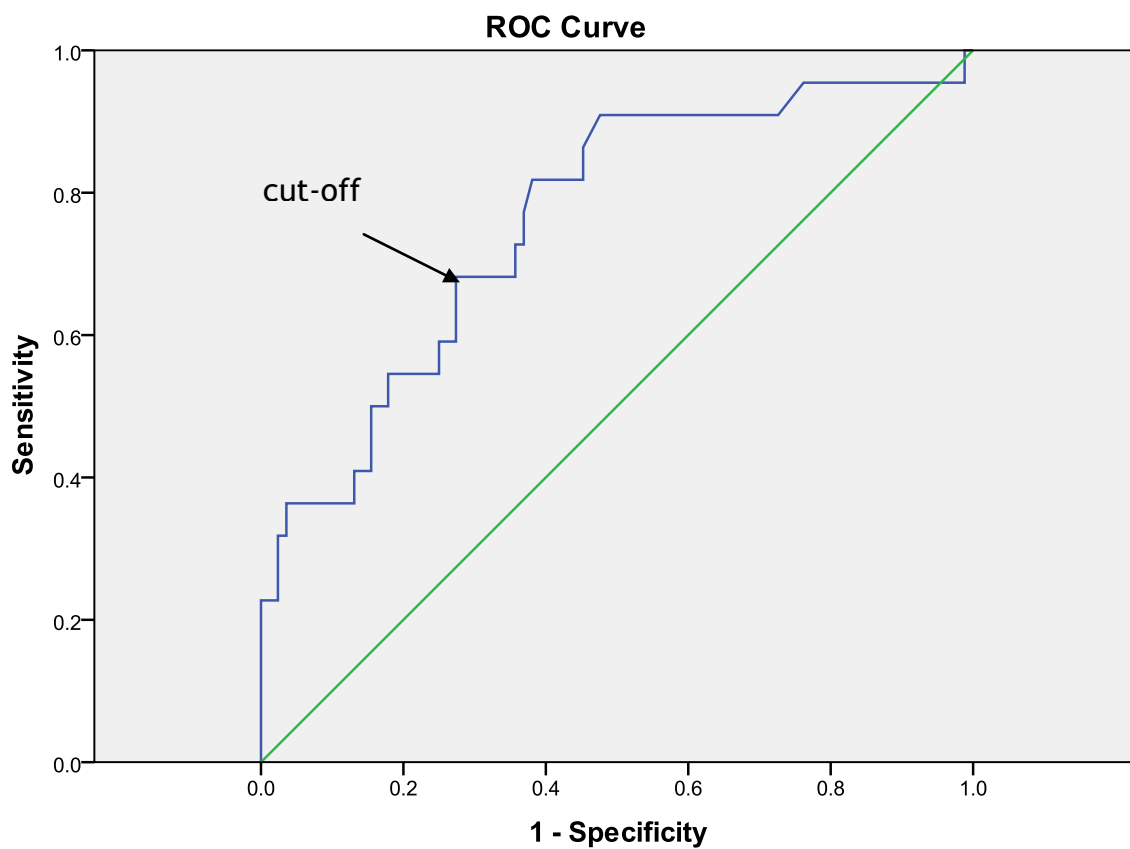
Diagonal segments are produced by ties.

ROC analysis revealed a cut-off value of 60.5 pg/ml and an area under the curve (AUC) of 0.761, with a sensitivity of 68% and specificity 73% (SE 0.060, 95% CI 0.645-0.878; p<0.001).

5.3.4 Survival Analysis

5.3.4.1 Cut-off BNP 99.5 pg/ml (MACE) and 93.0 pg/ml (perioperative death)

The mean survival of patients with a BNP >99.5 pg/ml was 1291 (95% CI 882-1701) days compared with 1916 (95% CI 1774-2057) days when BNP <99.5 pg/ml (p<0.001) [Figure 5.6]. During the first six months the rate of postoperative death in those with a BNP >99.5 pg/ml was 8.6 times greater than in those with a BNP below this threshold (32% vs 3.7%, p<0.001). At the minimum point of follow-up (3 postoperative years) the rate of death was 3.4 times greater in those with a BNP >99.5 pg/ml (48% vs 14%, p<0.001). In those who survived beyond the first 6 postoperative months, there was no significant difference in survival thereafter between those with a BNP >99.5 pg/ml (1923 [95% CI 1623-2334] days) and those with a BNP <99.5 pg/ml (1988 [95% CI 1866-2109] days) (p=0.442) [Figure 5.7].

Similarly significant differences in mean survival figures were observed between those with a BNP <93 pg/ml compared to a level of >93 pg/ml (1320 [95% CI 931-1708] days vs 1931 [95% CI 1791-2070) days, p<0.001) [Figure 5.8]. During the first six months the rate of postoperative death was 13.2 times higher in those with BNP levels above the threshold (33% vs 2.5%, p<0.001). At 3 years the rate of death was 3.2 times higher in those with BNP levels >93.0 pg/ml (44% vs 13.9%, p<0.001). When analysis was restricted to those who survived beyond 6 postoperative months there was no significant difference in outcome. Within this subgroup the mean survival in those with a BNP >93.0 pg/ml compared to those with a BNP <93.0 pg/ml was 1966 days (95% CI 1618-2236) vs 1980 days (95% CI 1856-2105), p=0.653.

Figure 5.6 Kaplan-Meier curve of survival according to BNP level with a cut-off of 99.5 pg/ml.
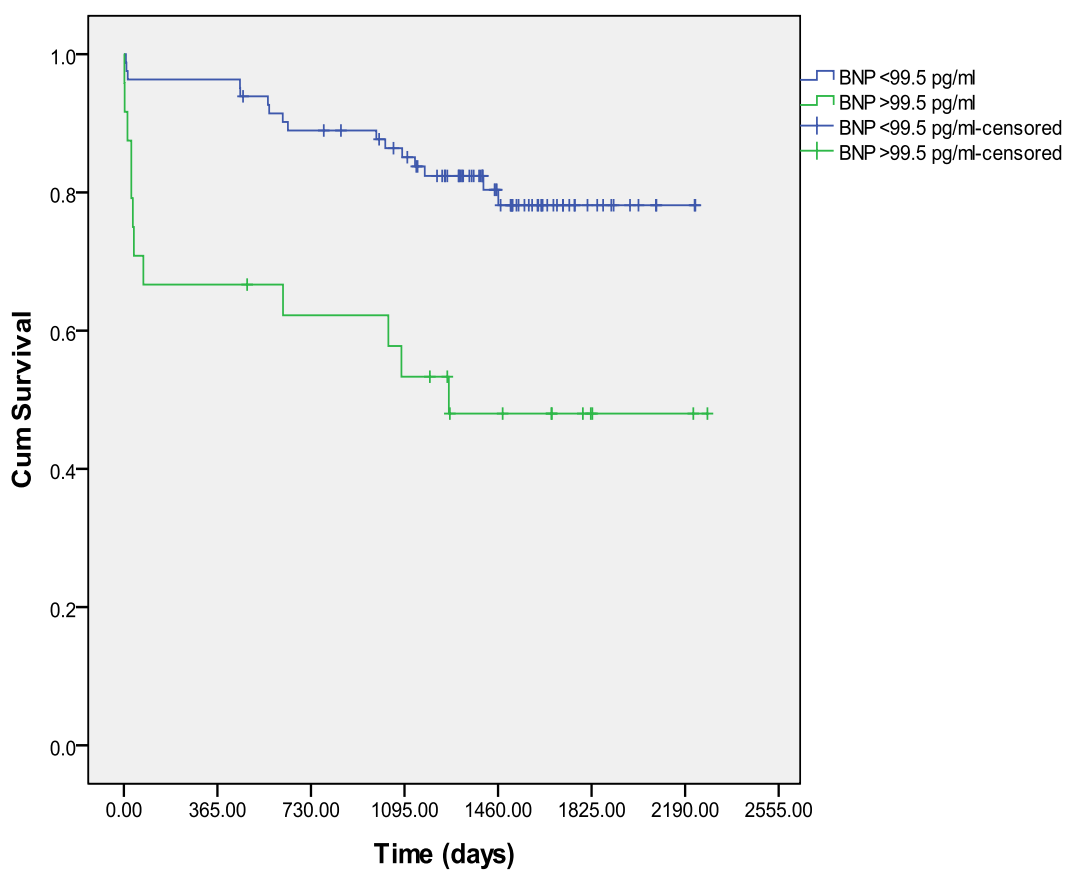
Patients at risk:

<99.5 pg/ml	82	79	72	66	35	15
>99.5 pg/ml	24	16	14	12	8	4

Kaplan-Meier survival analysis reveals a significant difference in long term outcome when comparing groups based on a cut-off BNP level of 99.5 pg/ml (mean survival 1291 [95% CI 882-1071] vs 1916 [95% CI 1774-2057] days, p<0.001). Longer survival was seen in those with lower BNP levels.

Figure 5.7 Kaplan-Meier curve of survival according to BNP level with a cut-off of 99.5 pg/ml in only those that survived beyond six postoperative months.
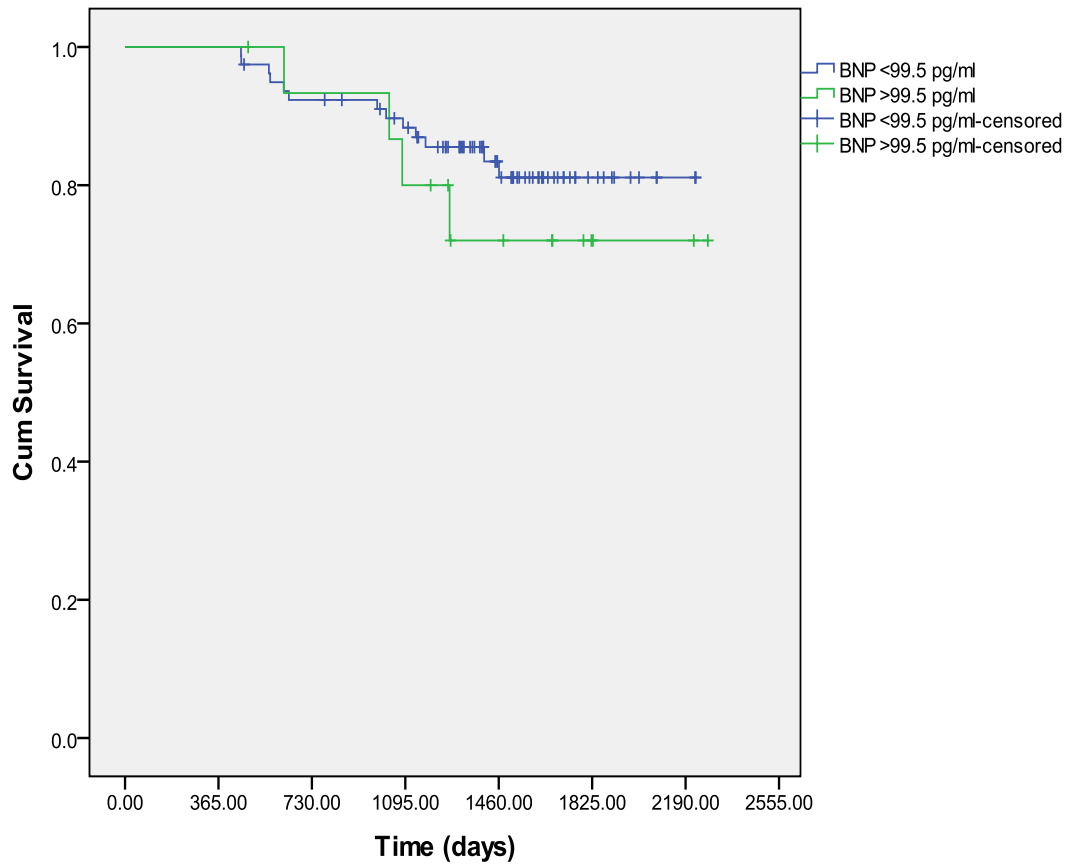
Patients at risk:

<99.5 pg/ml	79	79	72	66	35	15
>99.5 pg/ml	16	16	14	12	8	4

Kaplan-Meier survival analysis reveals no difference in long term outcome when including only those that survived beyond 6 months and comparing groups based on a cut-off BNP level of 99.5 pg/ml (mean survival 1923 [95% CI 1623-2334] vs 1988 [95% CI 1866-2109] days, p=0.442).

Figure 5.8 Kaplan-Meier curve of survival according to BNP level with a cut-off of 93 pg/ml.
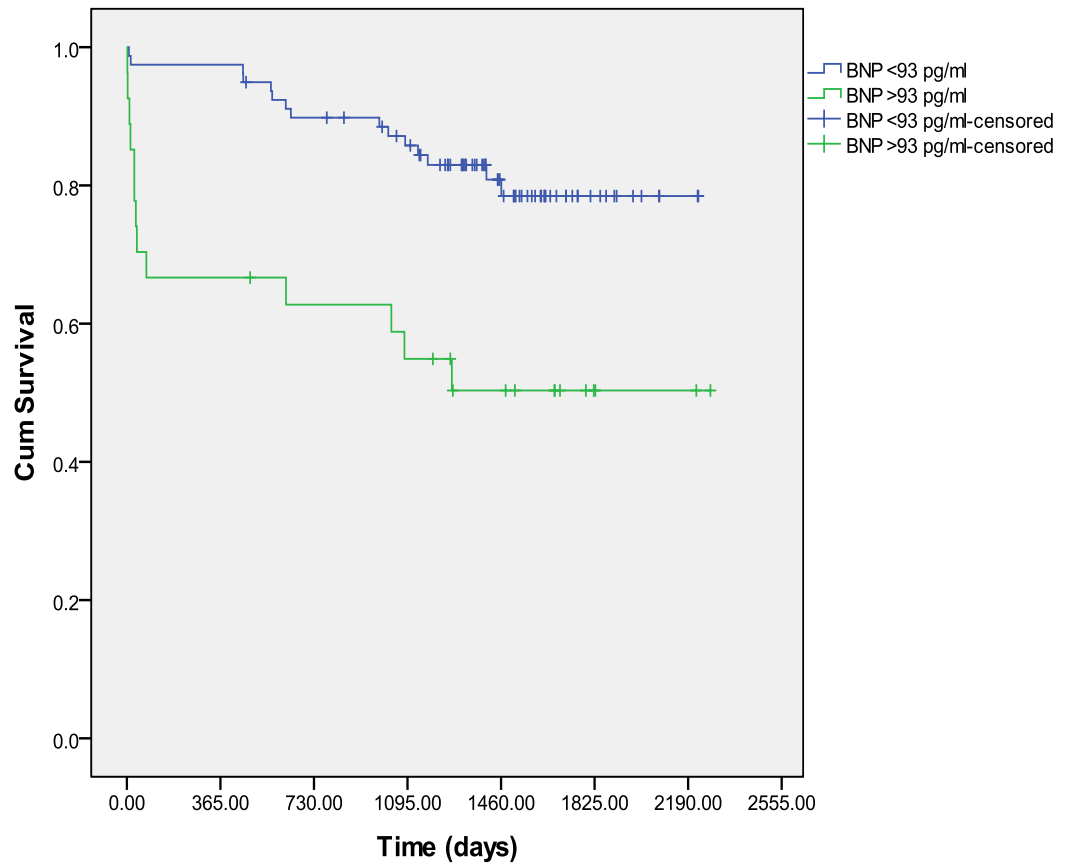
Patients at risk:

<93.0 pg/ml	79	76	69	63	32	12
>93.0 pg/ml	27	19	17	15	11	7

Kaplan-Meier survival analysis reveals a significant difference in long term outcome when comparing groups based on a BNP level of 93.0 pg/ml (mean survival 1320 [95% CI 931-1708] vs 1931 [95% CI 1791-2070] days, p<0.001). Longer survival was seen in those with lower BNP levels.

5.3.4.2 Cut-off BNP 60.5 pg/ml (3-year mortality)

The mean survival of patients with a BNP >60.5 pg/ml compared to a BNP <60.5 pg/ml was 1439 days (95% CI 1128-1751) vs 1967 days (95% CI 1825-2110) (p<0.001) [Figure 5.9]. During the first six months the rate of postoperative death in those with a BNP >60.5 pg/ml was 19 times greater (27% vs 1.4%, p<0.001) than in those with a BNP below this threshold. At the minimum point of follow-up (3 postoperative years) the rate of death was 3.8 times greater in those with a BNP > 60.5 pg/ml (38% vs 10%, p<0.001). Survival in only those that survived beyond the first 6 postoperative months revealed that there was no significant difference in outcome with the mean survival in those with a BNP >60.5 pg/ml of 1945 days (95% CI 1731-2159) vs 1996 days (95% CI 1864-2129) in those with a BNP below this level (p=0.298) [Figure 5.10].

Figure 5.9 Kaplan-Meier curve of survival according to BNP level with a cut-off of 60.5 pg/ml.
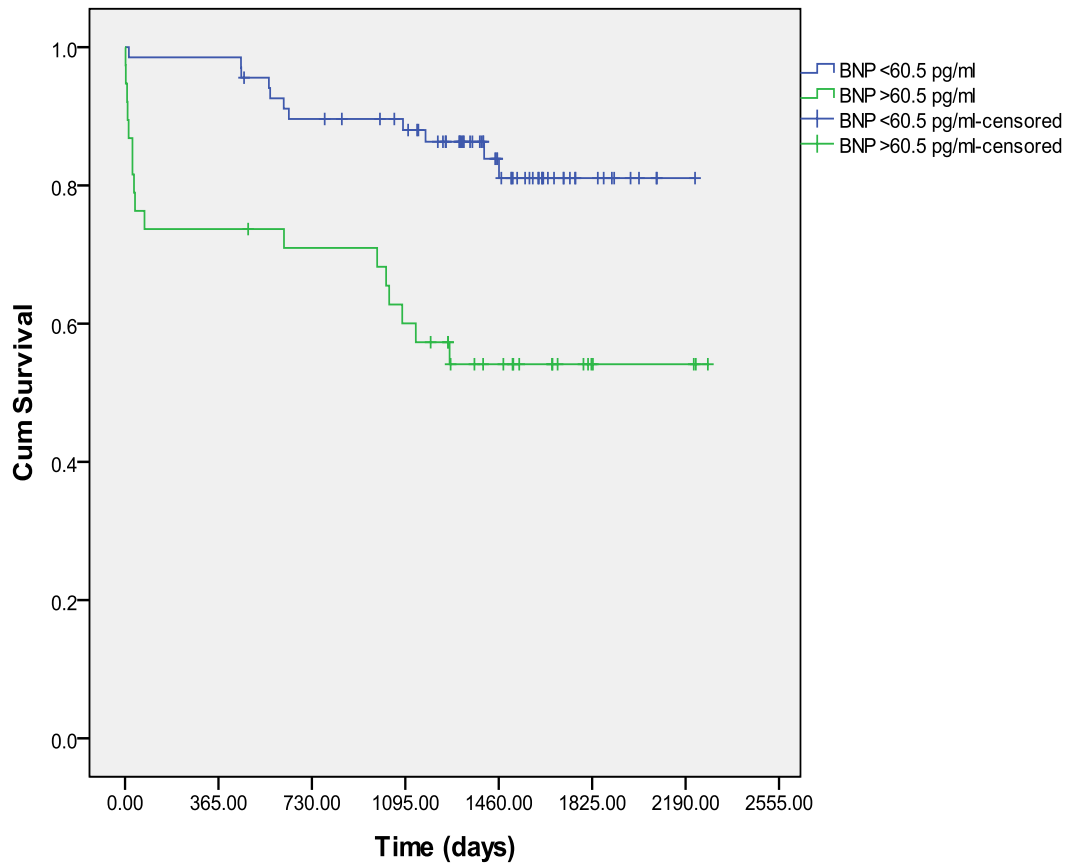
Patients at risk:

<60.5 pg/ml	68	67	60	55	31	9
>60.5 pg/ml	38	28	26	21	11	3

Kaplan-Meier survival analysis reveals a significant difference in long term outcome when comparing groups based on a BNP level of 60.5 pg/ml (mean survival 1439 [95% CI 1128-1751] vs 1967 [95% CI 1825-2110] days, p<0.001), with longer survival in those with lower BNP levels.

Figure 5.10 Kaplan-Meier curve of survival according to BNP level with a cut-off of 60.5 pg/ml in only those that survived beyond six postoperative months.
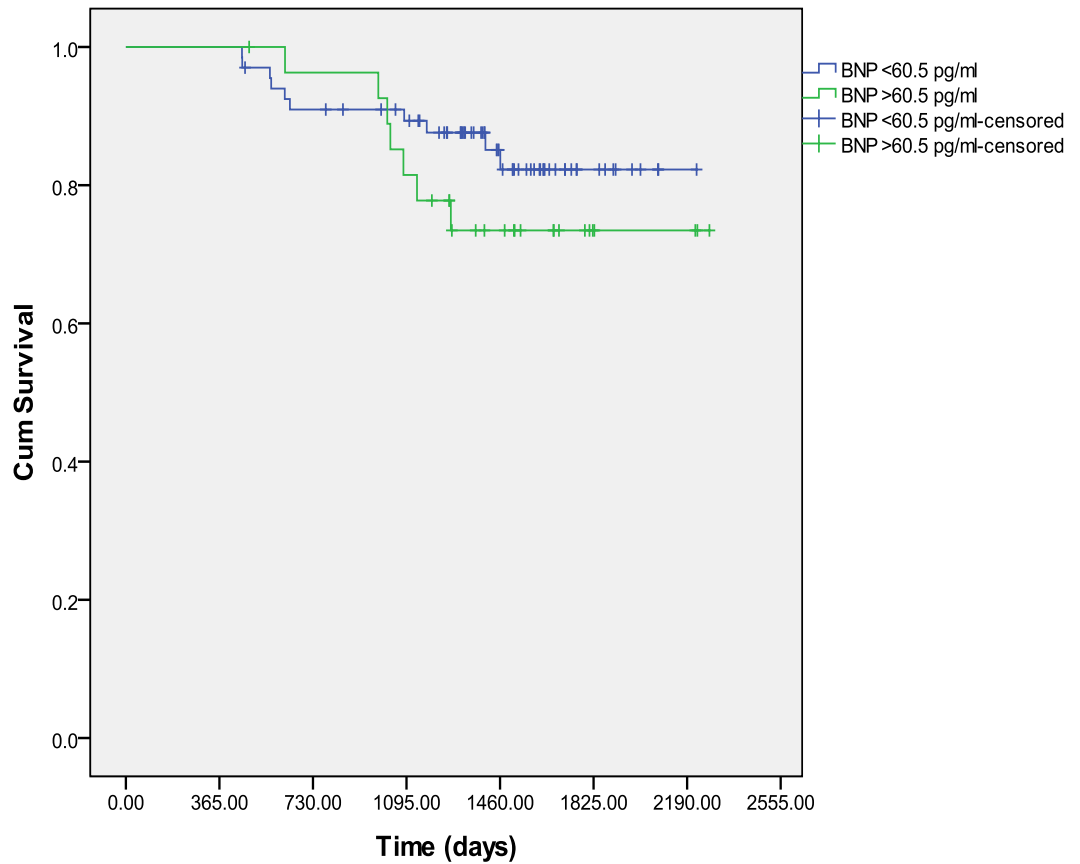
Patients at risk:

<60.5 pg/ml	67	67	60	55	31	9
>60.5 pg/ml	28	28	26	21	11	3

Kaplan-Meier survival analysis reveals no difference in long term outcome when including only those that survived beyond 6 months and comparing groups based on a cut-off BNP level of 60.5 pg/ml (mean survival 1945 [95% CI 1731-2159] vs 1996 [95% CI 1864-2129] days, p=0.298).

5.4 Discussion

This study demonstrates that, not only can a single preoperative serum BNP level predict perioperative outcome in elective open AAA repair, but it can also predict long-term all-cause mortality and specifically cardiac death. At all time points of follow-up BNP levels significantly predicted mortality outcomes. Only in the presence of CKD or CCF was late mortality more likely, although on multivariate analysis only BNP was found to be a significant predictor.

In chapter 4 the importance of BNP as a strong predictor of immediate postoperative outcome is clearly established. However in addition to its strength in the perioperative period the results of this study reveal that BNP also has a long term predictive value. ROC curve analysis reveals a lower cut-off value of serum BNP for predicting death over time. In addition BNP becomes a less sensitive and specific predictor of death, and its predictive values lose meaning over the same time period. The lowering cut-off level over time may be indicative that, at lower levels, BNP can predict long term mortality in the general population, as previously demonstrated in Glasgow where random population sampling in 1640 individuals revealed a significant difference in 4 year mortality (BNP ≥17.9 pg/ml mortality 14.9 % vs BNP <17.9 pg/ml mortality 3.1%, p<0.001).[275]

Although all analyses showed that preoperative serum BNP levels predicted 3 year mortality, when removing the outcome data relating to the first 6 postoperative months there was no significant difference in survival based on differing BNP levels. There was however an apparent, but not statistically significant, increased survival rate in those with lower BNP levels at 3 years in this same group.

Survival rates after open elective AAA repair were 89.6% at 1 year and 79.2% at 3 years. This is comparable to other larger studies [288, 289] including the recently published long term outcomes of 7697 patients following elective AAA repair in Sweden, with reported rates of 90.8% at 1 year and ~81% at 3 years.[290] The slightly poorer outcome seen in the West of Scotland could be in part due to the small sample size in this cohort. In addition, and despite similar age groups, there was greater comorbidity in the studied population and therefore the results are not unexpected.

In the UKSAT, long term survival outcomes in the operative group were similar to that described above. When using discriminatory BNP levels, the survival rates in the present studied population were higher in those with lower BNP levels. The survival rates in those with a BNP <99.5 pg/ml at 1 and 3 years were 96.7% and 86.7% respectively. Survival rates in those with a BNP >99.5 pg/ml were 65.2% at 1 year and 52.2% at 3 years. Crude estimates of the UKSAT reveal survival rates of approximately 91% and 81% at 1 and 3 years in the operative group, and of 95% and 81% at 1 and 3 years in the surveillance group. These survival rates from UKSAT are lower than in those patients with a BNP level <99.5 pg/ml in the current study. It is therefore not unreasonable to propose that, when considering the UKSAT data, selecting patients on the basis of BNP alone could reduce perioperative mortality and possibly improve long term outcomes in the operative group.

The main limitation of this study was the relatively low number of patients. However, the inclusion of consecutive patients makes this a representative sample of the patient population presenting for AAA repair in the West of Scotland and make the results relevant to current clinical practice. The incomplete 3 year follow-up data may impact on the results; however as neither GP nor hospital were notified of death or change of address an assumption of survival can be made. This assumption was taken into account through censoring on Kaplan Meier analyses, and, even after correction for this, a significant difference in survival persisted between the two groups with differing BNP levels.

Few studies have described the relation between long term outcomes and BNP levels in noncardiac surgery. These include the studies of Feringa et al[120], who found that NT-proBNP predicted long term outcome in 335 patients undergoing vascular surgery, and Cuthbertson et al[118], who found similar results in 204 patients undergoing noncardiac surgery. More recently, in a 345 patient cohort from Glasgow, BNP has been found to independently predict long term survival after major noncardiac surgery.[287] The present study, according to the current published literature, is the first to report on survival outcome following elective open AAA repair alone, whilst being appropriately powered to do so. The results highlight the importance of BNP in the perioperative period whilst revealing its value in predicting long term survival. Its value as a basis on which to select patients who would be suitable for repair of their small asymptomatic AAA remains unknown; however there is sufficient evidence to suggest that this question should now be addressed in a prospective trial.

Chapter 6

Objective Scoring Systems in Elective Open Abdominal Aortic Aneurysm Repair

6.1 Introduction

As previously discussed in detail, there is a need to identify patients whose risk of AAA rupture exceeds the risk of perioperative mortality and for whom surgery consequently offers a survival advantage. During the last two decades several surgical risk indices have been developed to help quantify the risk of perioperative death for a given patient. The risk scores available to date have been discussed in section 1.5.5 of chapter 1. The complexity and lack of validation of many of these scores make routine preoperative use rare and/or unreliable.

The Eagle[63] and Vanzetto[291] scores, which use physiological factors in conjunction with ECG analysis and thallium scanning, have been shown to be useful in predicting cardiac events in major vascular surgery. However, despite further external validation in predicting mortality after elective open AAA repair[161], their requirement for cardiac testing places them out of the reach of many centres.

The Leiden score and modifications[292] were derived from retrospective data of patients undergoing elective surgery between 1977 and 1988; they are unique in that they employ a corrective factor for institution-specific mortality rates. However, the Leiden score has never shown good predictive capabilities. When applied to UK Small Aneurysm Trial data it predicted death with only moderate accuracy (AUC 0.72), and was shown to have poor predictive power and calibration.[293]

The Estimation of Physiological Ability and Surgical Stress (E-PASS) was found to accurately predict postoperative outcome in open elective AAA surgery.[257] The E-PASS consists of a preoperative risk score (PRS) and a surgical stress score (SSS), combining to give a comprehensive risk score (CRS). As a preoperative risk scoring tool, this brings some limitations; however the PRS alone has been shown to give a positive predictive value similar to the overall CRS in AAA surgery.[161]

The Glasgow Aneurysm Score (GAS)[154], Physiological and Operative Severity Score for enumeration of Mortality (POSSUM)[162] and Vascular Biochemical and Haematological Outcome Model (VBHOM)[165,166] have all been validated, show good predictive capabilities and can be used as preoperative scoring systems.[294] In addition, Lee's revised cardiac risk index (RCRI)[295] has been shown to predict mortality in vascular surgery including elective open AAA repair.[296]

The aim of this chapter is to compare five validated preoperative risk stratification scoring systems and to assess their ability to predict major adverse cardiac events and all-cause mortality in the perioperative period. These risk scores will be the GAS, RCRI, VBHOM, the physiology only component of the Vascular-POSSUM and the PRS component of E-PASS.

6.2 Methods

6.2.1 Study Population

A prospective, observational, multi-centre cohort study was performed involving the 3 major vascular units within Glasgow (Gartnavel General Hospital, Glasgow Royal Infirmary and the Southern General Hospital). A cohort of consecutive patients admitted electively for open AAA repair was identified between August 2005 and September 2007.

6.2.2 Patients and Preoperative Assessment

Collection of patient data was identical to that described in chapter 4. Data were collected to allow calculation of the 5 scoring systems named above.

6.2.2.1 Glasgow Aneurysm Score

The Glasgow Aneurysm Score was calculated for each patient according to the following formula:

GAS = Age + (17 for shock) + (7 for myocardial disease) + (10 for cerebrovascular disease) + (14 for renal disease)

Refer to 2.5.1 for further definitions.

6.2.2.2 Vascular (physiology only) - Physiological and Operative Severity Score for enUmeration of Mortality

All 12 physiological parameters (age, degree of cardiac failure, degree of dyspnoea related to chronic obstructive airways disease, ECG changes, systolic BP, resting pulse rate, haemoglobin concentration, white cell count, urea, sodium, potassium and Glasgow Coma Score) were measured preoperatively in all patients and placed in the online calculator for the V(p)-POSSUM score at http://www.riskprediction.org.uk/vasc-index.php

6.2.2.3 Vascular Biochemical and Haematological Outcome Model

The results of preoperative serum urea, sodium, potassium, haemoglobin and white cell count, in addition to age and gender were applied to the following equation:

$$VBHOM = \ln_e(R/1\text{-}R) = -2{\cdot}257 + (0{\cdot}1511 \times sex) + (0{\cdot}9940 \times mode\ of\ admission) + (0{\cdot}05923 \times age\ on\ admission[years]) + (0{\cdot}001401 \times urea[mmol/l]) + (-0{\cdot}01303 \times sodium[mmol/l]) + (-0{\cdot}03585 \times potassium[mmol/l]) + (-0{\cdot}2278 \times haemoglobin[g/dl]) + (0{\cdot}02059 \times white\ cell\ count[\times10^9/l])$$

R is the risk of death. Sex takes the value 0 for female and 1 for male, and mode of admission takes the value 0 for elective and 1 for non-elective admissions.

6.2.2.4 Lee's Revised Cardiac Risk Index

The RCRI was calculated on the sum of the risk factors in each patient. These risk factors were high-risk surgery (intraperitoneal, intrathoracic or suprainguinal vascular), ischaemic heart disease, congestive heart failure, cerebrovascular disease, the use of insulin therapy for diabetes mellitus or a preoperative creatinine level >2mg/dl (>176µmol/l), each factor being attributed a value of 1. Refer to 2.5.4 for further definitions.

6.2.2.5 Preoperative Risk Score of the Estimation of Physiological Ability and Surgical Stress Score

The PRS component of the E-PASS score is calculated based on the following equation:

$$PRS = -0.0686 + 0.00345(age) + 0.323(cardiac\ score) + 0.205(pulmonary\ score) + 0.153(diabetes\ score) + 0.148(performance\ status\ index) + 0.0666(ASA)$$

Refer to 2.5.5 for further definitions.

6.2.3 Postoperative Follow-up

Immediate postoperative testing is described in detail in chapter 4. In cases of death, the date and cause of death were noted. Where the cause of death was not included review of the death certificate was performed.

6.2.4 Endpoints

Endpoints for the study were non-fatal MI and all-cause mortality. MACE was defined as described in chapter 4 and was determined by a review of postoperative data by two cardiologists who were unaware of preoperative BNP levels. All-cause mortality was immediate postoperative death (<30 days) of any cause.

6.2.5 Statistical Analysis

Statistical analysis was performed using the SPSS® statistical software package (SPSS, Chicago, Illinois, USA). Normal distributed data was reported as mean +/- standard deviation. Non-parametric data was reported as median and interquartile range. Mann-Whitney U test was used to test the differences between non-parametric continuous variables in different subgroups. A 2-sample t-test was used to compare continuous variables in normally distributed data. Receiver operating characteristics were plotted and the area under the curve estimated. A p-value <0.05 was considered significant.

6.2.6 Ethical Approval

Local Research and Development, and Central Ethics Committee approval was obtained for the study. All patients were provided with an information sheet and had signed a study consent form. GPs were sent individual letters to inform of their patients' inclusion in the study.

6.3 Results

6.3.1 Patient Characteristics, BNP Levels and Outcome

Patient characteristics are as detailed in chapter 4. Preoperative laboratory variables are further detailed in table 6.1. The majority of laboratory variables were within normal reference ranges for the local population. Laboratory variables by outcome are also detailed in table 6.1. Platelet levels were significantly lower, and prothrombin time levels significantly higher in those that died of a cardiac death. Serum urea levels were significantly higher in those patients that died of any cause. Serum urea levels were higher in those that suffered cardiac death, although this was not statistically significant. Haemoglobin levels were lower in those that died of any cause, although again this was not statistically significant.

Table 6.1 Preoperative laboratory results and their distribution according to outcome.

Laboratory Variable	Mean (+/- SD)	MACE	Cardiac Death	All-cause Mortality
Urea (mmol/l)	7.5 (3.7)			
Yes		8.43(4.48)	10.68(7.19)	9.98(5.66)
No		7.35(3.56)	7.36(3.44)	7.28(3.43)
		p=0.285	p=0.050	p=0.037
Serum Na$^+$ (mmol/l)	4.2 (0.48)			
Yes		139.7(1.82)	139.6(2.07)	138.8(2.68)
No		138.9(2.84)	139.0(2.75)	139.1(2.74)
		p=0.324	p=0.655	p=0.741
Serum K$^+$ (mmol/l)	139.1 (2.7)			
Yes		4.14(0.75)	4.24(0.53)	4.32(0.53)
No		4.22(0.41)	4.21(0.48)	4.20(0.47)
		p=0.558	p=0.880	p=0.456
Haemoglobin (g/dl)	13.3 (1.9)			
Yes		12.90(2.37)	11.96(3.48)	12.14(2.50)
No		13.34(1.77)	13.33(1.76)	13.38(1.78)
		p=0.391	p=0.108	p=0.058
White Cell Count (x10^3/µl)	7.9 (1.8)			
Yes		8.43(1.26)	8.08(1.70)	8.23(1.56)
No		7.79(1.93)	7.88(1.86)	7.86(1.88)
		p=0.208	p=0.818	p=0.574
Platelets (x10^3/µl)	231.4(83.2)			
Yes		214.5(111.2)	146.6(30.1)	212.2(115.7)
No		234.4(77.6)	235.6(82.8)	233.2(80.1)
		p=0.381	p=0.019	p=0.473
PT (seconds)	11.98(1.94)			
Yes		12.37(2.52)	14.2(3.96)	12.89(3.26)
No		11.91(1.83)	11.87(1.76)	11.9(1.78)
		p=0.382	p=0.008	p=0.144

Laboratory variables reveal a significant difference in platelet levels and prothrombin time in relation to cardiac death (p=0.019 and p=0.008 respectively), and in serum urea levels in relation to all-cause mortality (p=0.037). There was also a difference in serum urea levels in relation to cardiac death (p=0.050) and in haemoglobin in relation to all-cause mortality (p=0.058), although this was not significant. MACE – major adverse cardiac event, PT – Prothrombin time. All analyses performed using a 2-sample t-test.

6.3.2 Risk Indices and Outcome

Complete datasets required for the calculation of all 5 preoperative risk indices were collected in all 106 patients who underwent elective open AAA repair.

6.3.2.1 Glasgow Aneurysm Score

The median (interquartile range) GAS was 77 (72-84) [Table 6.2]. The median GAS in those who suffered MACE was not significantly different to that in those without (median GAS 79 [71-84] vs 71 [72-84], p=0.846) [Figure 6.1a]. The median GAS in patients suffering a cardiac death was again not significantly different (median GAS 77 [70-85] vs 71 [72-84], p=0.911) [Figure 6.1b]. The median GAS in all causes of mortality was also not significantly different (median GAS 84 [74-87] vs 77 [71-83], p=0.227) [Figure 6.1c]. ROC analysis revealed an AUC of 0.515, 0.515 and 0.622 for MACE, cardiac death and all-cause mortality respectively. Sensitivities and specificities were poor and the GAS appeared to perform poorly in all outcomes [Table 6.3].

Figure 6.1 Boxplots of the Glasgow Aneurysm Score and outcome.

a. GAS and MACE.
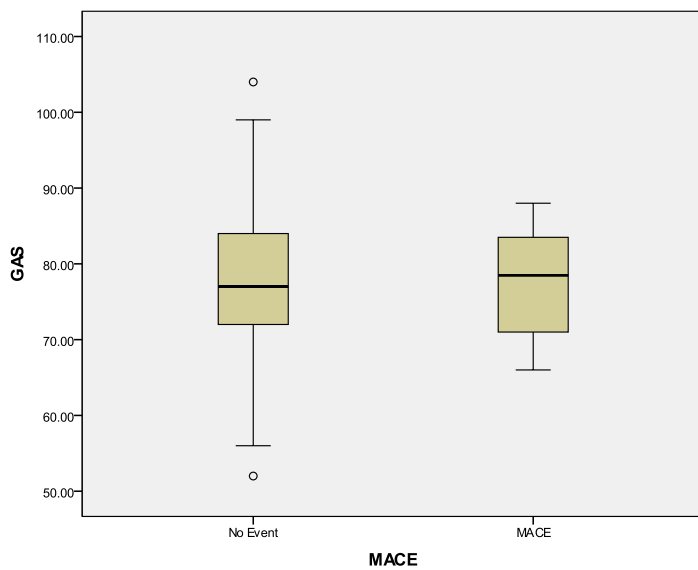
b. GAS and cardiac death.
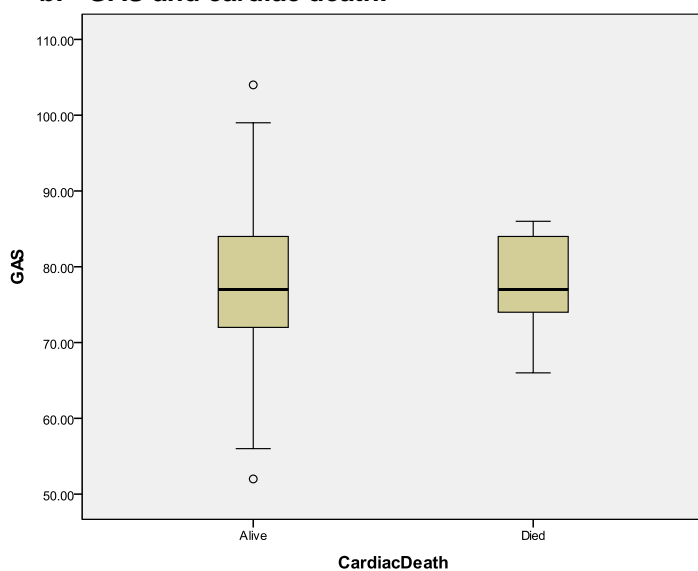
c. GAS and all-cause mortality.
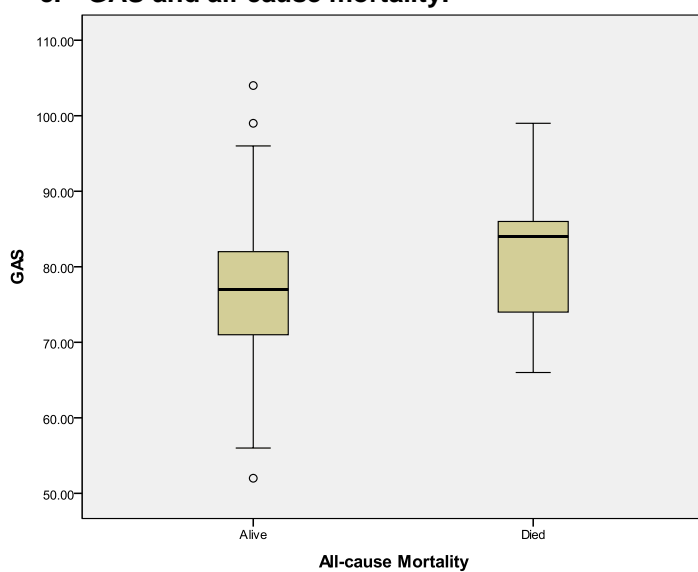
6.3.2.2 Vascular (physiology only) - Physiological and Operative Severity Score for enUmeration of Mortality

The median (interquartile range) V(p)-POSSUM was 29 (27-34). There was a significant difference in median V(p)-POSSUM with higher scores in those who suffered MACE than in those without (median V(p)-POSSUM 33 [28-37] vs 29 [26-32], p=0.028) [Table 6.2]. ROC analysis revealed an AUC of 0.681 (95% CI 0.549-0.814, SE 0.067; p=0.021) [Figure 6.2a]. The best cut off for V(p)-POSSUM in predicting MACE was 20.5 with a sensitivity of 63% and specificity of 67%. At this cut-off the PPV was 35% and the NPV was 93% [Table 6.3].

The median V(p)-POSSUM was significantly higher in those who suffered cardiac death than in those who did not (median V(p)-POSSUM 34 [32-37] vs 29 [26-33], p=0.030) [Table 6.2]. ROC analysis revealed an AUC of 0.762 (95% CI 0.596-0.928, SE 0.085; p=0.048) [Figure 6.2b] with a cut-off of again 20.5. Sensitivity at this cut-off was 80% and specificity was 65% with a PPV of 15% and NPV of 99% [Table 6.3].

The median V(p)-POSSUM was significantly higher in the all-cause mortality group than in the survivors (median V(p)-POSSUM 34 [29-37] vs 29 [26-33], p=0.038) [Table 6.2]. ROC analysis revealed an AUC of 0.780 (95% CI 0.667-0.893, SE 0.057; p=0.006) [Figure 6.2c] with once again a cut-off of 20.5. Sensitivity was 89% and specificity was 68% with a PPV of 21% and NPV of 99% [Table 6.3].

Figure 6.2 ROC curve: V(p)-POSSUM and outcome.

a. **V(p)-POSSUM and MACE (AUC 0.681).**
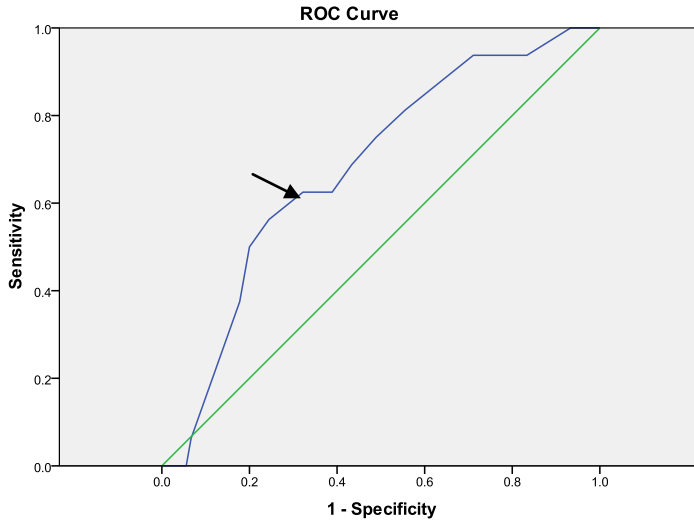
Diagonal segments are produced by ties.

b. **V(p)-POSSUM and cardiac death (AUC 0.762).**
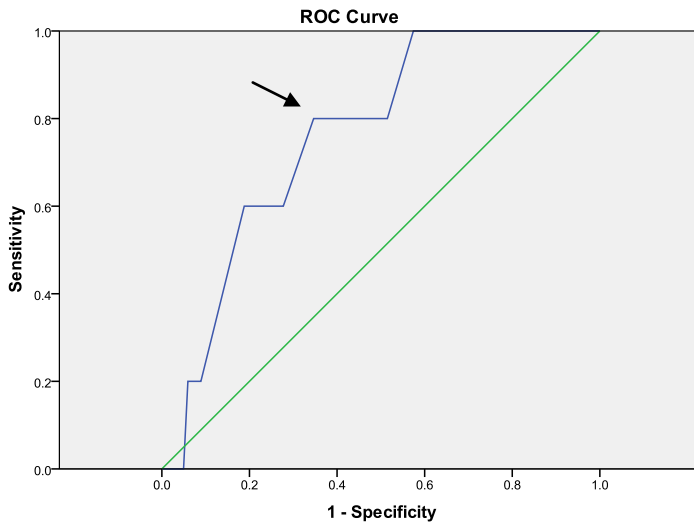
Diagonal segments are produced by ties.

c. **V(p)-POSSUM and all-cause mortality (AUC 0.780).**
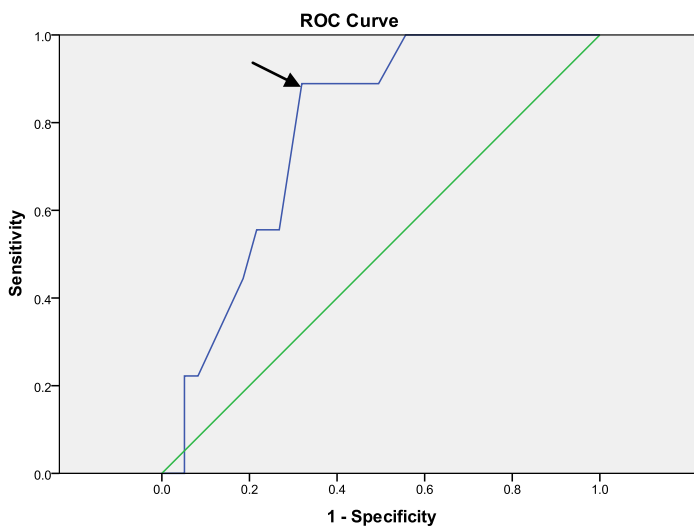
Diagonal segments are produced by ties.

6.3.2.3 Vascular Biochemical and Haematological Outcome Model

The median (interquartile range) VBHOM was -2.66 (-3.07 to -2.23) [Table 6.2]. There was no significant difference in median VBHOM in those who suffered MACE than in those who did not (median VBHOM -2.53 (-2.96 to -2.08) vs -2.67 (-3.12 to -2.26), p=0.232), although this did not reach statistical significance [Figure 6.3a]. There was again no significant difference in median VBHOM between those who suffered cardiac death and those who did not (median VBHOM -2.57 (-2.78 to -1.85) vs -2.66 (-3.08 to -2.23), p=0.340) [Figure 6.3b]. There was also no significant difference in median VBHOM score in the all-cause mortality group when compared to the survivors (median VBHOM -2.33 (-2.62 to -2.21) vs -2.72 (-3.10 to -2.30), p=0.069) [Figure 6.3c]. ROC analysis revealed an AUC of 0.592, 0.626 and 0.684 for MACE, cardiac death and all-cause mortality respectively. Sensitivities and specificities were poor and the VBHOM performed poorly in all outcomes [Table 6.3].

Figure 6.3 Boxplots for VBHOM and outcome.

a. **VBHOM and MACE.**
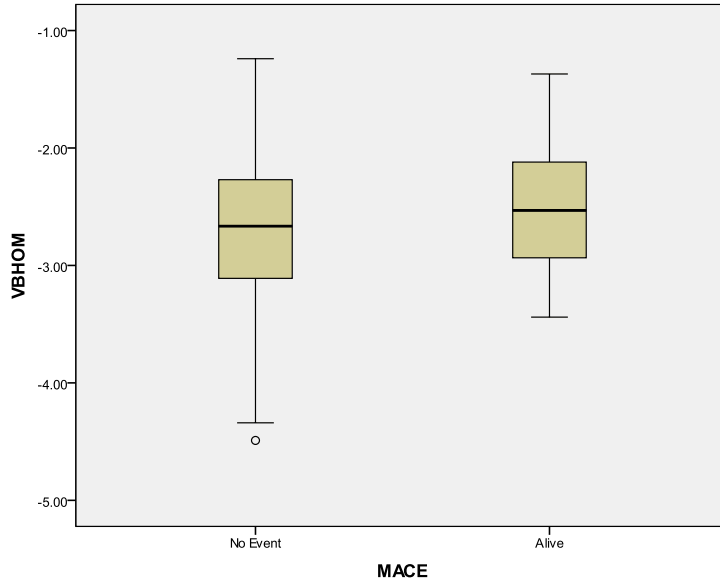
b. **VBHOM and cardiac death.**
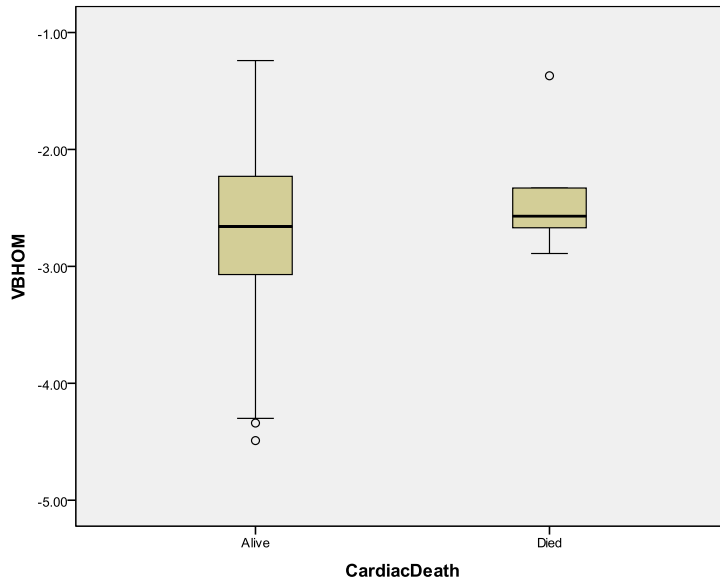
c. **VBHOM and all-cause mortality.**
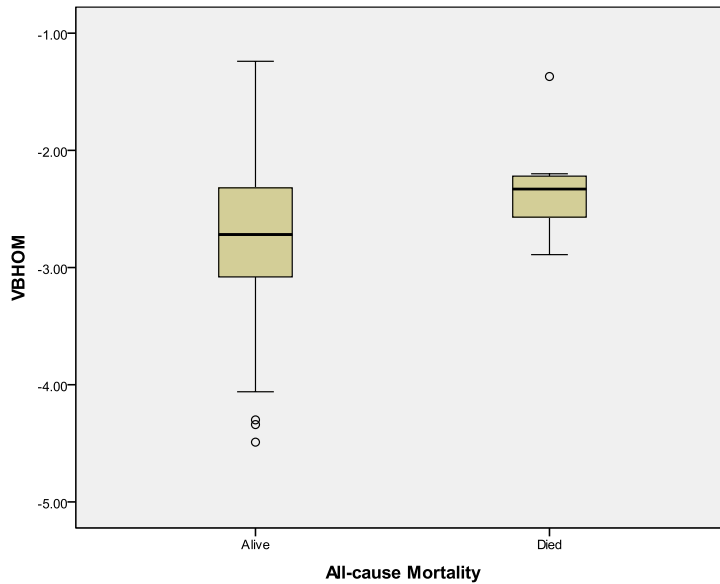
6.3.2.4 Lee's Revised Cardiac Risk Index

The median RCRI was 2 (interquartile range 1-3). There was no significant difference in median RCRI in those that suffered MACE, cardiac death and all-cause mortality (p=0.735, p=0.448 and p=0.415 respectively) [Table 6.2]. ROC analysis revealed an AUC of 0.525, 0.596 and 0.578 respectively. Sensitivities and specificities were poor and the RCRI appeared to perform poorly in all outcomes [Table 6.3].

6.3.2.5 Preoperative Risk Score of the Estimation of Physiological Ability and Surgical Stress Score

The median (interquartile range) PRS was 0.46 (0.26-0.64). The median PRS was significantly higher in those who suffered MACE than in those who did not (median PRS 0.63 [0.46-0.67] vs 0.42 [0.25-0.60], p=0.019) [Table 6.2]. ROC analysis revealed an AUC of 0.682 (95% CI 0.559-0.805, SE 0.063; p=0.021) [Figure 6.4a]. The best cut off for PRS in predicting MACE was 0.55 with a sensitivity of 69% and specificity of 64%. At this cut-off the PPV was 27% and the NPV was 93% [Table 6.3].

The median PRS was significantly higher between those who suffered cardiac death and those who did not (median PRS 0.65 [0.59-1.02] vs 0.44 [0.26-0.62], p=0.017) [Table 6.2]. ROC analysis revealed an AUC of 0.821 (95% CI 0.697-0.945, SE 0.063; p=0.016) [Figure 6.4b] with a cut-off of 0.63. Sensitivity at this cut-off was 80% and specificity was 76% with a PPV of 15% and NPV of 99% [Table 6.3].

The median PRS was higher in the all-cause mortality group than in the survivors (median PRS 0.65 [0.40-0.93] vs 0.44 [0.26-0.62], p=0.050) [Table 6.2], although this was just not significant. ROC analysis revealed an AUC of 0.703 (95% CI 0.516-0.890, SE 0.095; p=0.045) [Figure 6.4c] with a cut-off of 0.55. Sensitivity was 78% and specificity was 63% with a PPV of 15% and NPV of 97% [Table 6.3].

Figure 6.4 ROC curve: PRS and outcome.

a. PRS and MACE (AUC 0.682).

ROC Curve

Sensitivity

1 - Specificity
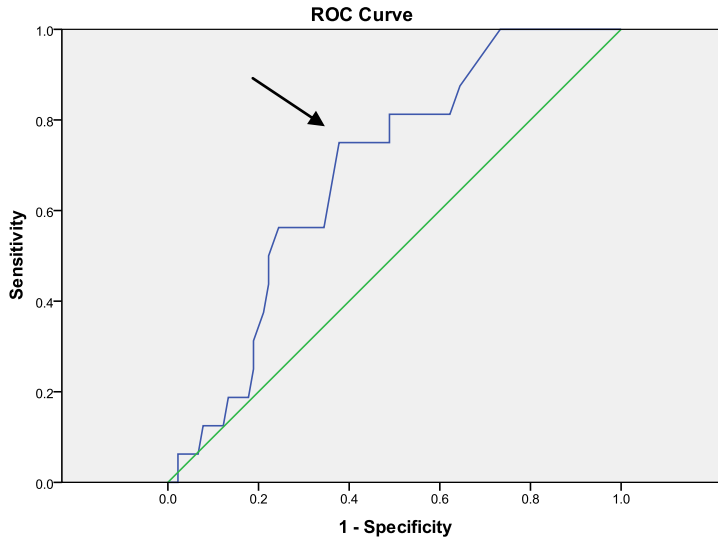
Diagonal segments are produced by ties.

b. PRS and cardiac death (AUC 0.821).

ROC Curve

Sensitivity

1 - Specificity
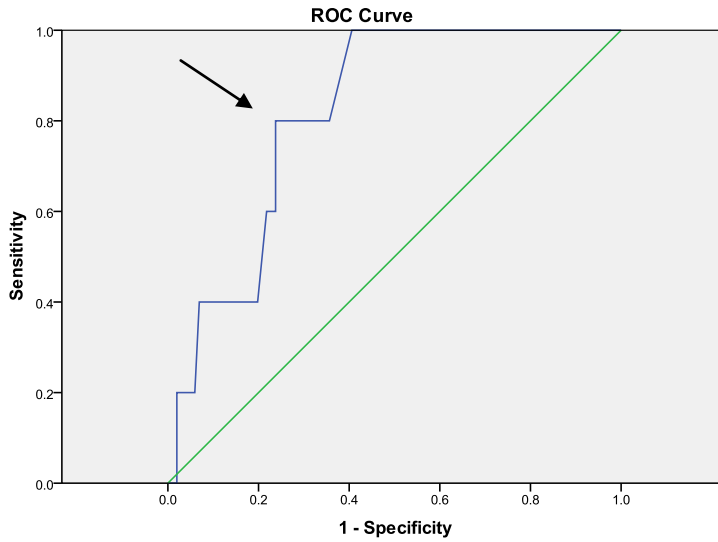
Diagonal segments are produced by ties.

c. PRS and all-cause mortality (AUC 0.703).

ROC Curve

Sensitivity

1 - Specificity
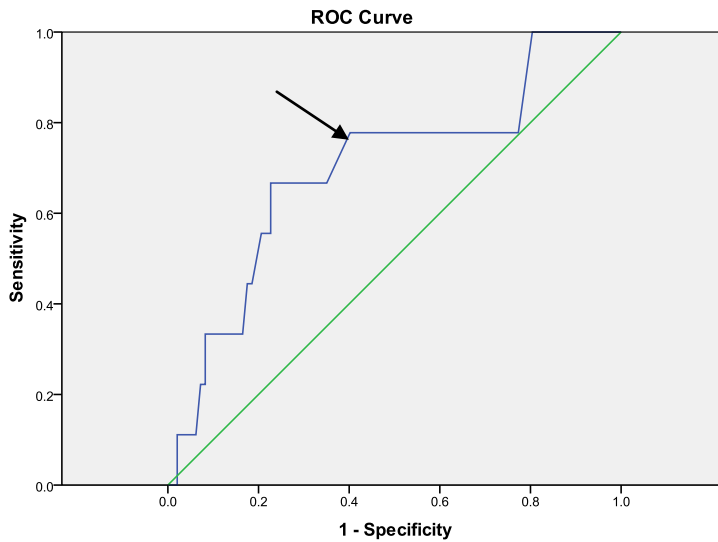
Diagonal segments are produced by ties.

Table 6.2 Preoperative risk indices and outcome.

	Median (IQR) Score	MACE	Cardiac Death	All-cause Mortality
GAS	77 (72-84)			
Yes		79 (71-84)	77 (70-85)	84 (74-87)
No		71 (72-84)	71 (72-84)	77 (71-83)
		p=0.846	p=0.911	p=0.227
V(p)-POSSUM	29 (27-34)			
Yes		33 (28-37)	34 (32-37)	34 (29-37)
No		29 (26-32)	29 (26-33)	29 (26-33)
		p=0.028	p=0.030	p=0.038
VBHOM	-2.66 (-3.07 to -2.23)			
Yes		-2.53 (-2.96to-2.08)	-2.57 (-2.78to-1.85)	-2.33 (-2.62to-2.21)
No		-2.67 (-3.12to-2.26)	-2.66 (-3.08to-2.23)	-2.72 (-3.10to-2.30)
		p=0.232	p=0.340	p=0.069
RCRI	2 (1-3)			
Yes		2 (1-3)	3 (1-4)	2 (1-4)
No		2 (1-3)	2 (1-3)	2 (1-3)
		P=0.735	P=0.448	P=0.415
PRS	0.46 (0.26-0.64)			
Yes		0.63 (0.46-0.67)	0.65 (0.59-1.02)	0.65 (0.40-0.93)
No		0.42 (0.25-0.60)	0.44 (0.26-0.62)	0.44 (0.26-0.62)
		p=0.019	p=0.017	p=0.050

IQR – interquartile range, MACE – Major Adverse Cardiac Event, GAS – Glasgow Aneurysm Score, V(p)-POSSUM – physiological component of Vascular Physiological and Operative Severity Score for enUmeration of Mortality, VBHOM - Vascular Biochemical and Haematological Outcome Model, RCRI – Revised Cardiac Risk Index, PRS – Preoperative Risk Score of Estimation of Physiological Ability and Surgical Stress. All analyses performed using Mann-Whitney U test.

Table 6.3 Results of receiver operating characteristic curve analysis for each score according to outcome.

	AUC	95% CI	SE	p-value	cut-off	Sens.	Spec.	PPV	NPV
MACE									
GAS	0.515	0.374-0.657	0.072	0.846	77.5	50%	53%	14%	86%
V(p)-POSSUM	0.681	0.549-0.814	0.067	0.021	20.5	63%	67%	35%	93%
VBHOM	0.592	0.455-0.730	0.070	0.241	-2.59	56%	56%	16%	88%
RCRI	0.525	0.364-0.687	0.082	0.747	>1	63%	38%	15%	85%
PRS	0.682	0.559-0.805	0.063	0.021	0.55	69%	64%	27%	93%
Cardiac Death									
GAS	0.515	0.285-0.745	0.117	0.911	76.5	60%	46%	5.2%	96%
V(p)-POSSUM	0.762	0.596-0.928	0.085	0.048	20.5	80%	65%	15%	99%
VBHOM	0.626	0.430-0.822	0.100	0.344	-2.59	60%	56%	5%	96%
RCRI	0.596	0.285-0.907	0.159	0.470	>2	60%	68%	9%	97%
PRS	0.821	0.697-0.945	0.063	0.016	0.63	80%	76%	15%	99%
All-cause mortality									
GAS	0.622	0.436-0.808	0.095	0.227	77.5	56%	54%	10%	93%
V(p)-POSSUM	0.780	0.667-0.893	0.057	0.006	20.5	89%	68%	21%	99%
VBHOM	0.684	0.555-0.813	0.066	0.069	-2.48	67%	73%	15%	95%
RCRI	0.578	0.361-0.796	0.111	0.438	>2	45%	68%	11%	93%
PRS	0.703	0.516-0.890	0.095	0.045	0.55	78%	63%	15%	97%

MACE – Major adverse cardiac event, GAS – Glasgow aneurysm score, V(p)-POSSUM – physiological component of Vascular Physiological and Operative Severity Score for enUmeration of Mortality, VBHOM - Vascular Biochemical and Haematological Outcome Model, RCRI – Revised cardiac risk index, PRS – preoperative risk score of. Estimation of Physiological Ability and Surgical Stress, AUC – area under the curve, CI – confidence interval, SE- standard error, Sens. – Sensitivity, Spec. – Specificity, PPV – positive predictive value, NPV – negative predictive value.

6.3.3 Tertile Analyses of Risk Indices

Tertile analysis was performed by dividing each index grouping into 3 equal classes based on even distribution with the aim of examining stepwise increase in MACE, cardiac death and mortality between groups. For the GAS there was no significant difference in the tertile rate of MACE, cardiac death and all-cause mortality with rates from 16% to 12% and 19% for MACE, 3% to 7% and 6% in cardiac death, and 3% to 7% and 16% in all-cause mortality (p=0.584, p=0.891 and p=0.264 respectively) [Figure 6.5a].

For V(p)-POSSUM sequential increases were seen in rates for MACE and all-cause mortality with rates in MACE of 4% to 13% and 29%, and in all-cause mortality of 0% to 8% and 16% (p=0.013 and p=0.030 respectively). In cardiac death there was no significant rate change between tertiles with rates of 0% to 4% and 10% (p=0.130) [Figure 6.5b].

For VBHOM, although there were sequential increases in rates for MACE and all-cause mortality, there was no significant difference in rates for outcome, with rates of 9% to 16% and 20 % in MACE, 0% to 8% and 6% in cardiac death, and 0% to 11% and 14% in all-cause mortality (p=0.395, p=0.174 and p=0.070 respectively) [Figure 6.5c].

For RCRI there was no significant difference in rates between tertiles for all outcomes. Rates for MACE were 15% to 13% and 17 %, for cardiac death 5% to 0% and 9%, and for all-cause mortality 9% to 6% and 11% (p=1.0, p=0.368 and p=0.867 respectively) [Figure 6.5d].

For the PRS component of E-PASS there were significant increases in rates for all outcome measures with rates of 6% to 13% and 27% in MACE, 0% to 3% and 12% in cardiac death, and rates of 6% to 3% and 18% in all-cause mortality (p=0.038, p=0.015 and p=0.032 respectively) [Figure 6.5e].

Figure 6.5. Tertile analysis for individual risk scores.

a.

GAS and outcome

b.

V(p)-POSSUM and outcome

c.

VBHOM and outcome

d.

RCRI and outcome

e.

PRS and outcome
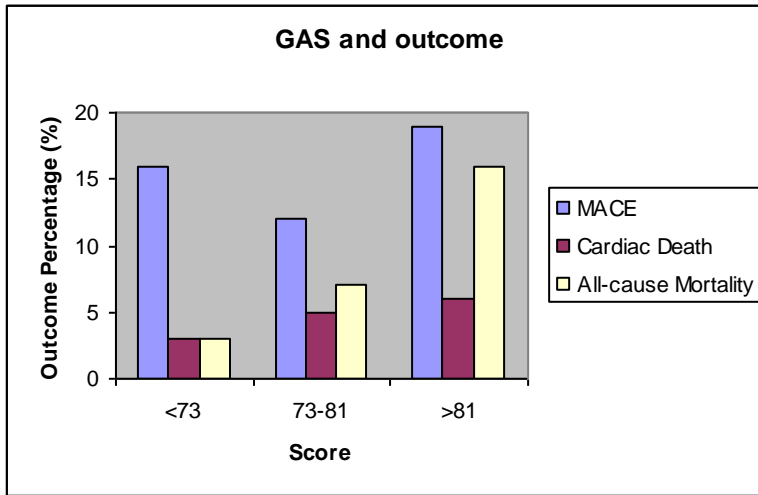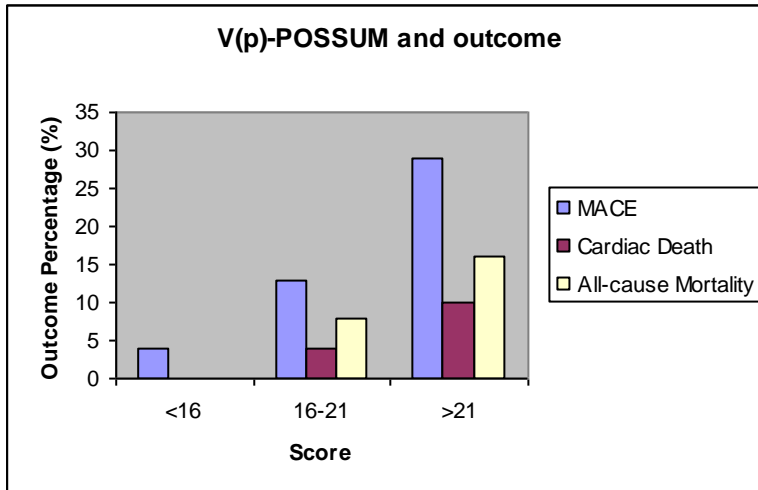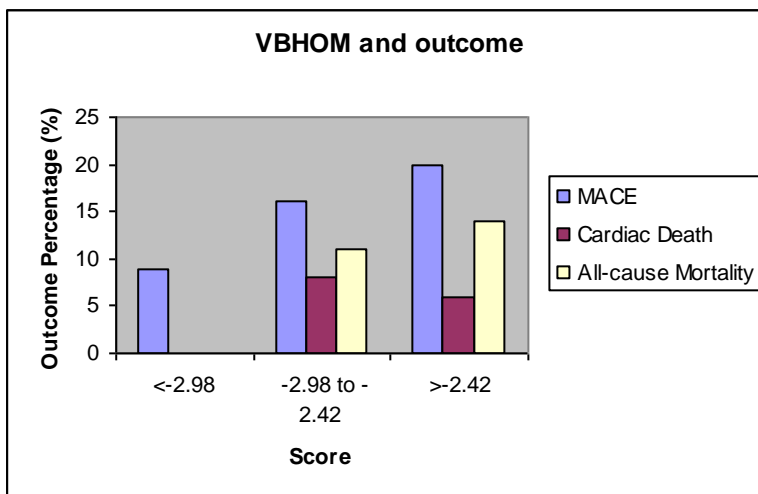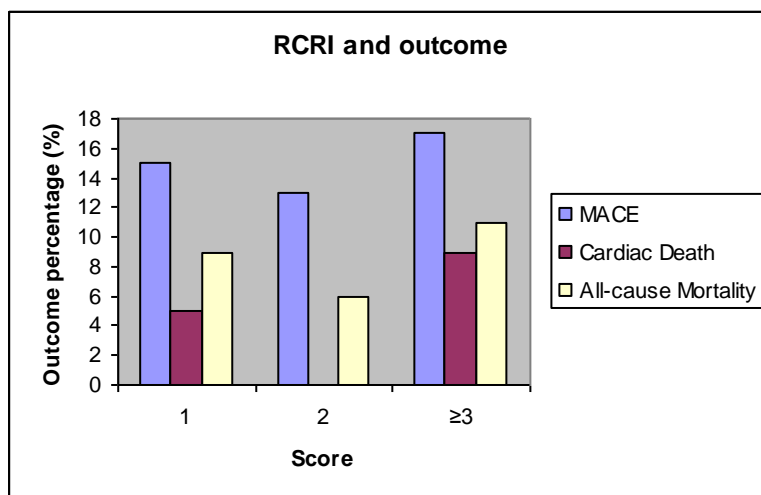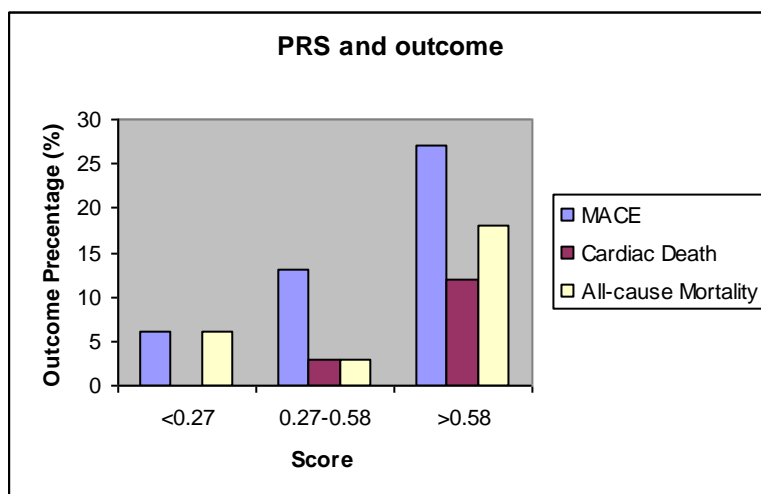
Tertile analysis reveals a significant difference in tertile rates for V(p)-POSSUM in predicting MACE and all-cause mortality (p=0.013 and p=0.030) and in the PRS component of E-PASS in predicting all outcome measures (p=0.038 in MACE, p=0.015 in cardiac death and p=0.032 in all-cause mortality). The RCRI and GAS indices performed poorly. All analyses were performed using Mann-Whitney U test. MACE – Major Adverse Cardiac Event, GAS – Glasgow Aneurysm Score, V(p)-POSSUM – Physiological component of Vascular Physiological and Operative Severity Score for enUmeration of Mortality, VBHOM - Vascular Biochemical and Haematological Outcome Model, RCRI – Revised Cardiac Risk Index, PRS – Preoperative Risk Score of Estimation of Physiological Ability and Surgical Stress.

6.4 Discussion

Preoperative risk stratification is of great importance in elective open AAA repair and, since opinion and experience alone are often the only tools of the vascular surgeon in selecting operative candidates, it is unsurprising that an ideal risk stratifier has been sought. A number of risk scoring systems derived from patients undergoing non-cardiac surgery have been devised over the last 20-30 years, but most seem to lack accuracy.[294-296] Based on a review of the literature, the 5 most suitable preoperative risk scoring indices have been identified and prospectively evaluated with an emphasis on predicting MACE, cardiac death and all-cause mortality in the immediate postoperative period.

The 2 scoring systems that performed well were the V(p)-POSSUM and the Preoperative Risk Score component of the E-PASS. In this cohort, the physiology component of the V(p)-POSSUM was a significant predictor of all outcome measures. POSSUM scoring has long been advocated as the most appropriate scoring system in non-cardiac surgery.[297] In addition, POSSUM has been shown to over-predict death in low risk patients[298], despite modification including the vascular adaption.[299] It is therefore expected that V(p)-POSSUM would perform well in predicting all-cause mortality in the elective open AAA patient, given the higher risk associated with this surgery type compared to other types of non-cardiac and vascular procedures. It was unexpected that it would perform well in predicting MACE, although this may reflect its ability to predict morbidity in general. Whilst this index appears to perform well, there is overriding concern with the effect of area variation, and whilst V(p)-POSSUM allows for variations in the hospital case mix it is not robust in different geographical locations.[299, 300]

The PRS component of the E-PASS score performed well in predicting MACE and cardiac death, and whilst it did not appear to predict all-cause mortality on univariate testing it did perform well on tertile analysis and in ROC curve analysis. The main concern with E-PASS is that the original scoring system requires operative data to calculate its overall score thus precluding its use for preoperative risk assessment. However a strong correlation between the PRS component and outcome has been shown which therefore permits its use in the preoperative setting.[257] It may be the very premise of this scoring system, where each patient's physiological reserve is scored, that gives a more accurate outcome measure.

Of the other scoring systems only VBHOM showed promise in predicting all-cause mortality. However, this did not reach statistical significance and VBHOM performed poorly in predicting MACE or cardiac death. This confirms previous validations where VBHOM was shown to under-predict perioperative complications and over-predict mortality.[297] This may be explained by the fact that VBHOM was devised including patients who underwent emergency AAA repair. The supposed advantage of VBHOM, including its universal applicability as it relies only on a minimal dataset of blood tests and does not use operative data, does not hold true in this cohort.

The GAS and RCRI performed poorly in this prospective cohort. The GAS was constructed using a population of 500 patients undergoing AAA repair in Glasgow over a 10 year period between 1980 and 1990.[154] This was a retrospective data analysis and produced a simple index of risk. Despite numerous validations in different populations[156-158, 301, 302] the GAS has been criticised for not reliably identifying individual high risk patients and being consistently inaccurate in predicting morbidity[158,161], whilst also performing poorly when compared to other scoring systems.[161] The GAS also fails to allow for treatment or optimisation of a patient's comorbid condition and scores for the presence of disease rather than the functional effects of the disease process. More surprising is that the score is a poor predictor in the very population from which it was derived, which may be in part explained by the increasing age and improving health states of the population.

The most unexpected finding is that the RCRI performed worst. This revised cardiac index not only failed to predict mortality but failed to predict cardiac events. This lack of predictive value may be due to the high risk population within which it was used, immediately scoring every patient 1 prior to further scoring. It is likely that this diminishes the sensitivity of the index, as has been suggested in the published literature, where concern has been expressed at the grouping of intraperitoneal and major vascular surgery together, and where open AAA repair has shown to have worse outcome than all other operation subgroups that are considered together in the RCRI.[66, 303] Despite this the RCRI was recently found to predict survival in the elective open AAA repair population in the UK when used with CPEX testing.[304]

The principal limitation of this prospective cohort is the small sample size. Although MACE occurred with sufficient frequency to draw reasonable conclusions, all-cause mortality and in particular cardiac death were low in real numbers. A larger cohort would have been more conducive to risk estimation. In contrast, however, the endpoints were well-defined and most vascular surgical practices will deal with numbers similar to this cohort. This therefore questions the utility of scoring systems that require large numbers to be clinically relevant.

It is apparent that, when compared to the scoring systems described in this chapter, BNP has superior predictive capabilities. Median BNP was highly significant in predicting MACE, cardiac death and all-cause mortality (p=0.001, p=0.043 and p=0.028). BNP therefore outperformed all indices with regards to MACE and all-cause mortality, and was only surpassed in cardiac death by both PRS (p=0.017) and V(p)-POSSUM (p=0.030). When comparing ROC curve analysis, BNP outperformed all risk indices with regards to all outcome measures [Table 6.4]. Further to this, on tertile analysis, although there was no stepwise increase in MACE and mortality there was a significant difference in tertile grouping of BNP in predicting all outcome measures [Figure 6.6]. More importantly, with tertile analysis there is little difference in outcome observed until the 3rd tertile, which demonstrates that BNP predicts those that are at high risk and at very low risk, negating the need for decision making in the difficult intermediate risk patient, as seen with other risk stratification indices.

In conclusion, it appears that a preoperative BNP sample not only predicts MACE, but also outperforms current risk indices in predicting cardiac death and all-cause mortality. Where BNP analysis is not available it appears both the PRS component of E-PASS and V(p)-POSSUM have advantages in outcome prediction over other scoring systems. Whilst V(p)-POSSUM appears to be the best stratification score (and easily accessible on the internet) with regard to all-cause mortality, its inability to predict mortality rates in individual patients may make E-PASS a more favourable alternative, having been developed specifically as an aid to clinical decision-making, although further validation is required.[257, 294]

Table 6.4 Results of receiver operating characteristic curve analysis for B-type natriuretic peptide.

	AUC	95% CI	SE	p-value	cut-off	Sens.	Spec.	PPV	NPV
MACE	0.927	0.850-1.004	0.039	<0.001	99.5 pg/ml	88%	89%	61%	98%
(PRS	0.682	0.559-0.805	0.063	0.021	0.55	69%	64%	27%	93%)
Cardiac Death	0.963	0.896-1.031	0.034	<0.001	448 pg/ml	80%	100%	100%	99%
(PRS	0.821	0.697-0.945	0.063	0.016	0.63	80%	76%	15%	99%)
All-cause Mortality	0.860	0.757-0.962	0.052	<0.001	93 pg/ml	78%	79%	30%	99%
(V(p)-POSSUM	0.780	0.667-0.893	0.057	0.006	20.5	89%	68%	21%	99%)

Comparison of BNP with the best performing of the five scoring indices (in brackets) reveals that BNP outperforms all scoring systems in terms of AUC, significance, sensitivity, specificity and predictive values. MACE – Major adverse cardiac event, V(p)-POSSUM – physiological component of Vascular Physiological and Operative Severity Score for enUmeration of Mortality, PRS – preoperative risk score of Estimation of Physiological Ability and Surgical Stress, AUC – area under the curve, CI – confidence interval, SE- standard error, Sens. – Sensitivity, Spec. – Specificity, PPV – positive predictive value, NPV – negative predictive value.

Figure 6.6. Tertile analysis for B-type natriuretic peptide and outcome.
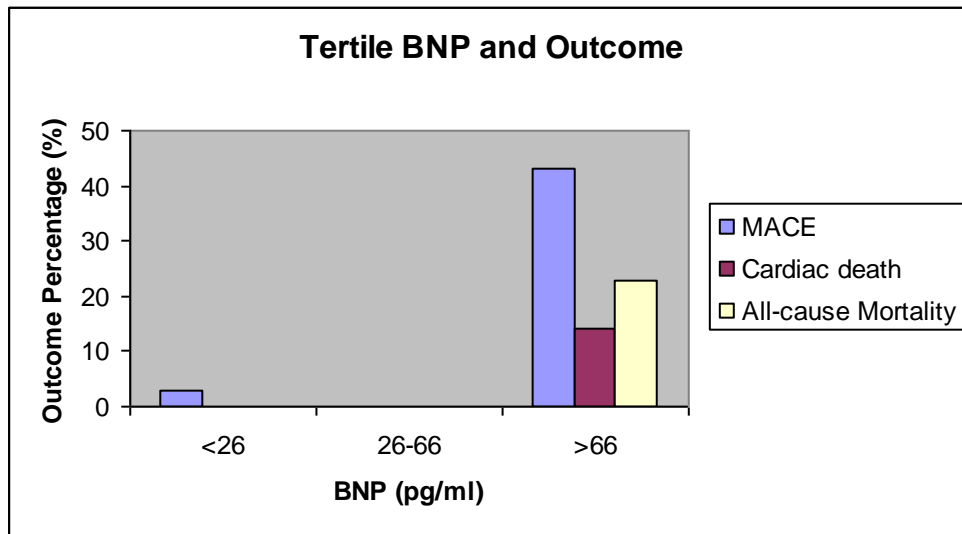
Tertile analysis reveals a significant difference in tertile rates for BNP in predicting MACE, cardiac death and all-cause mortality (p<0.001, p=0.007 and p=0.002 respectively). All analysis were performed using Mann-Whitney U test. MACE – Major adverse cardiac event.

Chapter 7

Endovascular Aneurysm Repair, BNP and Cardiac Outcome

7.1 Introduction

Since endovascular aneurysm repair was first introduced in the late 1980s it has been an area of controversy with regard to satisfactory aneurysm repair, long-term outcome measures, quality of life and cost. Potential advantages of EVAR over open repair include reduced time under general anaesthesia, elimination of the pain and trauma associated with major abdominal surgery, reduced length of stay in hospital and intensive care unit, and reduced blood loss.[305] Potential disadvantages include the development of endoleaks, which occur when blood continues to flow through the aneurysm due to incomplete exclusion of the aneurysm by the stent graft.[305] Thus, although open repair does not require any special follow-up, patients who have undergone EVAR require regular imaging to check for the presence of late endoleaks. In addition, if the EVAR procedure is unsuccessful or complications arise during the procedure, conversion to open repair may be necessary in patients who may initially have been considered unfit for open surgery.[305]

The recent EVAR 1, EVAR 2 and Dutch Randomized Endovascular Aneurysm Management (DREAM) trials addressed management of abdominal aortic aneurysms (AAAs) larger than 5.5 cm in diameter.[21, 22, 306-308] The DREAM and EVAR 1 trials randomized patients appropriate for open repair to EVAR or open repair, whilst the EVAR 2 trial randomized patients unfit for open repair to EVAR or nonoperative management. The EVAR 1 trial showed a 3% lower initial mortality for EVAR, with a persistent reduction in aneurysm-related death at 4 years. However improvement in overall late survival was not demonstrated. Similarly, the DREAM trial observed an initial mortality advantage for EVAR, but overall 1-year survival was equivalent in both groups. Both trials found significantly higher complication and intervention rates and higher hospital costs with EVAR, and by 1 year, no quality of life benefit was evident. The EVAR 2 trial did not demonstrate a survival advantage with EVAR over non-operative management, whilst observing that EVAR was associated with a greater likelihood of treatment complications, subsequent interventions, and threefold higher costs. A number of methodological problems, including the exclusion of 14 patients who died whilst awaiting EVAR, have meant that definitive conclusions are difficult to draw from the EVAR 2 trial.

It is clear from these trials, which show short-term mortality benefits but questionable long-term mortality benefits, that the role of EVAR has not yet been fully defined. Consequently, patient selection and risk stratification remain important. In this chapter the aim is to evaluate the use of preoperative serum BNP in predicting outcome in EVAR, with emphasis on MACE and all-cause mortality in the immediate perioperative period.

7.2 Methods

7.2.1 Study Population

A prospective, observational, multi-centre cohort study was performed involving the 3 major vascular units within Glasgow (Gartnavel General Hospital, Glasgow Royal Infirmary and the Southern General Hospital). A cohort of consecutive patients admitted electively for EVAR were identified between August 2005 and September 2007. As the use of EVAR was not fully established throughout Glasgow at the beginning of the study period, with only around 20 EVARs performed a year, a timescale was used, rather than a recruitment endpoint, that ran alongside the open AAA repair cohort (2005-2007 as described above).

7.2.2 Patients and Preoperative Assessment

Collection of patient data was identical to that described in chapter 4. Preoperative BNP was collected in the manner previously described in chapter 4.

7.2.3 Postoperative Follow-up

Immediate postoperative testing is described in detail in chapter 4. The only modification to this protocol was the preference of day 5 tests on the day of discharge when patients were discharged home before day 5, to ensure that there were two complete sets of post-op measurements. All patients were then followed through an area-wide interhospital computer database for 30 days. Where no recent contact was recorded during this period the patients' General Practice (GP) was contacted, as was required in 22 cases. If a patient died during this period, the date and cause of death were noted.

7.2.4 Endpoints

Endpoints for the study were non-fatal MI and all-cause mortality. The definition of MACE is that described in chapter 4 and was determined by a review of postoperative data by two cardiologists blinded to preoperative BNP levels. All-cause mortality was postoperative death of any cause.

7.2.5 Statistical Analysis

Statistical analysis was performed using the SPSS® statistical software package (SPSS, Chicago, Illinois, USA). BNP values were reported as median (interquartile range) with continuous variables compared using Mann-Whitney U and Kruskall-Wallis testing. Fisher's Exact test was used to analyse the differences between independent categorical data.

7.2.6 Ethical Approval

Local Research and Development, and Central Ethics Committee approval was obtained for the study. All patients were provided with an information sheet and signed a study consent form prior to inclusion. GPs were sent individual letters to inform of their patients' inclusion in the study.

7.3 Results

7.3.1 Patient Characteristics and BNP Levels

During the study period 42 patients met the inclusion criteria and were invited to participate. Two were found to have elevated preoperative cTnI (0.11 and 0.23 ng/ml) and were not included. Their preoperative serum BNP levels were 742 and 16 pg/ml respectively. Both patients underwent EVAR despite their elevated cTnI and neither developed a cardiac complication. The median age of the remaining 40 patients was 78 (71-80) years. The median preoperative BNP level was 40 (25-98) pg/ml. Further baseline characteristics are shown in table 7.1. The male to female ratio shows a male predominance of 8:1. The majority of patients had smoked at some point in their life (82%). Fifteen (38%) patients had suffered a previous MI and 7 (18%) suffered from CCF. Nine (23%) patients had been noted to suffer from chronic renal impairment. Other selected patient characteristics are detailed in table 7.2.

BNP levels were found to be significantly higher in those that had known CCF (median BNP 210 [69-420] vs 35 [19-64] pg/ml, p=0.018). Levels were proportionally higher in those with hypertension, hyperlipidaemia or a history of previous MI, although this was not significant.

Renal failure by chronic kidney disease stage did not show variation in BNP levels, although there was a tendency to higher levels with increasing degrees of chronic kidney disease. Two patients had an eGFR <30ml/min. Both patients had an uncomplicated recovery. BNP levels were 210 and 678 pg/ml respectively.

Table 7.1 Clinical details and BNP levels in elective EVAR patients.

	Patient Characteristic n=40	BNP level (pg/ml)	p value
Sex			
Male	35 (87%)	36 (22-99)	
Female	5 (13%)	44 (28-141)	0.893
Angina			
Present	11 (28%)	45 (27-210)	
Absent	29 (72%)	35 (19-88)	0.374
Previous MI			
Present	15 (38%)	56 (36-210)	
Absent	25 (62%)	33 (19-77)	0.268
Hypertension			
Present	27 (68%)	52 (26-112)	
Absent	13 (32%)	35 (13-47)	0.124
Hyperlipidaemia			
Present	19 (48%)	36 (26-112)	
Absent	21 (52%)	44 (24-88)	0.184
Diabetes			
Present	10 (25%)	29 (11-159)	
Absent	30 (75%)	45 (29-100)	0.721
Current smoker			
Present	11 (28%)	32 (6-99)	
Absent	29 (72%)	45 (28-98)	0.328
Smoked ever			
Present	33 (82%)	35 (24-83)	
Absent	7 (18%)	82 (26-103)	0.063
CVD			
Present	7 (18%)	36 (14-210)	
Absent	33 (82%)	45 (26-91)	1.0
CCF			
Present	7 (18%)	210 (69-420)	
Absent	33 (82%)	35 (19-64)	0.018
COPD			
Present	11 (28%)	34 (27-210)	
Absent	29 (72%)	45 (24-88)	0.423
CRF			
Present	9 (23%)	32 (15-171)	
Absent	31 (77%)	44 (26-83)	0.917

Patient characteristics by BNP reveal significant differences in BNP levels in patients that had CCF (p=0.018) when analysed using Mann-Whitney U test. MI – myocardial infarction, CVD – cerebrovascular disease, CCF – congestive cardiac failure, COPD – chronic obstructive pulmonary disease, CRF - chronic renal failure.

Table 7.2 Selected other patient details and BNP.

	Patient Characteristic n=40	BNP level (pg/ml)	p value
Anti-platelet			
Present	28 (70%)	41 (26-103)	
Absent	12 (30%)	40 (17-68)	0.784
Statin			
Present	27 (68%)	35 (26-101)	
Absent	13 (32%)	45 (19-91)	0.382
Beta-blocker			
Present	14 (35%)	51 (33-130)	
Absent	26 (65%)	35 (15-86)	0.198
Antianginal			
Present	9 (22%)	36 (20-64)	
Absent	31 (78%)	44 (26-101)	0.953
Diuretic			
Present	10 (25%)	55 (20-96)	
Absent	30 (75%)	36 (26-100)	0.575
RCRI			
0	11 (28%)	32 (10-45)	
1	15 (38%)	49 (26-83)	
2	5 (12%)	131 (59-457)	
≥3	9 (22%)	34 (21-161)	0.069
eGFR			
<60	22 (55%)	51 (32-102)	
≥60	18 (45%)	32 (16-65)	0.206
CKD			
1	3 (7%)	99 (32-145)	
2	15 (38%)	22 (10-49)	
3	20 (50%)	45 (30-91)	
4	2 (5%)	444 (210-678)	
5	0 (0%)	0	0.112
CRP			
<6	18 (45%)	36 (31-100)	
≥6	22 (55%)	45 (15-87)	0.777

Although not significant, BNP levels were higher in those with worsening renal failure and increasing risk by RCRI. Analyses were determined using Mann-Whitney U and Kruskall-Wallis for RCRI and CKD. RCRI – revised cardiac risk index, eGFR – estimated glomerular filtration rate, CKD – chronic kidney disease, CRP – C-reactive protein.

7.3.2 EVAR vs Open Repair Cohorts

When comparing the cohorts for elective EVAR and elective open repair (chapter 4) there was a significant difference in age [EVAR 78 (71-80) vs Open repair 73 (66-77) years, p=0.002]. There were also significant differences in the proportion of patients with hyperlipidaemia [EVAR 19/40 (48%) vs Open repair 15/106 (14%), p=0.003] or chronic renal impairment [EVAR 9/40 (23%) vs Open repair 8/106 (8%), p=0.035]. In general the EVAR cohort appeared more unhealthy with a greater incidence of angina, previous MI, hypertension, diabetes mellitus, cerebrovascular disease and chronic heart failure, although not significantly so. Patient characteristics are compared in tables 7.3 and 7.4.

Table 7.3 Patient characteristics in EVAR vs open repair.

		Patient Characteristic n=106 (open repair)	Patient Characteristic n=40 (EVAR)	p value
Age	(years)	73 (66-77)	78 (71-80)	0.002
AAA size	(cm)	6.4 (5.7-7.2)	6.2 (5.9-7.0)	0.259
Sex	Male	88 (83%)	35 (87%)	
	Female	18 (17%)	5 (13%)	0.317
Angina	Present	25 (24%)	11 (28%)	
	Absent	81 (76%)	29 (72%)	0.201
Previous MI	Present	23 (22%)	15 (38%)	
	Absent	83 (78%)	25 (62%)	0.371
Hypertension	Present	72 (67%)	27 (68%)	
	Absent	34 (33%)	13 (32%)	0.134
Hyperlipidaemia	Present	15 (14%)	19 (48%)	
	Absent	91 (86%)	21 (52%)	0.003
Diabetes	Present	9 (8%)	10 (25%)	
	Absent	97 (92%)	30 (75%)	0.083
CVD	Present	22 (21%)	7 (18%)	
	Absent	84 (79%)	33 (82%)	0.366
CCF	Present	13 (12%)	7 (18%)	
	Absent	93 (88%)	33 (82%)	0.366
COPD	Present	25 (24%)	11 (28%)	
	Absent	81 (76%)	29 (72%)	1.0
CRF	Present	8 (8%)	9 (23%)	
	Absent	98 (92%)	31 (77%)	0.035

There was a greater number of patients with hyperlipidaemia (p=0.003) and CRF (p=0.035) in the EVAR cohort and patients were older (p=0.002). There appeared to be greater co-morbidity in the EVAR cohort with greater incidence of angina, hypertension, and diabetes, although this did not reach statistical significance. Analyses were determined using Fisher's Exact Test. MI – myocardial infarction, CVD – cerebrovascular disease, CCF – congestive cardiac failure, COPD – chronic obstructive pulmonary disease, CRF - chronic renal failure.

Table 7.4 Other patient characteristics in EVAR vs open repair.

	Patient Characteristic n=106 (open repair)	Patient Characteristic n=40 (EVAR)	p value
Anti-platelet			
Present	63 (59%)	28 (70%)	
Absent	43 (41%)	12 (30%)	0.221
Statin			
Present	66 (62%)	27 (68%)	
Absent	40 (38%)	13 (32%)	1.0
Beta-blocker			
Present	43 (41%)	14 (35%)	
Absent	63 (59%)	26 (65%)	0.346
Antianginal			
Present	23 (22%)	9 (22%)	
Absent	83 (78%)	31 (78%)	0.763
Diuretic			
Present	35 (33%)	10 (25%)	
Absent	71 (67%)	30 (75%)	0.127
eGFR			
<60	42 (40%)	22 (55%)	
≥60	64 (60%)	18 (45%)	0.936
CKD			
1	9 (8%)	3 (7%)	
2	52 (49%)	15 (38%)	
3	43 (41%)	20 (50%)	
4	2 (2%)	2 (5%)	
5	0 (0%)	0 (0%)	0.691

Despite the apparent increased co-morbidity in the EVAR cohort there were no differences in cardiac medication or CKD between the two cohorts. Analyses were determined using Fisher's Exact Test. eGFR – estimated glomerular filtration rate, CKD – chronic kidney disease.

7.3.3 BNP and Outcome

There were 3 (7.5%) postoperative non-fatal MIs within 30 days. There were no cardiac deaths; however, there was 1 (2.5%) postoperative death attributed to a primarily pulmonary origin. There was no significant difference in BNP between those that suffered MACE and those that did not (median BNP in MACE 94 [36-101] vs 35 [24-91] pg/ml, p=0.320) [Figure 7.1]. The BNP in the patient who died was 69 pg/ml. There was no significant difference in any other risk factor, patient characteristic, intraoperative factor, current medication or preoperative blood testing between those that suffered MACE and those that did not. Only in preoperative creatinine [median serum creatinine in MACE 145 [122-172] vs 104 [91-108] µmol/l, p=0.069] and eGFR [median eGFR in MACE 43 [36-53] vs 57 [49-73] ml/min, p=0.116] was there a tendency to MACE in those with worse renal function, although this was not statistically significant. There were no asymptomatic postoperative elevations of cTnI without MACE. Overall 30-day morbidity in EVAR was 28% with 3 non-fatal MIs, 3 episodes of worsening renal failure (requiring dialysis in 2 cases), 2 episodes of peripheral critical ischaemia requiring reintervention, 1 episode of severe peptic ulceration, 1 case of florid post-procedure diarrhoea and 1 aspiration pneumonia. 30-day morbidity in the elective open repair cohort was 33% with (other than the 11 non-fatal MIs) 11 episodes of respiratory sepsis (2 requiring supportive ventilation), 4 episodes of acute renal failure (2 requiring dialysis), 4 episodes of postoperative ileus, 3 episodes of cardiac arrhythmia requiring intervention, 2 episode of congestive cardiac failure and 1 upper gastrointestinal bleed.

Figure 7.1 BNP by major adverse cardiac event (MACE).
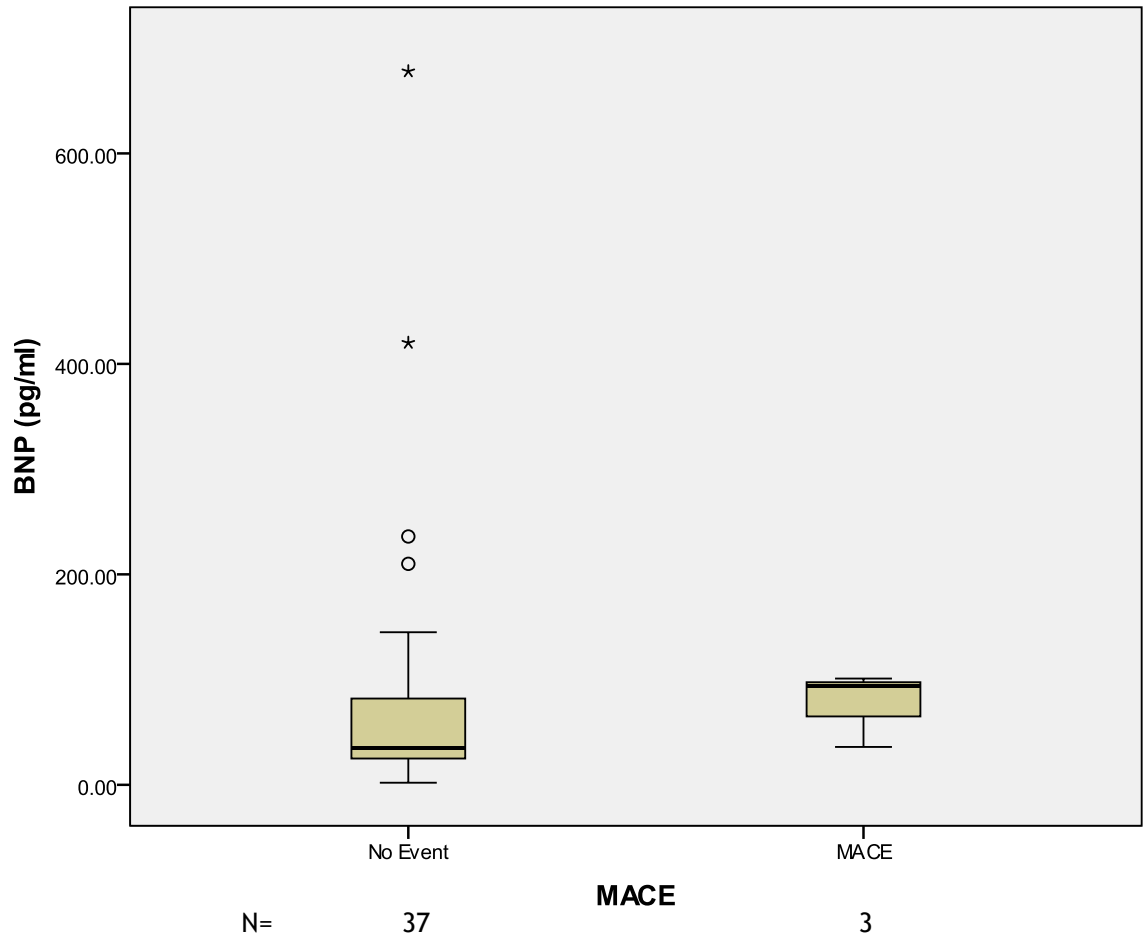
There was no difference in median preoperative BNP concentration between those that had MACE and those that did not (Median BNP in MACE 94 [36-101] vs 35 [24-91] pg/ml, p=0.320) as calculated by Mann-Whitney U test. The dots represent outliers. The asterisks/stars represent extreme outliers where the level marked is >3 times the height of the boxes. N is number of patients.

7.3.4 Preoperative Echocardiography

Preoperative transthoracic echocardiography was available in 27 (67.5%) patients. See table 7.5. Of these 27 patients, 8 were found to have mild LV dysfunction, 1 had moderate dysfunction and 2 had severe dysfunction. The remainder had normal LV systolic function. Median BNP rose with worsening LV function. There were no episodes of MACE in those with moderate or severe LV dysfunction. There were insufficient cases of MACE to allow meaningful statistical analysis.

Table 7.5. Left ventricular function, BNP levels and Major Adverse Cardiac Events (MACE).

	Patients (n=27)	BNP (pg/ml)	MACE	
LV Function				
Normal	16 (59%)	35 (18-63)	2/16	(13%)
Mild dysfunction	8 (30%)	112 (94-145)	1/8	(13%)
Mod dysfunction	1 (4%)	210	0/0	
Severe dysfunction	2 (7%)	549 (420-678)	0/0	

7.4 Discussion

In this prospective multi-centre cohort study no single factor was shown to predict MACE, cardiac death or all-cause mortality. The patients selected for EVAR were older than those considered for open repair. There appeared to be greater co-morbidity in the EVAR group, and although there were no objective selection criteria, in general those selected for EVAR would have been expected to have less favourable outcome if undergoing open repair. Given that there was no area-wide patient selection policy for EVAR, the results suggest that individual consultant preference selected similar patient types, possibly as a result of recently published EVAR trials.

This study was clearly limited by the small sample size and the low number of cardiac events. Recruitment was restricted by the lack of established EVAR practice in Glasgow and the uncertain cardiac event rate in this population. Previous studies of EVAR have shown low cardiac event and mortality rates, and therefore much larger numbers of patients would require to be recruited to result in meaningful data. The small numbers in this cohort make it very difficult to draw any firm conclusions.

From the results we have obtained, it would appear that in those who did suffer a cardiac event, BNP did not have the same predictive capabilities as that shown in open repair and in fact those with very high serum BNP levels survived the perioperative period without complication. These results would suggest that a group of patients with very high serum BNP levels who are deemed not suitable for open repair, due to perceived high risk, may nevertheless benefit from EVAR if deemed necessary. There is, however, an increasing bank of evidence that would not support this conclusion.

The hypothesis that EVAR might be better than surveillance for high risk patients has not been supported by the EVAR-2 trial. This study randomized 338 patients considered not suitable for open repair to EVAR or to no intervention.[308] The operative mortality of EVAR was 9%, and there was no survival benefit, although the survival curves for aneurysm-related mortality did cross at 2 years, suggesting the possibility of a late benefit. In addition, retrospective analysis of a large American EVAR database revealed that there was a high-risk cohort of patients with a very high mortality (>10%) that would not benefit from EVAR.[309]

The use of EVAR, rather than open repair, in treating large AAAs (>5.5cm) has also been questioned as the early mortality benefit of EVAR is not sustained in the long-term. In the 1082-patient EVAR-1 study, the 30-day mortality rate was 1.7% for EVAR versus 4.7% for open repair (p=0.001). At 4 years however, all-cause mortality was similar for EVAR and open repair (26% vs 29% respectively; p=0.460).[22] In addition, those who underwent EVAR were much more likely to need further intervention with health care costs swelling. Similarly, in the 351-patient DREAM trial, the 30-day mortality rate was 1.2% after EVAR versus 4.6% after open repair, but overall survival rates were not different at 2 years.[306, 307]

Recent publications have pointed towards a role of EVAR in small AAAs. Retrospective evaluations of EVAR have revealed that the use of EVAR in smaller AAAs results in favourable outcome. A 923-patient analysis concluded that patients with AAAs <5.0 cm were more favourable candidates for EVAR and had the best long-term outcomes, with 99% freedom from AAA death at 5 years; patients with large AAAs (≥6.0 cm) had shorter life expectancy and higher risks of rupture, surgical conversion, and AAA-related death.[310] An analysis of 6-year data from 700 patients in the Cleveland Clinic EVAR database yielded similar findings.[311] The largest retrospective analysis of 4392 patients from the EUROSTAR registry found correlations between large AAAs and all assessed outcome events (perioperative morbidity, 30-day mortality, 4-year mortality, freedom from AAA rupture and freedom from AAA-related death) which were independent and highly significant.[312]

In response to the low operative mortality rates associated with EVAR and in response to these retrospective analyses of EVAR databases, 2 randomised controlled trials of EVAR for small AAAs have commenced: the Positive Impact of endoVascular Options for Treating Aneurysm earLy (PIVOTAL) and Comparison of surveillance vs Aortic Endografting for Small Aneurysm Repair (CAESAR). Both of these large studies, which randomise patients to EVAR or surveillance, are due to publish early results soon, although CAESAR has already missed its expected publication of early results, initially planned for 2009.

With the results of the trials detailed above, it is more difficult to see in what way BNP, by identifying high risk patients not suitable for open repair, can help decision making in EVAR. Due to its durability, open repair should reasonably be proposed in younger patients at low risk, with large and possibly with small AAAs. In addition, numerous studies report comparable outcome following open repair in elderly patients when compared to younger patients.[313, 314] It is therefore reasonable to advocate open repair in the elderly with low perioperative risk, although many may prefer to negate the high perioperative risk of open repair and opt instead for EVAR, as has been demonstrated when studying patient preference.[315] Only in those at high risk, or with high serum BNP, does the decision become more difficult. With the poor prognosis associated with high levels of BNP [316] it is not possible to recommend EVAR in all given the disappointing long-term results, and decisions would have to be made on a case by case basis. It is therefore likely that at present EVAR is best suited to young patients with large AAAs who have been deemed unfit, who have a shorter life-expectancy, but in whom surveillance alone would be unacceptable. Further larger studies accounting for the low number of cardiac events and all-cause mortality are required.

Chapter 8

Discussion

8.1 Cardiac Risk in Vascular Surgery

The principal aim of this research was to attempt to provide a way of improving risk assessment in patients undergoing aortic aneurysm repair. However, it has also raised some important points in relation to the vascular surgical population as a whole.

The first is in relation to the ongoing high prevalence of cardiac morbidity in this group of patients in Glasgow. The results revealed a MACE rate of 14.6% and a cardiac death rate of 7.0%. This is certainly greater than many of the published reviews looking at cardiac risk in major vascular surgery.[3,24,64,79] Even when compared to those studies designed to screen for postoperative cardiac events the findings of this research remain concerning, with most other studies revealing a MACE rate of 6-8%.[111, 114] Only rarely have such high rates been reported, including the recently published study investigating preoperative BNP in Glasgow by Gibson et al, which revealed a MACE rate in vascular surgery of 12.5-26.8%.[116] This is likely to be indicative of the general health and lifestyle of the local population whom we treat. This is demonstrated in that of the entire studied cohort, 40% have a history of IHD, and 20% DM. To further exacerbate the problem, only 28% appear to be on a regular statin, known to be beneficial not only in those with IHD but also in those with peripheral vascular disease as described in section 1.6.2.2.

Secondly, the presence of a raised preoperative cTnI level is associated with poor outcome following a major vascular procedure. Whilst previous studies have described preoperative elevations in cTnI to be a rare event[265, 266, 317], this research has found it to occur in 5.2% of patients presenting for major vascular surgery. With the associated mortality rate of 50% in these patients, the findings again highlight that this is therefore a high risk population. On the basis of this, if indeed it was felt that management would be altered based on the result, there is evidence to suggest that preoperative cTnI should become a routine marker. When delay is possible it may be that either observation and rechecking cTnI, or alternatively cardiac optimisation, will alter outcome as seen in the patients whose surgery was delayed in chapter 3.

The numbers of patients is too small to make definite or practice-changing recommendations. Further research to investigate whether the presence of an elevated preoperative cTnI alone predicts death, and whether delay or optimisation can alter this, would require recruited numbers of over 2000 patients. These requisite numbers are outwith those possible in the West of Scotland and possibly still outwith those of a national level study.

8.2 Cardiac Risk in Elective Open AAA Repair

The numerous reviews and publications of cardiac risk in major vascular surgery often include patients who undergo open AAA repair. It is less common that these patients are considered as a separate cohort, despite the very specific decision making that comes with this prophylactic operation and its associated risks.

8.2.1 The Risk of Repair

The rate of MACE in the open AAA repair cohort in this thesis was 15%. This is consistent with studies of aortic surgery that include routine regular postoperative cTnI measurements with ECG analysis and review of clinical progress[51], although similar event screening studies occasionally quote lower rates for AAA repair [116, 318], whilst many do not specify for AAA repair alone. With cardiac death in 5 of 106 patients the mortality rate from a cardiac cause alone was 4.7%, whilst the all-cause mortality was 8.5%. Whilst this mortality rate appears high, reports throughout the literature vary greatly between 0-12%.[319] Of the 11 non-fatal MIs, 3 suffered asymptomatic ST-elevation MIs (the 'silent' MI), that would not have been picked up without postoperative cardiac screening. This equates to 27% of events and is consistent again with many previous studies that have screened for cardiac events.[26, 320]

As established in this research, the most common cause of postoperative mortality is cardiac.[18, 286] Not only is cardiac disease a concern with regard to mortality in the short term, but both a history of a perioperative MI and elevated postoperative cTnI confer an increased risk of mortality in the intermediate and long-term.[140, 143] In this research the presence of postoperative MACE, without associated mortality, did confer a significantly increased risk of death at 1 year. There were also higher death rates at 2 and 3 years in those who had suffered MACE, although this was not significant. Similar findings were found with regard to postoperative elevations of cTnI and late mortality, although again this was not significant.

8.2.2 BNP as a Predictor

As anaesthetists have attempted to improve perioperative outcomes by focusing on the diagnosis, prevention and treatment of myocardial ischaemia in high risk surgical patients, BNP has become an increasingly recognised stratification tool in cardiac risk assessment. This marker has attracted the interest of surgeons, who have seen the advantages it offers in the decision-making process, balancing surgical risk and the need to operate. The interest in this marker has resulted in numerous publications, including most recently three meta-analyses.[321-323] These publications reviewed the evidence relating to the utility of preoperative BNP and NT-proBNP in predicting MACE. In addition, two of these looked at BNPs predictive capabilities with regard to short- and intermediate-term mortality.[321, 322] It was found that both BNP and NT-proBNP predicted MACE, cardiac mortality and all-cause mortality. However, none of the papers published to date, or included in the meta-analyses, studied the elective open AAA repair population alone.

8.2.2.1 Discriminatory BNP Levels

The results of this research show that a single preoperative serum BNP level can predict MACE, cardiac death and all-cause mortality within 30 days of elective open AAA repair. The cut-off value on ROC curve analysis for predicting MACE was 99.5 pg/ml. This value is similar to the optimal cut-off in diagnosing heart failure in both chronic cardiac failure and those presenting with acute dyspnoea (>100 pg/ml).[101, 324] Further, a level of 99.5 pg/ml is greater than that associated

with the diagnosis of heart failure in the ambulatory patient, which on consensus of expert opinions and manufacturers is >70 pg/ml [325], and is just above the cut-off of the normal age-adjusted value for BNP in those aged >60 years of age at <98 pg/ml.[326]

Not only does a BNP level <100 pg/ml exclude the likelihood of acute heart failure, but levels >400 pg/ml confer a positive likelihood greater than 10 in diagnosing heart failure.[273, 327, 328] The cut-off in this research for cardiac death was 448 pg/ml with a PPV of 100%. This would suggest that, although there are many other possible reasons for an elevated BNP [Table 1.7], a degree of heart failure is most likely in these patients and confers a high perioperative risk.

Of the studies performed to date there is no consensus of which BNP (or NT-proBNP) level predicts MACE, with wildly divergent discriminatory thresholds [Table 1.8]. Variations in patient cohorts with respect to age, gender, co-morbidity, BMI and degree of pre-existing cardiac failure may make attempts to find a single, universally applicable, BNP discrimination point futile. The optimal discrimination point would therefor likely be a factor of the prevalence of cardiac pathology in the population being examined. Groups with high numbers of patients with cardiac dysfunction would have high median BNP levels, which would result in higher discrimination points. Alternatively, it can be argued that a single BNP value is acceptable when using a standardised assay with international quality control, and that the proportion of patients with values above this threshold is a marker of that population's demographics and comorbidity, as is the degree of postoperative cardiac morbidity and mortality. In addition, the period of observation for each study influences any derived threshold, with the threshold decreasing as the event horizon is extended. Patients with high levels of BNP have events earlier in their observation periods resulting in higher thresholds. This is demonstrated when looking at the decreasing BNP thresholds over time for predicting death in the current thesis, where an initial threshold of 93 pg/ml for immediate mortality reduces to 60.5 pg/ml at 3 years.

Other interesting findings in the published literature include the finding that a BNP level >40 pg/ml was associated with a five-fold increase in the risk of developing new ECG abnormalities or a raised postoperative cardiac troponin.[114] Whilst in the present research BNP in relation to ECG changes was not investigated, postoperative elevations in cTnI were recorded. The median preoperative BNP was found to be significantly higher in those with postoperative elevations of cTnI (p=0.002), and ROC curve analysis revealed a cut-off of 54 pg/ml. This is of interest in relation to the increased intermediate and long term mortality associated with these elevations. Although this association appeared to be present on long-term analysis in the studied cohort (section 5.3.3), this was not statistically significant.

To establish whether there is a single threshold or a few important BNP thresholds, a substudy of the 40,000 patient international Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) study is underway.[329] This will evaluate whether NT-proBNP is an independent predictor of MACE or other major complications in the first 30 days after vascular surgery, and will determine if there is one or multiple NT-proBNP thresholds that substantially influence risk prediction.

8.2.2.2 BNP or NT-proBNP?

In this research BNP was used for all analyses, however, whether BNP or NT-proBNP is preferable for vascular surgical patients remains unclear. While the reliability of NT-proBNP may be limited by renal dysfunction[86, 88], there is some evidence to suggest that NT-proBNP may be a slightly better predictor of outcomes in medical patients with congestive cardiac failure and ischaemic heart disease.[101, 330] It is possible that the longer half-life of NT-pro BNP may result in it being less affected by perioperative haemodynamic shifts, than BNP. However there are no known studies that examine this phenomenon, and further, recent meta-analyses have shown that both BNP and NT-proBNP are good independent predictors of postoperative cardiac events. In addition, the way in which the blood samples were collected prior to analysis in this research was in a manner that would minimise haemodynamic stress, and samples were immediately centrifuged and frozen prior to later batch analysis.

8.2.3 Risk Scoring in Elective Open AAA Repair

The present thesis studies the value of the five most recognised and validated risk scores in open AAA repair, specifically for use in the preoperative period. The results show that most do not perform well in the currently studied cohort. The finding that the RCRI performed poorly to the extent that it showed no predictive capabilities is an unexpected finding. The reasons for this have been explored in section 6.1, and include lack of sub-grouping for differing types of high risk surgery, and lack of predictive capabilities when applied to highest risk populations (such as open AAA repair). Of greater concern is the fact that, as one of the simplest forms of risk score, this is possibly the most often used in the clinical environment. Based on the results of this thesis it would be advisable not to base clinical decision-making in aneurysm surgery on RCRI scoring.

The GAS displayed similarly poor predictive capabilities despite numerous validation studies. Despite the fact that GAS was devised as a means of predicting all-cause mortality after AAA surgery, what difference it did demonstrate did not reach statistical significance. As RCRI and GAS were relatively simple scores to calculate, the finding that they lack predictive power is disappointing for clinical practice. Furthermore, although VBHOM is more complex to calculate, it remained relatively easy to use given the objective data entry required. However, again, this score did not show statistically significant predictive capabilities for any of the outcome measures. Only the most complex scores, E-PASS and V(p)-POSSUM, showed significant prognostic ability for all outcome measures.

Both V(p)-POSSUM and PRS showed significant predictive capabilities with regard to all outcome measures. However, both V(p)-POSSUM and PRS contain a number of subjective elements making them vulnerable to miscalculation, and although on p-value alone these scores occasionally performed better than BNP, ROC analysis demonstrated that preoperative BNP had an associated PPV of 100% (NPV 99%) for cardiac death, and a NPV of 99% (PPV 30%) for all-cause mortality. In both cases therefore, these clinically relevant values outperform all risk scores.

A risk score that determines an individual patient's predicted risk in a specific hospital, that was validated in different geographical areas and that was based on routinely obtained objective measurements, would be of value in guiding surgical management of those with an expanding AAA that may require intervention. At present such a scoring system does not exist. Based on the superior predictive capabilities of BNP, and its ease of measurement, it is difficult to justify the routine use of any of the scoring systems listed for risk assessment in AAA surgery.

8.2.4 Long-term Outcome and the Small AAA

The results of this research show that BNP has predictive capabilities for intermediate and long-term mortality. This is consistent with published research[118, 122], and demonstrates, bearing in mind both the present and the published research, that BNP can predict mortality outcomes as well as cardiac outcomes. The value of BNP in the decision regarding the small AAA is therefore noteworthy in two aspects.

The first is as a simple predictor of mortality. The ability to identify those patients who will survive not only the perioperative period but long-term to at least 3 years, makes BNP unique. Whilst some markers perform well in one of these outcome measures, few perform well in both. Non-invasive cardiac testing predicts in the immediate postoperative period, but has not been shown to be effective in predicting long-term outcome. Of the available scoring systems only GAS has been shown to potentially predict long-term outcome.[156, 160, 301] However, as discussed above, it appears to perform poorly in the very cohort for which it was devised.

Secondly, BNP has the ability to predict both immediate postoperative MACE and postoperative elevations of cTnI. As discussed, both non-fatal MI and postoperative elevations of cTnI are associated with increased intermediate and long-term mortality.

Although BNP has superior predictive capabilities in the long term, the actual serum level at which a decision could be made to proceed with surgery with a small AAA is uncertain. Whilst a threshold of 99.5 pg/ml allows the selection of a greater proportion of patients who are unlikely to survive the long-term postoperative period, a level of 60.5 pg/ml predicts a greater proportion of patients that will survive to 3 years. It may therefore be that a lower BNP level should be considered as a threshold if choosing to use BNP in the decision making process regarding surgical repair of small aneurysms.

8.2.5 BNP and EVAR

In this research BNP does not aid clinical decision making in endovascular aneurysm repair. This may be due to the low numbers recruited, and larger studies of BNP in EVAR may clarify this further. It seems more likely, however, that BNP will be of limited use in this setting due to the fact that MACE is not a common cause of perioperative death following EVAR.[22] Further, although BNP can predict intermediate and long-term mortality in open AAA, much of this ability is related to its capacity to predict outcome in the perioperative period.

The importance of BNP in EVAR is therefore not yet defined. As described in section 7.4, although EVAR remains a preference for some, its place in AAA repair is currently limited. Its use in those deemed unfit (by BNP or other means) for open repair is not all-encompassing due to the poor long-term results of the EVAR trials. It may be that EVAR will be a therapeutic option for the small AAA, and may even be preferable to open repair if durability is proven; however currently no recommendations can be made to this effect.

8.2.6 Other Predictors of Outcome

With regard to perioperative MACE in open AAA repair, only CCF was found to be a predictor of outcome (p=0.026) on univariate analysis. With BNP, a marker of heart failure, and CCF predicting MACE, there is clear support for the historic findings of Goldman that preoperative ventricular dysfunction is a strong risk factor for perioperative cardiac morbidity and mortality.[108] Not only was CCF implicated in MACE, but it was found to be a risk factor in perioperative all-cause mortality (p=0.002) and 3-year mortality (p<0.001). Despite this knowledge, the results of the data collection for this thesis identified that only 75 of the 106 patients had undergone a preoperative echocardiogram. This highlights the importance of diagnosing and recording the presence of heart failure prior to making any decision regarding operative intervention.

The only other factor that was found to correlate with MACE was the operative time. Although on univariate analysis this was not significant (p=0.098), on multivariate analysis, it was found to correlate (p=0.0065) with MACE, along with CCF (p=0.033) and elogBNP (p<0.001). Although this is unlikely to alter preoperative decision making, this raises the importance of minimising operative time, whilst taking into consideration any anatomical and previous surgical factors that might complicate and lengthen an already complicated operative procedure.

With regard to perioperative, intermediate and late mortality, renal dysfunction was the only significant risk factor other than CCF with regard to open AAA repair. Both worsening stages of CKD (p=0.010) and eGFR (p=0.027) correlated with perioperative mortality, whilst only CKD stage (p=0.031) correlated with 3-year mortality. Renal function is a factor that has been considered for many years to impart an increased operative risk when considering postoperative complications and death, and is an element in all of the scoring systems that were investigated in this thesis. Indeed, further subgroup analysis based on a BNP threshold of 99.5 pg/ml, as seen in table 4.6, selects out a group based on an eGFR ≥60 ml/min who are likely to do well. In addition there were no deaths over 3 years in those classified as CKD stage 1. Accurate diagnosis and equally accurate documentation is once again advocated based on these findings.

8.3 Changes to Clinical Practice

Were the findings of this thesis to be taken at face value, they would promote the routine use of preoperative BNP to guide decision-making in the treatment of patients with an AAA. This is, however, in contradiction to the recommendations of a review article by Rodseth.[107] This review reports on the finding of a community-based study, in which when BNP is used to identify patients with subclinical cardiac failure, with ejection fractions ≤50% or mild diastolic dysfunction, BNP resulted in an area under the curve <0.70, which is insufficient to be considered as a screening test.[331] The implication was therefore that BNP would not be useful, or cost effective, in every patient. Rodseth suggested the use of clinical risk factors to identify higher risk patients, and promoted the AHA/ACC guidelines as a structure around which to guide the use of BNP.[107] It has therefore been suggested that BNP should only be measured and used as a non-invasive risk stratification tool in patients undergoing major or intermediate risk surgery, who can not function at ≥4 METS without symptoms. The counter-argument would be that elective open AAA surgery is always classed as major surgery, and, that the assessment of metabolic equivalents is a subjective matter. In deciding on whether to proceed with a prophylactic operation, one would desire all available information before making the appropriate decision.

If BNP is routinely measured, it should be possible to identify patients who are suitable for repair of their AAA (and possibly their small AAA) based on a BNP level <99.5 pg/ml. A preoperative CRP <6 mg/dl and an eGFR ≥60 ml/min would strengthen the case. It would also identify those with very high BNP levels (>448 pg/ml) that should not undergo operative repair. However, there is no published evidence that has investigated what to do in the presence of an elevated BNP level that does not immediately negate a surgical option (>99.5 pg/ml). Whilst evidence exists with regard to BNP modification in the non-surgical population, none exists in the preoperative surgical population.[105, 279] There is also a lack of evidence on whether further cardiac testing would be of benefit in reducing risk. This and some other untouched areas for research will be discussed more in section 8.5.

8.4 Study Limitations

The main findings of this thesis, as detailed in chapters 4 and 5, present an adequately powered study with considerable heterogeneity in regard to patient characteristics. There were however limitations. Although adequately powered to investigate the value of BNP in predicting MACE in the elective open AAA repair population, the sample size remained relatively low, precluding adequate multivariate analysis. In addition, not all patients had a preoperative echocardiogram performed. This made comparisons with what would be considered the most accessible non-invasive cardiac investigation difficult.

In long-term analysis, five patients were lost prior to the full 3 year follow-up. Although this could alter the findings of long-term outcome analysis, when correcting for these patients on Kaplan-Meier analysis, meaningful results were returned.

The greatest limitation of the thesis was the small sample size studied in the EVAR cohort. This combined with the low incidence of perioperative death and MACE, greatly limits the power of this area of research.

In general many potential limitations were accounted for. Defined endpoints were used and a power calculation performed prior to commencing study. BNP analysis was explored for confounding variables, such as renal failure and BMI, and these were found not to be significant. Rigorous postoperative testing was performed, in order not to miss potential sub-clinical cardiac events, and all deaths were investigated to identify the cause. All patients had adequate data collection to allow complete risk scoring, and data were analysed using uniform statistical analyses throughout, whilst a number of BNP thresholds were chosen to account for the event time horizon.

8.5 Areas for Further Research

A large observational cohort study of preoperative BNP would allow validation of the many studies of preoperative BNP that have been described, as in the already commenced VISION study. This and other large prospective studies would potentially benefit from the use of a Net Reclassification Index statistic to assess the added value of BNP over current used preoperative measures of risk. Further, there is as yet no research that has randomised treatment based on a patients' BNP level. Research comparing; surgery vs non-operative management, surgery vs best medical therapy, and surgery vs optimisation followed by later surgery, are all potential areas of interest. It is also unknown whether management aimed at lowering a patients' serum BNP would impart a reduced risk for delayed surgery with a now reduced serum level, and indeed what that lower level of BNP should be.

Another area of uncertainty is the optimal time for preoperative BNP testing. In the majority of published studies, BNP samples were taken the evening prior to surgery. In this study this was the case for logistic reasons alone. Only 2 published studies took samples >3 weeks prior to surgical intervention.[112,120] Revised ACC/AHA guidelines advise preoperative BNP testing some 4-5 weeks prior to elective surgery to allow initiation and benefit of medical therapy, should this be the chosen intervention.[69] However it has been agreed that this is speculative, and needs evaluated in well-designed trials.

Finally, a significant rise in postoperative NT-proBNP has been identified in patients who suffered a cardiac event compared to those that did not (609 vs 183 pg/ml; p<0.001).[122] This has raised the possibility that postoperative BNP may identify patients who are unable to cope with the myocardial strain imposed on them and are undergoing a degree of myocardial decompensation. This holds the promise of postoperative secondary risk stratification, similar to that seen in postoperative elevation of cTnI. It may therefore be of interest to study postoperative discrimination levels of BNP that require altered postoperative management, and to determine what management options these may be.

8.6 Conclusion

The ability to accurately predict cardiovascular morbidity and mortality in patients undergoing elective open AAA repair remains an elusive goal. Whilst preoperative cTnI may have a role in high risk patients undergoing major vascular surgery (when it might change management), its use in AAA repair is limited by its infrequent incidence. The prognostic performance of preoperative BNP, however, is at least equivalent to, if not better than, most traditional preoperative tests, including the varied risk scores. Its ability to predict in both the perioperative, intermediate and long-term periods make it a unique test. In addition, its ability to predict all-cause mortality over the same time periods makes it a potentially useful risk stratifier when considering the small AAA.

When considering EVAR, BNP seems to have no clear role. It is of use in selecting patients that would be better considered for EVAR rather than open surgery, but does not appear to predict outcome within this group. When EVAR is not considered an appropriate option, there is some uncertainty as to what is the acceptable next step in those deemed high risk. Immediate and obvious choices include further noninvasive cardiac investigation followed by best medical therapy, or coronary revascularisation. Exactly what medical therapy, or coronary revascularisation technique is chosen, remains controversial. It also remains unknown how to monitor therapy prior to a decision to reconsider surgery. Other possibilities include change in anaesthetic technique, use of epidural anaesthesia, intensified intra and postoperative monitoring, and a longer stay in ICU.

Regardless of the above uncertainties, BNP offers a test that gives an immediate result and that helps in the decision making process for a prophylactic operation. The test gives prognostic information that is superior to any current non-invasive cardiac investigation, or currently considered risk index, and on that basis should be considered a routine part of the work up in any patient being considered for open repair of their AAA.

Appendix 1: Information sheet/consent form for cTnI study

THIS SHEET HAS BEEN APPROVED BY THE WEST ETHICS COMMITTEE INFORMATION SHEET FOR PATIENTS/VOLUNTEERS IN CLINICAL RESEARCH PROJECT

Brief Title of Project
Can B-type natriuretic peptide measurement aid risk assessment in general/vascular surgical patients?

PARTICIPANT INFORMATION SHEET
We invite you to take part in a research project.

BACKGROUND
Surgery is associated with a risk of problems that may arise during or after the procedure. Normally, a patient will be assessed for their risk of developing a problem, such as a heart attack or stroke. This assessment may include clinical examination a chest x-ray, and sometimes, an ultrasound scan of the heart. Despite these measures, heart attacks and strokes still occur. B-type natriuretic peptide, or BNP, is a chemical produced by the heart. The amount of BNP in the blood is increased in patients with a heart problem. We are interested to know whether a BNP blood test could help identify patients who are at risk of having a heart problem around the time of vascular and general surgery.

WHAT WILL HAPPEN TO YOU?
If you decide to go ahead, your participation will involve one extra blood test at the time of your admission for surgery. The blood sample will be taken from a forearm vein and will be 30mls in volume (i.e. three tablespoons). This blood sample will be tested for BNP, for troponin and CRP, which are chemicals produced in the body when the heart is under strain. This blood test will be repeated at 48 hours (on the ward), before discharge and at the outpatient clinic after your operation.

CAN YOU CHANGE YOUR MIND? WHAT WILL HAPPEN IF YOU SAY NO?
Participation in this study may not be of direct benefit to you but information from this study could help in the development of treatment for patients in the future. You should not take part if you are pregnant, or could become pregnant. If you wish to take part in the study, your General Practitioner will be advised of your participation and the clinical management that you will undergo. Participation in this study would be strictly confidential. If the results show new and important findings the results may be published in a scientific journal in order that other doctors may learn of this new information. The results would be published in a way that you cannot be identified. No payment will be made for your participation in this project. You may not wish to participate in this study, or may wish to withdraw at any time after commencing the trial. In this circumstance your care will in no way be affected. Should you come to any harm as a result of taking part in this study you may be entitled to compensation. Taking part in this study will not affect your ability to drive.

DO YOU HAVE TO DECIDE AT ONCE?
Please feel free to discuss this with your relatives and then let us know your decision either way. If you have any questions about the study at any time please telephone Dr SC Gibson at 0141 211 3000 (during or out with working hours).

WEST ETHICS COMMITTEE
FORM OF CONSENT FOR PATIENTS/VOLUNTEERS IN CLINICAL RESEARCH PROJECT

Title of Project
Can B-type natriuretic peptide measurement aid risk assessment in surgical patients? By signing this form you give consent to your participation in the project whose title is at the top of this page. You should have been given a complete explanation of the project to your satisfaction and been given the opportunity to ask questions. You should have been given a copy of the patient information sheet approved by the West Ethics Committee to read and to keep. Even though you have agreed to take part in the research procedures you may withdraw this consent at any time without the need to explain why and without prejudice to your care.

Consent:

I,………………………………………………………………. (PRINT)

of………………………………………………………………

give my consent to the research project above, the nature, purpose and possible consequences of which have been described to me

by…………………………………………………………….

Patient's signature……………………………………………

Date ………………………………….

Doctor's signature…………………………………………….....

Appendix 2: Information sheet/consent form for BNP AAA study

Patient Information Sheet: The Role Of BNP In Cardiac Risk Stratification In Patients Undergoing Aortic Aneurysm Repair

We invite you to take part in a research project:

Background
All major surgery has a risk of problems with the heart that may arise during or after surgery. All patients going to get an operation have the risk of surgery estimated using clinical examination, a heart tracing, chest X ray, and sometimes, an ultrasound scan of the heart. Despite these measures, heart attacks still occur. Brain natriuretic peptide, or BNP, is a chemical produced by the heart. The amount of BNP in the blood is increased in patients with a heart problem. We are interested to know whether a BNP blood test could help identify patients who are at risk of having a heart problem around the time of surgery, or who may have heart problems in the next few years. You have been asked to be part of this study because you are going to undergo surgery.

What Will Happen To You?
If you decide to go ahead, your participation will involve one extra blood test before surgery. The blood sample will be taken from a forearm vein and will be 30ml in volume (i.e. three tablespoons). You may experience some discomfort and have a bruise as a result of this blood test. This blood sample will be tested for BNP and troponin levels, chemicals produced in the body when the heart is under strain. This blood test will be repeated at 48 hours (on the ward), and at discharge. An ECG (heart tracing) will be performed before and after the operation. We will also be asking your GP how you are getting on for three years after your operation.

Can You Change Your Mind? What Will Happen If You Say No?

Participation in this study may not be of direct benefit to you but information from this study could help in the development of treatment for patients in the future. Participation in this study would be strictly confidential. If the results show new and important findings the results may be published in a scientific journal in order that other doctors may learn of this new information. The results would be published in a way that you cannot be identified. No payment will be made for your participation in this project. You may withdraw from the project at any point without needing to give a reason. If you do not wish to participate in this study, or wish to withdraw at any time, your care will in no way be affected. Should you come to any harm as a result of taking part in this study you may be entitled to compensation. Taking part in this study will not affect your ability to drive.

Do You Have To Decide At Once?

Please feel free to discuss this with your relatives and then let us know your decision either way. If you have any questions about the study at any time please telephone Dr G Bryce at 0141 211 2000 page 4045 or 07973 48 22 06.

WEST ETHICS COMMITTEE

CONSENT FOR PATIENTS IN CLINICAL RESEARCH PROJECT

"The Role Of BNP In Cardiac Risk Stratification In Patients Undergoing Aortic Aneurysm Repair?"

By signing this form you give consent to your participation in the project whose title is at the top of this page. You should have been given a complete explanation of the project to your satisfaction and have been given the opportunity to ask questions. You should have been given a copy of the patient information sheet approved by the West Ethics Committee to read and to keep. Even though you have agreed to take part in the research procedures you may withdraw this consent at any time without the need to explain why and without any prejudice to your care.

Consent:

I,………………………………………………………………….(Print Name)

of……………………………………………………………...(Address)

give my consent to the research procedures above, the nature, the purpose and possible consequences of which have been described to me

by……………………………………………………….(Print Dr Name)

Patient's signature……………………………………… Date………………….

Doctor's Signature……………………………………Date………………….

Appendix 3: Data Sheet

B.N.P. Study

Name
Hospital Number
Date of Birth
Phone no.

Diagnosis-
Operation-
Operation date -

Consultant-

_____

Male   Female

Smoker   Yes   per day   No, never   Stopped   ago

Diabetic   Yes   No
Previous MI   Yes   No
Hypertensive   Yes   No

Hyperlipidaemia   Yes   No

Angina   Canadian classification   0   1   2   3   4

Heart failure   NYHA   0   1   2   3   4

 LVH: none
                                   diuretic/digoxin/Rx for angina/hypertension
                                   periph. Oedema/warfarin/b-line cardiomyopathy
                                   raised JVP/cardiomegaly

COPD: mild disease
                                   dypsnoea on exertion
                                   moderate, limiting dypsnoea
                                   dypsnoea at rest, pulm. fibrosis

Renal disease: Yes   No

Cerebrovascular: CVA   TIA   None

Relevant medications:

Pulse   Blood pressure   GCS

Specialised investigation: Result

Echo

Exercise testing

Stress thallium

Pulmonary function tests

Coronary angiography

Bloods:	Taken	Result
CRP		
Hb		
WCC		
Platelets		
PT		
PTT		
pFib		
Na		
K		
Urea		
Creatinine		
Cr Clearance		

Lipids -   cholesterol   LDL
             Triglycerides   HDL

Magnesium

Troponin

ECG   done   normal
abnormal

Sats on air

Weight   -   Height -

Intraoperatively:
Operation type -
CEPOD -
No. of procedures -

Blood loss -
Peritoneal contamination -

Hypothermia (34.5 degrees) -

Hypotension -

Beta blockers -

X-clamp time -   supra-renal X-clamp -

Length of procedure

ABGs - pO_2
               pCO_2
               H^+
               BE
               Lact.

Post operatively:

ITU   days
HDU   days
Ward   days

P-POSSUM

Physiology score

Operative severity score

Morbidity

Mortality

At 48 hours:

Bloods	Taken	Result
Urea		
Creatinine		
Troponin		
CRP		

ECG	done		normal	abnormal

5 days:

Urea
Creatinine

Troponin
ECG

Complications

After 6 weeks:

Bloods	Taken	Result
Urea		
Creatinine		
Troponin		
CRP		

ECG	done		normal	abnormal

Complications in interim:

Respiratory status

New meds

References

1. Poldermons D, Hoeks SE, Feringa HH. Preoperative risk assessment and risk reduction before surgery. *J Am Coll Cardiol* 2008;51:1913-24

2. Mangano DT. Adverse outcomes after surgery in the year 2001 – a continuing odyssey. *Anesthesiology* 1998;88:561-4

3. Mangano DT, Goldman L. Preoperative assessment of patients with known or suspected coronary disease. *N Eng J Med* 1995;333:1750-6

4. Abraham N, Lemech L, Sandroussi C, Sullivan D, May J. A prospective study of subclinical myocardial damage in endovascular versus open repair of infrarenal abdominal aortic aneurysms. *J Vasc Surg* 2005;41:377-80

5. Ashton CM, Peterson NJ, Wray NP et al. The incidence of perioperative myocardial infarction in men undergoing noncardiac surgery. *Ann Intern Med* 1993;118:504-10

6. Badner NH, Knill RL, Brown JE, Novick TV, Gelb AW. Myocardial infarction after noncardiac surgery. *Anesthesiology* 1998;88:572-8

7. Sprung J, Warner ME, Contreras MG et al. Predictors of survival following cardiac arrest in patients undergoing noncardiac surgery: a study of 518,294 patients at a tertiary referral centre. *Anesthesiology* 2003;99:259-69

8. Mangano DT, Browner WS, Hollenberg M, Li J, Tateo IM. Long-term cardiac prognosis following noncardiac surgery. The Study of Perioperative Ischaemia Research Group. *JAMA* 1992;268:233-9

9. Charlson M, Peterson J, Szatrowski TP, MacKenzie R, Gold J. Long-term prognosis after perioperative cardiac complications. *J Clinic Epidemiol* 1994;47:1389-400

10. McGregor JC, Pollock JG, Anton HC. The value of ultrasonography in the diagnosis of abdominal aortic aneurysm. *Scott Med J* 1975;20:133-7

11. Lederle FA, Johnson GR, Wilson SE. Abdominal aortic aneurysm in women. *J Vasc Surg* 2001;34:122-6

12. Vardulaki KA, Walker NM, Couto E et al. Late results concerning feasibility and compliance from a randomised trial of ultrasonographic screening for abdominal aortic aneurysm. *Br J Surg* 2002;89:861-4

13. Reed WW, Hallett JW Jr, Damiano MA, Ballard DJ. Learning from the last ultrasound: a population-based study of patients with abdominal aortic aneurysm. *Arch Intern Med* 1997;157:2064-8

14. Brown L, Powell JT. Risk factors for aneurysm rupture in patients kept under ultrasound surveillance. The UK Small Aneurysm Trial Participants. *Ann Surg* 1999;230:289-96

15. Basnyat PS, Biffin AH, Moseley LG, Hedges AR, Lewis MH. Mortality from ruptured aortic aneurysm in Wales. *Br J Surg* 1999;86:765-70

16. Johnston KW. Ruptured aortic aneurysm: six year follow-up results of a multi-center prospective study. *J Vasc Surg* 1994;19:888-900

17. Ernst CB. Abdominal aortic aneurysm. *N Engl J Med* 1993;328:1167-72

18. Powell JT, Brown LC, Forbes JF et al. Mortality results for randomised controlled trial of early elective surgery or ultrasonographic surveillance for small abdominal aortic aneurysms. The UK Small Aneurysm Trial Participants. Lancet 1998;352:1649-55

19. Brady AR, Fowkes FG, Greenhalgh RM, Powell JT, Ruckley CV, Thompson SG. Risk factors for postoperative death following elective surgical repair of abdominal aortic aneurysm: results from the UK Small Aneurysm Trial. On behalf of the UK Small Aneurysm Trial participants. *Br J Surg* 2000;87:742-9

20. Powell JT, Brown LC, Forbes JF et al. Final 12-year follow-up of surgery versus surveillance in the UK Small Aneurysm Trial. *Br J Surg* 2007;94:702-8

21. Greenhalgh RM, Brown LC, Kwong GP, Powell JT, Thompson SG; EVAR trial participants. Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR 1), 30-day operative mortality results: randomised controlled trial. *Lancet* 2004;364:843-8

22. EVAR trial participants. Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm (EVAR 1): randomised controlled trial. *Lancet* 2005;365:2179-86

23. Dawood MM, Gutpa DK, Southern J, et al. Pathology of fatal perioperative myocardial infarction: Implications regarding pathophysiology and prevention. *Int J Cardiol* 1996;57:37-44

24. Mangano DT. Perioperative cardiac morbidity. *Anesthesiology* 1990;72:153-84

25. Cohen MC, Aretz TH. Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. *Cardiovasc Pathol* 1999;8:133-9

26. Badner NH, Knill RL, Brown JE et al. Myocardial infarction after noncardiac surgery. *Anesthesiology* 1998;88:572-8

27. Landesberg G, Mosseri M, Zahger D et al. Myocardial infarction following vascular surgery: the role of prolonged, stress induced ST-depression-type ischaemia. *J Am Coll Cardiol* 2001;37:1858-63

28. Cruickshank AM, Fraser WD, Burns HJ, Van Damme J, Shenkin A. Response of serum interleukin-6 in patients undergoing elective surgery of varying severity. *Clin Sci (Lond)* 1990;79:178-82

29. Rosenfeld BA, Beattie C, Christopherson R et al. The effects of different anaesthetic regimens on fibrinolysis and the development of postoperative arterial thrombosis. Perioperative Ischaemia Randomised Anaesthesia Trial Study Group. *Anesthesiology* 1993;79:435-43

30. Priebe HJ. Triggers of perioperative myocardial ischaemia and infarction. *Br J Anaesth* 2004;93:9-20

31. Schug SA, Torrie JJ. Safety assessment of postoperative pain management by an acute pain service. *Pain* 1993;55:387-91

32. Nelson AH, Fleisher LA, Rosenbaum SH. Relationship between postoperative anaemia and cardiac morbidity in high-risk vascular patients in the intensive care unit. *Crit Care Med* 1993;21:860-6

33. Frank SM, Beattie C, Christopherson R et al. Unintentional hypothermia is associated with postoperative myocardial ischaemia. Perioperative Ischaemia Randomised Anaesthesia Trial Study Group. *Anesthesiology* 1993;78:468-76

34. Devereaux PJ, Goldman L, Cook DJ, Gilbert K, Leslie K, Guyatt GH. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. *CMAJ* 2005;173:627-34

35. Gelman S. The pathophysiology of aortic cross-clamping and clamping. *Anesthesiology* 1995;82:1026-60

36. Roizen MF, Beaupre PM, Alpert RA et al. Monitoring and two-dimensional transoesophageal echocardiography. Comparison of myocardial function in patients undergoing supracoeliac, suprarenal-infracoeliac, or infrarenal aortic occlusion. *J Vasc Surg* 1984;1:300-5

37. Papia G, Klein D, Lindsay TF. Intensive care of the patient following open abdominal aortic surgery. *Curr Opin Crit Care* 2006;12:340-5

38. Dauchot PJ, DePalma R, Grum D et al. Detection and prevention of cardiac dysfunction during cardiac surgery. *J Surg Res* 1979;26:574-80

39. Attia RR, Murphy JD, Snider M et al. Myocardial ischaemia due to infrarenal aortic cross-clamping during aortic surgery in patients with severe coronary artery disease. *Circulation* 1976;53:961-4

40. Gooding JM, Archi JP, McDowell H. Haemodynamic response to infrarenal aortic cross-clamping in patients with and without coronary artery disease. *Crit Care Med* 1980;8:382-5

41. Carroll RM, Laravuso RB, Schauble JF. Left ventricular function during aortic surgery. *Arch Surg* 1976;111:740-3

42. Meloche R, Pottecher J, Audet J et al. Haemodynamic changes due to clamping of the abdominal aorta. *Can Anaesth Soc J* 1977;24:20-34

43. Devereaux PJ, Goldman L, Yusuf S, Gilbert K, Leslie K, Guyatt GH. Surveillance and prevention of major perioperative ischaemic cardiac events in patients undergoing noncardiac surgery: a review. *CMAJ* 2005;173:779-88

44. Sheifer SE, Monolio TA, Gersh BJ. Unrecognised myocardial infarction. *Ann Intern Med* 2001;135:801-11

45. Mangano DT, Browner WS, Hollenberg M, London MJ, Tubau JF, Tateo IM. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. The study of Perioperative Ischaemia Research Group. *N Engl J Med* 1990;323:1781-8

46. Fleischmann KE, Golman L, Young B, Lee TH. Association between cardiac and noncardiac complications in patients undergoing noncardiac surgery: outcomes and effects on length of stay. *Am J Med* 2003;115:515-20

47. Gillum RF, Fortmann SP, Prineas RJ, Kottke TE. International diagnostic criteria for acute myocardial infarction and acute stroke. *Am Heart J* 1984;108:150-8

48. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined-a consensus document of 'The Joint European Society of Cardiology/American College of Cardiology Committee' for the redefinition of myocardial infarction". *J Am Coll Cardiol* 2000;36:959–69

49. Healey JH, Kagen LJ, Velis KP, Levine DB. Creatinine kinase MB in skeletal muscle and serum of spine-fusion patients. *Clin Orthop Relat Res* 1985;195:282-8

50. Adams JE 3rd, Sicard GA, Allen BT et al. Diagnosis of perioperative myocardial infarction with measurement of cardiac troponin I. *N Engl J Med* 1994;330:670-4

51. Haggart PC, Adam DJ, Ludman PF, Bradbury AW. Comparison of cardiac troponin I and creatinine kinase rations in the detection of myocardial injury after aortic surgery. *Br J Surg* 2001;88:1196-200

52. DeBakey ME, Lawrie GM. Combined coronary artery and peripheral vascular disease: recognition and treatment. *J Vasc Surg* 1984;1:605-7

53. Ruby ST, Whittemore AD, Couch NP et al. Coronary artery disease in patients requiring abdominal aortic aneurysm repair. Selective use of a combined operation. *Ann Surg* 1985;201:758-62

54. Hlatky MA, Boineau RE, Higginbotham MB et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). *Am J Cardiol* 1989;64:651-54

55. Reilly DF, McNeely MJ, Doerner D et al. Self-reported exercise tolerance and the risk of serious perioperative complications. *Arch Inter Med* 1999;159:2185-92

56. Girish M, Trayner Jr E, Dammann O et al. Symptom-limited stair climbing as a predictor of postoperative cardiopulmonary complications after high-risk surgery. *Chest* 2001;120:1147-51

57. Browner WS, Li J, Mangano DT. In-hospital and long-term mortality in male veterans following non-cardiac surgery. The Study of Perioperative Ischaemia Research Group. *J Am Med Assoc* 1992;268:228-32

58. Keats AS. The ASA classification of physical status – a recapitulation. *Anesthesiology* 1978;49:233-6

59. Menke H, Klein A, John KD, Junginger T. Predictive value of ASA classification for the assessment of the perioperative risk. *Int Surg* 1993;78:266-70

60. Goldman L, Caldera DL, Nussbaum SR et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med* 1977;297:845-50

61. Detsky AS, Abrams HB, McLaughlin JR et al. Predicting cardiac complications in patients undergoing non-cardiac surgery. *J Gen Intern Med* 1986;1:211-9

62. Kumar R, McKiney WP, Raj G et al. Adverse cardiac events after surgery: assessing risk in a veteran population. *J Gen Intern Med* 2001;16:507-18

63. Eagle KA, Coley CM, Newell JB et al. Combining clinical and thallium data optimises preoperative assessment of cardiac risk before major vascular surgery. *Ann Intern Med* 1989;110:859-66

64. Lee TH, Marcantonio ER, Mangione CM et al. Derivation and prospective validation of a simple index of prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999;100:1043-9

65. Boersma E, Kertai MD, Schouten O et al. Perioperative cardiovascular mortality in noncardiac surgery: validation of the Lee Cardiac Risk Index. *Am J Med* 2005;118:1134-41

66. Jeffrey CC, Kunsman J, Cullen DJ, Brewster DC. A prospective evaluation of cardiac risk index. *Anesthesiology* 1983;58:462-4

67. Eagle KA, Brundage BH, Chaitman BR et al. Guidelines for perioperative cardiovascular evaluation for noncardiac surgery. Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Committee on Perioperative Cardiovascular Evaluation for Noncardiac Surgery. *Circulation* 1996;93:1278-317

68. Eagle KA, Berger PB, Calkins H et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery – executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Circulation* 2002;105:1257-67

69. Fleisher LA, Beckman JA, Brown KA et al. ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines in collaboration. *J Am Coll Cardiol* 2007;50:e159-241

70. Bartels C, Bechtel JF, Hossmann V et al. Cardiac risk stratification for high-risk vascular surgery. *Circulation* 1997;95:2473-75

71. Morgan PB, Panomitros GE, Nelson AC et al. Low utility of dobutamine stress echocardiography in the preoperative evaluation of patients scheduled for noncardiac surgery. *Anesth Analg* 2002;95:512-6

72. Kertai MD, Boersma E, Bax JJ et al. A metanalysis comparing the prognostic accuracy of six diagnostic tests for predicting perioperative cardiac risk in patients undergoing major vascular surgery. *Heart* 2003;89:1327-34

73. Rose EL, Liu XJ, Henley M et al. Prognostic value of non-invasive cardiac tests in the assessment of patients with peripheral vascular disease. *Am J Cardiol* 1993;71:40-4

74. Poldermans D, Fioretti PM, Boersma E et al. Safety of dobutamine-atropine stress echocardiography in patients with suspected or proven coronary artery disease. *Am J Cardiol* 1994;73:456-9

75. Picano E, Mathias Jr W, Pingitore A et al. Safety and tolerability of dobutamine-atropine stress echocardiography: A prospective, multicentre study. Echo Dobutamine International Cooperative Study Group. *Lancet* 1994;344:1190-2

76. Poldermans D, Rambaldi R, Bax JJ et al. Safety and utility of atropine addition during dobutamine stress echocardiography for the assessment of viable myocardium in patients with severe left ventricular dysfunction. *Eur Heart J* 1998;19:1712-8

77. Pellikka PA, Roger VL, Oh JK et al. Safety of performing dobutamine stress echocardiography in patients with abdominal aortic aneurysm > or = 4cm in diameter. *Am J Cardiol* 1996;77:413-416

78. Mantha S, Roizen MF, Barnard J et al. Relative effectiveness of four preoperative tests for predicting adverse cardiac outcomes after vascular surgery: A meta-analysis. *Anesth Analg* 1994;79:422-33

79. Kertai MD, Klein J, Bax JJ and Poldermans D. Predicting Perioperative Cardiac Risk. *Prog Cardiovasc Dis* 2005;47:240-57

80. Kertai MD, Boersma E, Sciari R et al. Which stress test is superior for perioperative cardiac risk stratification in patients undergoing major vascular surgery. *Eur J Vasc Endovasc Surg* 2002;24:222-9

81. Beattie WS, Abdelnaem E, Wijeysundera DN and Buckley DN. A Meta-analytic comparison of preoperative stress echocardiography and nuclear scintigraphy imaging. *Anesth Analg* 2006;102:6-16

82. Mukoyama M, Nakao K, Hosoda K et al. Brain Natriuretic Peptide as a novel cardiac hormone in humans. *J Clin Invest* 1991;87:1402-12

83. Hunt PJ, Espiner EA, Nicholls MG, Richards AM, Yundle TG. Differing biological effects of equimolar atrial and brain natriuretic peptide infusion in normal man. *J Clin Endocrinol Metab* 1996;81:3871-6

84. Wu AH, Smith A, Wieczoreck S et al. Biological variation for N-terminal pro- and B-type natriuretic peptides and implications for therapeutic monitoring of patients with congestive heart failure. *Am J Cardiol* 2003;92:628-31

85. Richards M, Nicholls MG, Espiner EA et al. Comparison of B-type natriuretic peptides for assessment of cardiac function and prognosis in stable ischaemic heart disease. *J Am Coll Cardiol* 2006;47:52-60

86. McCullough PA, Sandberg KR. Sorting out the evidence on natriuretic peptides. *Rev Cardiovasc Med* 2003;4:S13-9

87. Ng LL, Loke IW, Davies JE et al. Community screening for left ventricular systolic dysfunction using plasma and urinary natriuretic peptides. *J Am Coll Cardiol* 2005;45:1043-50

88. Austin WJ, Bhalla V, Hernandez-Arce I et al. Correlation and prognostic utility of B-type natriuretic peptide and its amino-terminal fragment in patients with chronic kidney disease. *Am J Clin Path* 2006;126:506–12

89. Hunt PJ, Espiner EA, Nicholls MG et al. The role of the circulation in precessing pre-brain natriuretic peptide (proBNP) to amino-terminal BNP and BNP. *Peptides* 1997;18:147581

90. Yeo KTJ, Wu AHB, Apple FS et al. Multicenter evaluation of the Roche NT-proBNP asay and comparison to the Biosite triage BNP asay. *Clin Chim Acta* 2003;338:107-15

91. Arbab-Zadeh A, Dijk E, Prasad A et al. Effect of aging and physical activity on left ventricular compliance. *Circulation* 2004;110:1799-805

92. McCullough PA, Duc P, Omland T et al. B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing Not Properly Multinational Study. *Am J Kidney Dis* 2003;41:571–9

93. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr. Plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol* 2002;40:976–82

94. Koller KJ, Goeddel DV. Molecular biology of the natriuretic peptides and their receptors. *Circulation* 1992;86:1081–8

95. Maack T, Suzuki M, Almeida FA et al. Physiological role of silent receptors of atrial natriuretic factor. *Science* 1987;238:675–8

96. Allgren RL, Marbury TC, Rahman SN et al. Anaritide in acute tubular necrosis. Auriculin Anaritide Acute Renal Failure Study Group. *N Engl J Med* 1997;336:828–34

97. Munger MA, Ng TM, Van Tassell BW. Controversy and conflict in the treatment of acute decompensated heart failure: nesiritide as evidence-based treatment. *Pharmacotherapy* 2007;27:619–25

98. McDowell G, Coutie W, Shaw C, Buchanan KD, Struthers AD, Nicholls DP. The effect of the neutral endopeptidase inhibitor drug, candoxatril, on circulating levels of two of the most potent vasoactive peptides. *Br J Clin Pharmacol* 1997;43:329–32

99. Nishikimi T, Yoshihara F, Morimoto A et al. Relationship between left ventricular geometry and natriuretic peptide levels in essential hypertension. *Hypertension* 1996;28:22–30

100. Tsutamoto T, Sakai H, Nishiyama K et al. Direct comparison of transcardiac increase in brain natriuretic peptide (BNP) and N-terminal proBNP and prognosis in patients with chronic heart failure. *Circulation* 2007;71:1873–8

101. Mueller C, Scholar A, Laule-Killian K et al. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnoea. *N Engl J Med* 2004;350:647-54

102. Masson S, Latini R, Anand IS et al. Direct comparison of B-type natriuretic peptide (BNP) and amino-terminal proBNP in a large population of patients with chronic and symptomatic heart failure: the Valsartan Heart Failure (Val-HeFT) data. *Clin Chem* 2006;52:1528–38

103. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. *Lancet* 2000;355:1126–30

104. Jourdain P, Jondeau G, Funck F et al. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. *J Am Coll Cardiol* 2007;49:1733–9

105. Valle R, Aspromonte N, Giovinazzo P et al. B-type natriuretic Peptide-guided treatment for predicting outcome in patients hospitalized in sub-intensive care unit with acute heart failure. *J Card Fail* 2008;14:219–24

106. Bassan R, Potsch A, Maisel A et al. B-type natriuretic peptide: a novel early blood marker of acute myocardial infarction in patients with chest pain and no ST-segment elevation. *Eur Heart J* 2005;26:234–40

107. Rodseth R. B type natriuretic peptide – a diagnostic breakthrough in perioperative cardiac risk assessment? *Anaesthesia* 2009;64:165-78

108. Goldman L, Caldera DL, Nussbaum SR et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med* 1977;297:845-50

109. Hammill BG, Curtis LH, Bennett-Guerrero E et al. Impact of heart failure on patients undergoing major noncardiac surgery. *Anesthesiology* 2008;108:559-67

110. Hernandez AF, Whellan DJ, Stroud S, Sun JL, O'Connor CM, Jollis JG. Outcomes in heart failure patients after major noncardiac surgery. *J Am Coll Cardiol* 2004;44:1446–53

111. Yeh HM, Lau HP, Lin JM et al. Preoperative plasma N-terminal pro-brain natriuretic peptide as a marker of cardiac risk in patients undergoing elective non-cardiac surgery. *Br J Surg* 2005;92:1041-5

112. Feringa HH, Bax JJ, Elhendy A et al. Association of plasma N-terminal pro-B-type natriuretic peptide with postoperative cardiac events in patients undergoing surgery for abdominal aortic aneurysm or leg bypass. *Am J Cardiol* 2006;98:111-5

113. Dernellis J, Panaretou M. Assessment of cardiac risk before non-cardiac surgery:brain natriuretic peptide in 1590 patients. *Heart* 2006;92:1645-50

114. Cuthbertson BH, Amiri AR, Croal BL et al. The utility of B-type natriuretic peptide in predicting perioperative cardiac events in patients undergoing major noncardiac surgery. *Br J Anaesth* 2007;99:170-6

115. Berry C, Kingsmore D, Gibson SC et al. Predictive value of plasma brain natriuretic peptide for cardiac outcome after vascular surgery. *Heart* 2006;92:401-2

116. Gibson SC, Payne CJ, Byrne DS et al. B-type natriuretic peptide predicts cardiac morbidity and mortality after major surgery. *Br J Surg* 2007;94:903-9

117. Cuthbertson BH, Card G, Croal BL, McNeilly J, Hillis GS. The utility of B-type natriuretic peptide in predicting postoperative cardiac events and mortality in patients undergoing major emergency non-cardiac surgery. *Anaesthesia* 2007;62:875–81

118. Cuthbertson BH, Amiri AR, Croal BL, Rajagopalan S, Brittenden J, Hillis GS. Utility of B-type natriuretic peptide in predicting medium-term mortality in patients undergoing major non-cardiac surgery. *Am J Cardiol* 2007;100:1310–3

119. Leibowitz D, Planer D, Rott D, Elitzur Y, Chajek-Shaul T, Weiss AT. Brain natriuretic peptide levels predict perioperative events in cardiac patients undergoing noncardiac surgery: a prospective study. *Cardiology* 2007;110:266–70

120. Feringa HH, Schouten O, Dunkelgrun M et al. Plasma N-terminal pro-B-type natriuretic peptide as long-term prognostic marker after major vascular surgery. *Heart* 2007;93:226–31

121. Goei D, Schouten O, Boersma E et al. Influence of renal function on the usefulness of N-terminal pro-B-type natriuretic peptide as a prognostic cardiac risk marker in patients undergoing noncardiac vascular surgery. *Am J Cardiol* 2008;101:122–6

122. Mahla E, Baumann A, Rehak P et al. N-terminal pro-brain natriuretic peptide identifies patients at high risk for adverse cardiac outcome after vascular surgery. *Anesthesiology* 2007;106:1088–95

123. Antman EM. Decision making with cardiac troponin tests. *N Engl J Med* 2002;346:2079-82

124. Chapelle JP. Cardiac troponin I and troponin T: recent players in the field of myocardial markers. *Clin Chem Lab Med* 1999;37:11-20

125. Sacks DB. Acute coronary ischaemia: troponin I and T. *Vasc Med* 1999;4:253-6

126. Sobel BE, Le Winter MM. Ingenuous interpretation of elevated blood levels of macromolecular markers of myocardial injury: a recipe for confusion. *J Am Coll Cardiol* 2000;35:1355-8

127. James TN. The variable morphological coexistence of apoptosis and necrosis in human myocardial infarction: significance for understanding its pathogenesis, clinical course, diagnosis and prognosis. *Coron Artery Dis* 1998;9:291-307

128. McDonough JL, Arrell DK, Van Eyk JE. Troponin I degradation and covalent complex formation accompanies myocardial ischaemia/reperfusion injury. *Circ Res* 1999;84:9-20

129. Higgins JP, Higgins JA. Elevation of cardiac troponin I indicates more than myocardial ischaemia. *Clin Invest Med* 2003;26:133-47

130. Cummins B, Auckland ML, Cummins P. Cardiac-specific troponin-I radioimmunoassay in the diagnosis of acute myocardial infarction. *Am Heart J* 1987;113:1333-44

131. Katus HA, Remppis A, Scheffold T, Diederich KW, Kuebler W. Intracellular compartmentation of cardiac troponin T and its release kinetics in patients with reperfused and nonreperfused myocardial infarction. *Am J Cardiol* 1991;67:1360-7

132. Pervaiz S, Anderson FP, Lohmann TP et al. Comparative analysis of cardiac troponin I and CK-MB as markers of acute myocardial infarction. *Clin Cardiol* 1997;20:269-71

133. Apple FS, Falahati A, Paulsen PR et al. Improved detection of minor ischaemic myocardial injury and measurement of serum cardiac troponin I. *Clin Chem* 1997;43:2047-51

134. Kaul P, Newby LK, Fu Y et al. Troponin T and quantitative ST-segment depression offer complimentary prognostic information in the risk stratification of acute coronary syndrome patients. *J Am Coll Cardiol* 2003;41:371-80

135. Lindahl B, Toss H, Siegbahn A et al. the Fragmin during Instability in Coronary Artery Disease (FRISC) Study Group. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. *N Engl J Med* 2000;343:1139-47

136. The Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined – a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J* 2000;21:1502-13

137. Lee TH, Thomas EJ, Ludwig LE et al. Troponin T as a marker for myocardial ischaemia in patients undergoing major noncardiac surgery. *Am J Cardiol* 1996;77:1031-6

138. Metzler H, Gries M, Rehak P, Lang T, Fruhwald S, Toller W. Perioperative myocardial cell injury: the role of troponins. *Br J Anaesth* 1997;78:386-90

139. Andrews N, Jenkins J, Andrews G et al. Using postoperative cardiac Troponin-I levels to detect myocardial ischaemia in patients undergoing vascular surgery. *Cardiovasc Surg* 2001;9:254-65

140. Kim LJ, Martinez EA, Faraday N et al. Cardiac troponin I predicts short term mortality in vascular surgery patients. *Circulation* 2002;106:2366-71

141. Lopez-Jimenez F, Goldman L, Sacks DB et al. Prognostic value of cardiac troponin T after noncardiac surgery: 6-month follow-up data. *J Am Coll Cardiol* 1997;29:1241-5

142. Kertai MD, Boersma E, Klein J et al. Long-term prognostic value of asymptomatic cardiac troponin T elevations in patients after major vascular surgery. *Eur J Vasc Endovasc Surg* 2004;28:59-66

143. Landesberg G, Shatz V, Akopnik I et al. Association of cardiac troponin, CK-MB and postoperative myocardial ischaemia with long-term survival after major vascular surgery. *J Am Coll Cardiol* 2003;42:1547-54

144. Libby P, Theroux P. Pathophysiology of coronary artery disease. *Circulation* 2005;111:3481-8

145. Ray KK, Cannon CP, Ganz P. Beyond lipid lowering: what have we learned about the benefits of statins from the acute coronary syndromes trials? *Am J Cardiol* 2006;98:18P-25P

146. Padayachee L, Rodseth RN, Biccard BM. A meta-analysis of the utility of C-reactive Protein in predicting early, intermediate-term and long term mortality and major adverse cardiac events in vascular surgery patients. *Anaesthesia* 2009;64:416-24

147. Wolowczyk L, Nevin M, Day A, Smith FC, Baird RN, Lamont PM. The effect of acute normovolaemic haemodilution on the inflammatory response and clinical outcome in abdominal aortic aneurysm repair – results of a pilot trial. *Eur J Vasc Endovasc Surg* 2005;30:12-9

148. Pearson TA, Mensah GA, Alexander RW et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement to health care professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;107:499-511

149. Vainas T, Lubbers T, Stassen FR et al. Serum C-reactive protein level is associated with abdominal aortic aneurysm size and may be produced by aneurysmal tissue. *Circulation* 2003;107:1103-5

150. Badger SA, Soong CV, O'Donnell ME et al. C-reactive protein (CRP) elevation in patients with abdominal aortic aneurysm is independent of the most important CRP genetic polymorphism. *J Vasc Surg* 2009;49:178-84

151. Mamode N, Docherty G, Lowe GD et al. The role of myocardial perfusion scanning, heart rate variability and D-dimers in predicting the risk of perioperative cardiac complications after peripheral vascular surgery. *Eur J Vasc Endovasc Surg* 2001;22:499-508

152. Woodburn KR, Rumley A, Lowe GD et al. Clinical, biochemical and rheologic factors affecting the outcome of infrainguinal bypass grafting. *J Vasc Surg* 1996;24:639-46

153. Lubarsky DA, Fisher SD, Slaughter TF et al. Myocardial ischaemia correlates with reduced fibrinolytic activity following peripheral vascular surgery. *J Clin Anesth* 2000;12:136-41

154. Samy AK, Murray G, MacBain G. Glasgow Aneurysm Score. *Cardiovasc Surg* 1994;2:41-4

155. Samy AK, Murray G, MacBain G. Prospective evaluation of the Glasgow Aneurysm Score. *J R Coll Surg Edinb* 1996;41:105-7

156. Biancari F, Leo E, Yonen K, Vaarala MH, Rainio P, Juvonen T. Value of the Glasgow Aneurym Score in predicting the immediate and long-term outcome after elective open repair of infrarenal abdominal aortic aneurysm. *Br J Surg* 2003;90:838-44

157. Biancari F, Heikkinen M, Lepantalo M, Salenius JP. Glasgow Aneurysm Score in patients undergoing elective open repair of abdominal aortic aneurysm: a Finnvasc study. *Eur J Vasc Endovasc Surg* 2003;26:612-7

158. Hirzalla O, Emous M, Ubbink DT, Legemate D. External validation if the Glasgow Aneurysm Score to predict outcome in elective open abdominal aortic aneurysm repair. *J Vasc Surg* 2006;44:712-6

159. Tang TY, Walsh SR, Prytherch DR et al. POSSUM models in open abdominal aortic aneurysm surgery. *Eur J Vasc Endovasc Surg* 2007;34:499-504

160. Biancari F, Hobo R, Juvonen T. Glasgow Aneurysm Score predicts survival after endovascular stenting of abdominal aortic aneurysm in patients from the EUROSTAR registry. *Br J Surg* 2006;93:191-4

161. Nesi F, Leo E, Biancari F et al. Preoperative risk stratification in patients undergoing elective infrarenal aortic aneurysm surgery: evaluation of five risk scoring methods. *Eur J Vasc Endovasc Surg* 2004;28:52-8

162. Copeland G, Jones D, Walters M. POSSUM: a scoring system for surgical audit. *Br J Surg* 1991;78:355-60

163. Whiteley MS, Prytherch DR, Higgins B, Weaver PC, Prout WG. An evaluation of the POSSUM surgical scoring system. *Br J Surg* 1996;83:812-5

164. Midwinter M, Ashley S. Risk stratification in vascular patients using modified POSSUM scoring system. *Br J Surg* 1997;84:A568

165. Prytherch DR, Sutton GL, Boyle JR. Portsmouth POSSUM models for abdominal aortic aneurysm surgery. *Br J Surg* 2001;88:958-63

166. Prytherch DR, Ridler BM, Ashley S. Risk-adjusted predictive models of mortality after index arterial operations using a minimal data set. *Br J Surg* 2005;92:714-8

167. Tang TY, Walsh SR, Fanshawe TR et al. Comparison of risk-scoring methods in predicting the outcome after open abdominal aortic aneurysm surgery. *Eur J Vasc Endovasc Surg* 2007;34:505-13

168. Tang T, Walsh SR, Prytherch DR, Lees T, Varty K, Boyle JR. VBHOM, a data economic model for predicting the outcome after open abdominal aortic aneurysm surgery. *Br J Surg* 2007;94:717-21

169. Beckles MA, Spiro SG, Colice GL, Rudd RM. The physiological evaluation of patients with lung cancer being considered for resectional surgery. *Chest* 2003;123:105-14

170. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* 1991;83:778-86

171. Carlise J, Swart M. Mid-term survival after abdominal aortic aneurysm surgery predicted by cardiopulmonary exercise testing. *Br J Surg* 2007;94:966-9

172. Nugent AM, Riley M, Megarry J, O'Reilly MJ, MacMahon J, Lowry R. Cardiopulmonary exercise testing in the preoperative assessment of patients for repair of abdominal aortic aneurysm. *Ir J Med Sci* 1998;167:238-41

173. J.R. Allen, T.S. Helling, G.O. Hartzler. Operative procedures not involving the heart after percutaneous transluminal coronary angioplasty. *Surg Gynecol Obstet* 1991;173:285–8.

174. J.R. Elmore, J.W. Hallett Jr et al. Myocardial revascularization before abdominal aortic aneurysmorrhaphy: Effect of coronary angioplasty. *Mayo Clin Proc* 1993;68:637–41.

175. A. Gottlieb, M. Banoub and J. Sprung et al. Perioperative cardiovascular morbidity in patients with coronary artery disease undergoing vascular surgery after percutaneous transluminal coronary angioplasty. *J Cardiothorac Vasc Anesth* 1998;12:501–6

176. K.L. Posner, G.A. Van Norman, V. Chan. Adverse cardiac outcomes after noncardiac surgery in patients with prior percutaneous transluminal coronary angioplasty. *Anesth Analg* 1999;89:553–60

177. G.L. Kaluza, J. Joseph, J.R. Lee et al. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. *J Am Coll Cardiol* 2000;35:1288–94

178. S.H. Wilson, P. Fasseas, J.L. Orford et al. Clinical outcome of patients undergoing non-cardiac surgery in the two months following coronary stenting. *J Am Coll Cardiol* 2003;42:234–40.

179. McFalls EO, Ward HB, Moritz TE et al. Coronary-artery revascularisation before elective major vascular surgery. *N Engl J Med* 2004;351:2795-804

180. Ward HB, Kelly RF, Thottapurathu L et al. Coronary artery bypass grafting is superior to percutaneous coronary intervention in prevention of perioperative myocardial infarction during subsequent vascular surgery. *Ann Thorac Surg* 2006;82(3):795-800

181. McFalls EO, Ward HB. Coronary revascularisation before vascular surgery (author reply). *N Engl J Med* 2005;352:1492-5

182. Landesberg G, Mosseri M, Wolf YG et al. Preoperative thallium scanning, selective coronary revascularisation, and long-term survival after major vascular surgery. *Circulation* 2003;108:177-83

183. Landesberg G, Berlatzky Y, Bocher M et al. A clinical survival score predicts the likelihood to benefit from preoperative thallium scanning and coronary revascularisation before major vascular surgery. *Eur Heart J* 2007;28:533-9

184. Landesberg G, Mosseri M, Shatz V et al. Cardiac troponin after major vascular surgery: the role of perioperative ischaemia, preoperative thallium scanning and coronary artery revascularisation. *J Am Coll Cardiol* 2004;44:569-75

185. Poldermans D, Schouten O, Vidakovic R et al. A clinical randomised trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery: the DECREASE-V Pilot Study. *J Amer Coll Cardiol* 2007;49:1763-9

186. Yeager MP, Fillinger MP, Hettleman BD, Hartman GS. Perioperative beta-blockade and late cardiac outcomes: a complimentary hypothesis. *J Cardiothorac Vasc Anesth* 2005;19:237-41

187. Devereaux PJ. Perioperative Ischaemic Evaluation (POISE) trial. Presented at AHA Scientific Sessions 2007; November 2007, Orlando.

188. Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischaemia Research Group. *N Engl J Med* 1996;335:1713-20

189. Poldermans D, Boersma E, Bax JJ et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing major vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. *N Engl J Med* 1999;341:1789-94

190. Schouten O, Shaw LJ, Boersma E et al. A meta-analysis of safety and effectiveness of perioperative beta-blocker use for the prevention of cardiac events in different types of non-cardiac surgery. *Coron Artery Dis* 2006;152:983-90

191. Anzai T, Yoshikawa T, Takahashi T et al. Early use of beta-blockers is associated with attenuation of serum C-reactive protein elevation and favourable short-term prognosis after acute myocardial infarction. *Cardiology* 2003;99:47-53

192. Yang H, Raymer K, Butler R, Parlow J, Roberts R. The effects of perioperative beta-blockade: results of the Metoprolol After Vascular Surgery (MAVS) study, a randomised controlled trial. *Am Heart J* 2006;152:983-90

193. Brady AR, Gibbs JS, Greenhalgh RM, Powell JT, Sydes MR. Perioperative beta-blockade (POBBLE) for patients undergoing infrarenal vascular surgery: results of a randomised double-blind controlled trial. *J Vasc Surg* 2005;41:602-9

194. Juul AB, Wetterslev J, Gluud C et al. Effect of perioperative beta blockade in patients with diabetes undergoing major noncardiac surgery: a randomised placebo controlled, blinded multicentre trial. *BMJ* 2006;332:1482

195. Sipahi I, Tuzcu EM, Wolski KE et al. Beta-blockers and progression of coronary atherosclerosis: pooled analysis of 4 intravascular ultrasonography trials. *Ann Intern Med* 2007;147:10-8

196. Redelmeier D, Scales D, Kopp A. Beta-blockers for elective surgery in elderly patients: population based, retrospective cohort study. *BMJ* 2005;331:932

197. Cruikshank JM. Are we misunderstanding beta-blockers? *Int J Cardiol* 2007;120:10-27

198. Raby KE, Brull SJ, Timimi F et al. The effect of heart rate control on myocardial ischaemia among high-risk patients after vascular surgery. *Anesth Analg* 1999;88:477-82

199. Feringa HH, Bax JJ, Boersma E et al. High-dose beta-blockers and tight heart rate control reduce myocardial ischaemia and troponin T release in vascular surgery patients. *Circulation* 2006;114:SI344-9

200. Lindenauer PK, Pekow P, Wang K, Mamidi DK, Gutierrez B, Benjamin EM. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. *N Engl J Med* 2005;353:349-61

201. Davignon J. Beneficial cardiovascular pleiotropic effects of statins. *Circulation* 2004;109(S):III39-43

202. Crisby M, Nordin-Fredriksson G, Shah PK, Yano J, Zhu J, Nilsson J. Pravastatin treatment increases collagen content and decreases lipid content, inflammation, metalloproteinases, and cell death in human carotid plaques: implications for plaque stabilisation. *Circulation* 2001;103:926-33

203. Pederson TR, Kjekshus J, Berg K et al. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). 1994. *Atheroscler Suppl* 2004;5:81-7

204. Pederson TR, Kjekshus J, Pyorala K et al. Effect of simvastatin on ischaemic signs and symptoms in the Scandinavian Simvastatin Survival Study (4S). *Am J Cardiol* 1998;81:333-5

205. Durazzo AE, Machado FS, Ikeoka DT et al. Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomised trial. *J Vasc Surg* 2004;39:967-76

206. Poldermans D, Bax JJ, Kertai MD et al. Statins are associated with a reduced incidence of perioperative mortality in patients undergoing major noncardiac vascular surgery. *Circulation* 2003;107:1848-51

207. Kertai MD, Boersma E, Westerhout CM et al. A combination of statin and beta-blockers is independently associated with a reduction in the incidence of perioperative mortality and nonfatal myocardial infarction in patients undergoing abdominal aortic aneurysm surgery. *Eur J vasc Endovasc Surg* 2004;28:343-52

208. Lindenauer PK, Pekow P, wang K, Gutierrez B, Benjamin EM. Lipid-lowering therapy and in-hospital mortality following major noncardiac surgery. *JAMA* 2004;291:2092-9

209. Kertai MD, Boersma E, Westerhout CM et al. Association between long-term statin use and mortality after successful abdominal aortic aneurysm surgery. *Am J Med* 2004;116:96-103

210. Hindler K, Shaw AD, Samuels J et al. Improved postoperative outcomes associated with preoperative statin therapy. *Anesthesiology* 2006;105:1260-72

211. Bicard BM, Sear JW, Foex P. Statin therapy: a potentially useful perioperative intervention in patients with cardiovascular disease. *Anaesthesia* 2005;60:1106-14

212. Wilhelmi M, Winterhalter M, Fischer S et al. Massive postoperative rhabdomyolysis following combined CABG/abdominal aortic replacement: a possible association with HMG-CoA reductase inhibitors. *Cardiovasc Drugs Ther* 2002;16:471-5

213. Forestier F, Breton Y, Bonnet E, Janvier G. Severe rhabdomyolysis after laparoscopic surgery for adenocarcinoma of the rectum in two patients treated with statins. *Anesthesiology* 2002;97:1019-21

214. Tong J, Laport G, Lowsky R. Rhabdomyolysis after concomitant use of cyclosporine and simvastatin in a patient transplanted for multiple myeloma. *Bone Marrow Transplant* 2005;36:739-40

215. Schouten O, Kertai MD, Bax JJ et al. Safety of perioperative statin use in high risk patients undergoing major vascular surgery. *Am J Cardiol* 2005;95:658-60

216. Heeschen C, Hamm CW, Laufs U, Bohm M, Snapinn A, White HD. Withdrawal of statins in patients with acute coronary syndromes. *Circulation* 2003;107:e27

217. Schouten O, Hoeks SE, Welten GM et al. Effects of statin withdrawal on frequency of cardiac events after vascular surgery. *Am J Cardiol* 2007;100:316-20

218. Lindblad B, Persson NH, Takolander R, Bergqvist D. Does low-dose acetylsalicylic acid prevent stroke after carotid surgery? A double-blind, placebo-controlled randomized trial. *Stroke* 1993;24:1125-8

219. Taylor DW, Barnett HJ, Haynes RB et al. ASA and Carotid Endarterectomy (ACE) Trial Collaborators low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomised controlled trial. *Lancet* 1999;353:2179-84

220. Robless P, Mikhailidis DP, Stansby G. Systematic review of antiplatelet therapy for the prevention of myocardial infarction, stroke or vascular death in patients with peripheral vascular disease *Br J Surg* 2001;88:787-800

221. Burger W, Chemnitius JM, Kneissl GD, Rucker G. Low-dose aspirin for secondary cardiovascular prevention—cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation—review and meta-analysis. *J Intern Med* 2005;257:399-414

222. Biondi-Zoccai GG, Lotrionte M, Agostoni P et al. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. *Eur Heart J* 2006;27:2667-74

223. Heusch G, Schipke J, Thamer V. Clonidine prevents the sympathetic initiation and aggravation or post-stenotic myocardial ischemia. *J Cardiovasc Pharmacol* 1985;7:1176–82

224. Talke P, Li J, Jain U et al. Effects of perioperative dexmedetomidine infusion in patients undergoing vascular surgery. The Study of Perioperative Ischemia Research Group. *Anesthesiology* 1995;85:620–33

225. Ellis JE, Drijvers G, Pedlow S et al. Premedication with oral and transdermal clonidine provides safe and efficacious postoperative sympatholysis. *Anesth Analg* 1994;79:1133–40

226. Stuhmeier KD, Mainzer B, Cierpka J et al. Small, oral dose of clonidine reduces the incidence of intraoperative myocardial ischemia in patients having vascular surgery. *Anesthesiology* 1996;85:706–12

227. Wijeysundera DN, Naik JS, Scott Beattie W. Alpha-2 adrenergic agonists to prevent perioperative cardiovascular complications: A meta-analysis. *Am J Med* 2003;114:742–52

228. Stevens RD, Burri H, Tramer MR. Pharmacologic myocardial protection in patients undergoing noncardiac surgery: A quantitative systematic review. *Anesth Analg* 2003;97:623–33

229. Oliver MF, Goldman L, Julian DG et al. Effect of mivazerol on perioperative cardiac complications during non-cardiac surgery in patients with coronary heart disease: The European Mivazerol Trial (EMIT). *Anesthesiology* 1999;91:951–61

230. Coriat P, Daloz M, Bousseau D et al. Prevention of intraoperative myocardial ischemia during noncardiac surgery with intravenous nitroglycerin, *Anesthesiology* 1984;61:193–6

231. Godet G, Coriat P, Baron JF et al. Prevention of intraoperative myocardial ischemia during noncardiac surgery with intravenous diltiazem: A randomized trial versus placebo. *Anesthesiology* 1987;66:241–5

232. Dodds TM, Stone JG, Coromilas J et al. Prophylactic nitroglycerin infusion during noncardiac surgery does not reduce perioperative ischemia. *Anesth Anal*g 1993;76:705–13

233. Warltier DC, Al Wathigui MH, Kampine JP, Schmeling WT. Recovery of contractile function of stunned myocardium in chronically instrumented dogs is enhanced by halothane or isoflurane. *Anesthesiology* 1988;69:552-65

234. Cope DK, Impastato WK, Cohen MV, Downey JM. Volatile anaesthetics protect the ischemic rabbit myocardium from infarction. *Anesthesiology* 1997;86:699-709.

235. Zaugg M, Lucchinetti E, Spahn DR, Pasch T, Schaub MC. Volatile anaesthetics mimic cardiac preconditioning by priming the activation of mitochondrial KATP channels via multiple signalling pathways. *Anesthesiology* 2002;97:4-14

236. Siegmund B, Schlack W, Ladilov YV, Balser C, Piper HM. Halothane protects cardiomyocytes against reoxygenation induced hypercontracture. *Circulation* 1997;96:4372-9

237. Kowalski C, Zahler S, Becker BF et al. Halothane, isoflurane, and sevoflurane reduce postischaemic adhesion of neutrophils in the coronary system. *Anesthesiology* 1997;86:188-95

238. Forrest JB, Cahalan MK, Rehder K et al. Multicenter study of general anesthesia. II. Results. *Anesthesiology* 1990;72:262-8

239. Rooke GA, Ebert TJ, Muzi M, Kharasch ED. The hemodynamic and renal effects of sevoflurane and isoflurane in patients with coronary artery disease and chronic hypertension. *Anesth Analg* 1996;82:1159-65

240. Ebert TJ, Kharasch ED, Rooke GA, Shroff A, Muzi M. Myocardial ischemia and adverse cardiac outcomes in cardiac patients undergoing non-cardiac surgery with sevoflurane and isoflurane. *Anesth Analg* 1997;85:993-9

241. Ebert TJ, Harkin CP, Muzi M. Cardiovascular responses to sevoflurane: a review. *Anesth Analg* 1995;81:S11-22

242. Gal J, Bogar L, Acsady G, Kertai MD. Cardiac risk reduction in non-cardiac surgery: the role of anaesthesia and monitoring techniques. *Eur J Anaesth* 2006;23:641-8

243. Rigg JR. Does regional block improve outcome after surgery? *Anaesth Intensive Care* 1991;19:404-11

244. Liu S, Carpenter RL, Neal JM. Epidural anesthesia and analgesia. Their role in postoperative outcome. *Anesthesiology* 1995;82:1474-1506

245. Garnett RL, MacIntyre A, Lindsay P et al. Perioperative ischaemia in aortic surgery: combined epidural/general anaesthesia and epidural analgesia vs general anaesthesia and i.v. analgesia. *Can J Anaesth* 1996;43:769-77

246. Baron JF, Bertrand M, Barre E et al. Combined epidural and general anesthesia versus general anesthesia for abdominal aortic surgery. *Anesthesiology* 1991;75:611-8

247. Norris EJ, Beattie C, Perler BA et al. Double-masked randomized trial comparing alternate combinations of intraoperative anesthesia and postoperative analgesia in abdominal aortic surgery. *Anesthesiology* 2001;95:1054-67

248. Bois S, Couture P, Boudreault D et al. Epidural analgesia and intravenous patient-controlled analgesia result in similar rates of postoperative myocardial ischemia after aortic surgery. *Anesth Analg* 1997;85:1233-9

249. Boylan JF, Katz J, Kavanagh BP et al. Epidural bupivacaine-morphine analgesia versus patient-controlled analgesia following abdominal aortic surgery: analgesic, respiratory, and myocardial effects. *Anesthesiology* 1998;89:585-93

250. Rodgers A, Walker N, Schug S et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. *BMJ* 2000;321:1493-1505

251. Park WY, Thompson JS, Lee KK. Effect of epidural anesthesia and analgesia on perioperative outcome: a randomized, controlled Veterans Affairs cooperative study. *Ann Surg* 2001;234:560-69

252. Rigg JR, Jamrozik K, Myles PS et al. Design of the multicenter Australian study of epidural anesthesia and analgesia in major surgery: the MASTER trial. *Control Clin Trials* 2000;21:244-56

253. Frank SM, Higgins MS, Breslow MJ et al. The catecholamine, cortisol, and haemodynamic responses to mild perioperative hypothermia. A randomised clinical trial. *Anesthesiology* 1995;82:83-93

254. Bay J, Nunn JF, Prys-Roberts C. Factors influencing arterial PO2 during recovery from anaesthesia. *Br J Anaesth* 1968;40:398-407

255. Frank SM, Fleisher LA, Breslow MJ et al. Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events. A randomised clinical trial. *JAMA* 1997;277:1127-34

256. Recommendations for Chamber Quantification: A Report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, Developed in Conjunction with the European Association of Echocardiography, a Branch of the European Society of Cardiology. Members of the Chamber Quantification Writing Group. *J Amer Soc Echo* 2005;18:1440-63

257. Tang T, Walsh SR, Fanshawe TR et al. Estimation of physiologic ability and surgical stress (E-PASS) as a predictor of immediate outcome after elective abdominal aortic aneurysm surgery. *Am J Surg* 2007;194:176-82

258. Chronic Kidney Disease. Early identification and management of chronic kidney disease of adults in primary and secondary care. NICE Clinical guidelines CG73. September 2008

259. Diagnosis and management of chronic kidney disease. SIGN guideline 103. June 2008

260. Guidelines – CKD, 2009. http://www.renal.org/Clinical/GuidelinesSection/CKD.aspx

261. Hertzer NR, Beven EG, Young JR et al. Coronary artery disease in peripheral vascular patients: a classification of 1000 coronary angiograms and results of surgical management. *Ann Surg* 1984;199:223-33.

262. Adams JE 3rd, Bodor GS, Davila-Roman VG et al. Cardiac Troponin I - A marker with high specificity for cardiac injury. *Circulation.* 1993;88:101-6

263. Filipovic M, Jeger R, Probst C et al. Heart rate variability and cardiac troponin I are incremental and independent predictors of one-year all-cause mortality after major non-cardiac surgery in patient at risk of coronary artery disease. *J Am Coll Cardiol* 2003;42:1767-76

264. Oscarsson A, Eintrei C, Anskar S et al. Troponin T-values provide long-term prognosis in elderly patients undergoing non-cardiac surgery. *Acta Anaesthesiol Scand* 2004;48:1071-9

265. Hobbs SD, Yapanis M, Burns PJ, Wilmink AB, Bradbury AW, Adam DJ. Perioperative myocardial injury in patients undergoing surgery for critical limb ischaemia. *Eur J Vasc Endovasc Surg* 2005;29:301-4

266. Gibson SC, Marsh A, Berry C et al. Should preoperative troponin be a standard requirement in patients undergoing major lower extremity amputation? *Eur J Vasc Endovasc Surg* 2006;31:637-41

267. Back MR, Schmacht DC et al. Critical appraisal of cardiac risk stratification before elective vascular surgery. *Vasc Endovasc Surg* 2003;37(6):387

268. Ammann P, Fehr T, Minder EI, Gunter C, Bertel O. Elevation of Troponin I in sepsis and septic shock. *Intensive Care Med* 2001;27:965-9

269. Fehr T, Knoflach A, Ammann P, Pei P, Binswanger U. Differential use of cardiac troponin T versus I in Haemodialysis patients. *Clin Nephrol* 2003;59:35-9

270. Musso P, Cox I, Vidano E, Zambon D, Panteghini M. Cardiac troponin elevations in chronic renal failure: prevalence and clinical significance. *Clin Biochem* 1999;32:125-30

271. Lang K, Schindler S, Forberger C, Stein G, Figulla HR. Cardiac Troponins have no prognostic value for acute and chronic cardiac events in asymptomatic patients with end-stage renal failure. *Clin Nephrol* 2001;56:44-51

272. Dasgupta A, Chow L, Wells A, Datta P. Effect of elevated concentration of alkaline phosphotase on cardiac troponin I assays. *J Clin Lab Anal* 2001;15:175-7

273. Dasgupta A, Wells A, Biddle DA. Negative interference of bilirubin and haemoglobin in the MEIA troponin I assay but not in the MEIA CK-MB assay. *J Clin Lab Anal* 2001;15:76-80

274. Wenk RE. Mechanism of interference by haemolysis in immunoassays and requirements for sample quality. *Clin Chem* 1998;44:2554

275. McDonagh TA, Cunningham AD, Morrison CE et al. Left ventricular dysfunction, natriuretic peptides and mortality in an urban population. *Heart* 2001;86:21-6

276. McDonagh TA, Robb SD, Murdoch DR et al. Biochemical detection of left-ventricular systolic dysfunction. *Lancet* 1998;351:9-13

277. Maisel AS, Krishnaswamy P, Nowak RM et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Eng J Med* 2002;347:161-7

278. Suttner S, Lang K, Piper SN, Schultz H, Rohm KD, Boldt J. Continuous intra- and postoperative thoracic epidural analgesia attenuates brain natriuretic peptide release after major abdominal surgery. *Anesth Analg* 2005;101:896-903

279. Murdoch DR, McDonagh TA, Byrne J et al. Titration of vasodilator therapy in chronic heart failure according to plasma brain natriuretic peptide concentration: randomised comparison of the haemodynamic and neuroendocrine effects of tailored versus empirical therapy. *Am Heart J* 1999;138:1126-32

280. Ballard DJ, Fowkes FGR, Powell JT. Surgery for small asymptomatic abdominal aortic aneurysms. Cochrane Database of Systematic Reviews 1999, Issue 3

281. Brewster DC, Cronenwett JL, Hallett JW Jr, Johnson KW, Krupski WC, Matsumura JS. Guidelines for the treatment of abdominal aortic aneurysms. Report of a subcommittee of the Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery. *J Vasc Surg* 2003;37:1106-17

282. Cole C. Canadian trial. Published through Cochrane Review – Surgery for small asymptomatic abdominal aortic aneurysms. The Cochrane Library 2008, Issue 4

283. Cao P. CAESAR Trial Collaborators. Comparison of surveillance vs aortic endografting for small aneurysm repair (CAESAR) trial: study design and progress. *Eur J Vasc Endovasc Surg* 2005;30:245-51

284. Ouriel K. The PIVOTAL study: a randomized comparison of endovascular repair versus surveillance in patients with smaller abdominal aortic aneurysms. *J Vasc Surg* 2009;49:266-9

285. Lederle FA, Johnson GR, Wilson SE et al. The aneurysm detection and management study screening programme: validation cohort and final results. Aneurysm Detection and Management Veterans Affairs Cooperative Study Investigators. *Arch Intern Med* 2000;160:1425-30

286. Lederle FA, Wilson SE, Johnson GR et al. Immediate repair compared with surveillance of small abdominal aortic aneurysms. *N Engl J Med* 2002;346:1437-44

287. Payne C, Gibson SC, Bryce G, Jardine A, Berry C, Kingsmore D. B-type natriuretic peptide (BNP) predicts long term survival following major non-cardiac surgery. *Br J Anaesth* 2010;in print.

288. Steinar A, Amundsen AR, Evjensvold J, Trippestad A. Operative mortality and long-term relative survival of patients operated on for asymptomatic abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg* 1995;9:293-8

289. The UK Small Aneurysm Trial Participants. Long term outcomes of immediate repair compared to surveillance of small abdominal aortic aneurysms. N Engl J Med 2002;346:1445-52

290. Mani K, Björck M, Lundkvist J, Wanhainen A. Improved long term survival after abdominal aortic aneurysm repair. *Circulation* 2009;120:201-11

291. Vanzetto G, Machecourt J, Blendea D et al. Additive value of thallium single-photon emission computed tomography myocardial imaging for prediction of perioperative events in clinically selected high cardiac risk patient having abdominal aortic surgery. *Am J Cardiol* 1996;77:143-8

292. Steyerberg EW, Kievit J, de Mol Van Otterloo JC, van Bockel JH, Eijkemans MJ, Habbema JD. Perioperative mortality of elective abdominal aortic aneurysm surgery. A clinical prediction rule based on literature and individual patient data. *Arch Intern Med* 1995;155:1998-2004

293. Kertai MD, Steyerberg EW, Boersma E et al. Validation of two risk models for perioperative mortality in patients undergoing elective abdominal aortic aneurysm surgery. *Vasc Endovasc Surg* 2003;37:13-21

294. Patterson BO, Holt PJE, Hinchliffe R, Loftus IM, Thompson MM. Predicting risk in elective abdominal aortic aneurysm repair: A systematic review of current evidence. *Eur J Vasc Endovasc Surg* 2008;36:637-45

295. Haga Y, Ikei S, Ogawa M. Estimation of Physiologic Ability and Surgical Stress (E-PASS) as a new prediction scoring system for postoperative morbidity and mortality following gastrointestinal surgery. *Surg Today* 1999;29:219-25

296. Gilbert K, Larocque BJ, Patrick LT. Prospective evaluation of cardiac risk indices for patients undergoing noncardiac surgery. *Ann Intern Med* 2000;133:356-9

297. Jones HJ, de Cossart L. Risk scoring in surgical patients. *Br J Surg* 1999;86:149–57

298. Shuhaiber JH, Hankins M, Robless P, Whitehead SM. Comparison of POSSUM with P-POSSUM for prediction of mortality in infrarenal abdominal aortic aneurysm repair. *Ann Vasc Surg* 2002;16:736-41

299. Prytherch DR, Ridler BM, Beard JD, Earnshaw JJ. Audit and Research Committee TVSSoGBaI. A model for national outcome audit in vascular surgery. *Eur J Vasc Endovasc Surg* 2001;21:477-83

300. Earnshaw JJ, Ridler BMF, Kinsman R. The Vascular Surgical Society of Great Britain and Ireland National Outcome Audit Report. London: Vascular Surgical Society of Great Britain and Ireland;1999

301. Baas AF, Janssen KJ, Prinssen M, Buskens E, Blankensteijn JD. The Glasgow Aneurysm Score as a tool to predict 30-day and 2-year mortality in the patients from the Durch Randomised Endovascular Aneurysm Management trial. *J Vasc Surg* 2008;47:277-81

302. Antonello M, Lepidi S, Kechagias A et al. Glasgow Aneurysm Score predicts the outcome after emergency open repair of symptomatic unruptured abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg* 2007;33:272-6

303. Kumar R, McKinney WP, Raj G et al. Predicting cardiac complications in patients undergoing non-cardiac surgery. *J Ger Intern Med* 2001;16:507-18

304. Carlisle J, Stewart M. Mid-term survival after abdominal aortic aneurysm surgery predicted by cardiopulmonary exercise testing. *Br J Surg* 2007;94:966-9

305. Medicare Services Advisory Committee. Endoluminal grafting for abdominal aortic aneurysm. Canberra: Medicare Services Advisory Committee. 1999

306. Prinssen M, Verhoeven ELG, Buth J et al. A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. *N Engl J Med* 2004;351:1607–18

307. Blankensteijn JD, de Jong SEC, Prinssen M et al. Two year outcomes after conventional or endovascular repair of abdominal aortic aneurysms. *N Engl J Med* 2005;352:2398–405

308. EVAR trial participants. Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): randomised controlled trial. *Lancet* 2005;365:2187–92

309. Mendonca CT, de Carvalho CA, Weingartner J et al. Endovascular treatment of abdominal aortic aneurysms in high-surgical-risk patients using commercially available stent-grafts. *J Vasc Surg* 2007;146:735-41

310. Zarins CK, Crabtree T, Bloch DA, et al. Endovascular aneurysm repair at 5 years: does aneurysm diameter predict outcome? *J Vasc Surg* 2006;44:920–30

311. Ouriel K, Srivastava SD, Sarac TP et al. Disparate outcome after endovascular treatment of small versus large abdominal aortic aneurysm. *J Vasc Surg* 2003;37:1206–12

312. Harris PL, Buth J. Update on the EUROSTAR Registry. For the EUROSTAR Collaborators. http://www.evtoday.com/AAA/2004%20Files/Update%20on%20the%20EUROSTAR%20Registry.html

313. Ballotta E, Da Giau G, Bridda A, Gruppo M, Pauletto A, Martella B. Open abdominal aortic aneurysm repair in octogenarians before and after the adoption of endovascular grafting procedures. *J Vasc Surg* 2008;47:23-30

314. Ballotta E, Da Giau G, Gruppo M, Mazzalai F, Spirch S, Terranova O. Elective abdominal aortic aneurysm repair in the very elderly: a systematic review. *Eur J Vasc Endovasc Surg* 2008;36:646-52

315. Winterborn RJ, Amin I, Lyratzopoulos G, Walker N, Varty K, Campbell WB. Preferences for endovascular (EVAR) or open surgical repair among patients with abdominal aortic aneurysms under surveillance. *J Vasc Surg* 2009;49:576-81

316. Daniels LB, Maisal AS. Natriuretic peptides. *J Am Coll Cardiol* 2007;50:2357-68

317. Higham H, Sear J.W, Sear et al. Perioperative troponin I concentration as a marker of long-term postoperative adverse cardiac outcomes-a study in high-risk surgical patients. *Anaesthesia* 2004;59:318-23

318. Cruz CP, Drouilhet JC, Southern FN et al. Abdominal aortic aneurysm repair. *Vasc Surg* 2001;35:335-44

319. Hallin A, Bergqvist D, Holmberg L. Literature review of surgical management of abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg* 2001;22:197-204

320. Raby K E, Barry J, Creager MA, Cook EF, Weisberg MC, Goldman L. Detection and significance of intraoperative and postoperative myocardial ischemia in peripheral vascular surgery. *JAMA* 1992;268:222-7

321. Rodseth RN, Padayachee L, Biccard BM. A meta-analysis of the utility of preoperative brain natriuretic peptide in predicting early and intermediate-term mortality and major adverse cardiac events in vascular surgical patients. *Anaesthesia* 2008;63:1226-33

322. Ryding ADS, Kumar S, Worthington AM, Burgess D. Prognostic value of brain natriuretic peptide in noncardiac surgery. *Anesthesiology* 2009;111:311-9

323. Karthikeyan G, Moncur RA, Levine O et al. Is a preoperative brain natriuretic peptide or N-terminal pro-B-type natriuretic peptide measurement an independent predictor of adverse cardiovascular outcomes within 30 days of noncardiac surgery? *J Am Coll Cardiol* 2009;54:1599-606

324. National Institute for Health and Clinical Excellence. Chronic heart failure: the management of adults with chronic heart failure in primary and secondary care (partial update). Clinical Guideline 108. 2010. www.nice.org.uk/CG108

325. Bettencourt PM. Clinical usefulness of b-type natriuretic peptide measurement: present and future perspectives. *Heart* 2005;91:1489-94

326. Alehagen U, Goetze JP, Dahlstrom U. Reference intervals and decision limits for b-type natriuretic peptide (BNP) and its precursor (NTproBNP) in the elderly. *Clin Chim Acta* 2007;382:8-14

327. Korenstein D, Wisnivesky JP, Wyer P, Adler R, Ponieman D, McGinn T. The utility of b-type natriuretic peptide in the diagnosis of heart failure in the emergency department: a systematic review. *BMC Emerg Med* 2007;7:6

328. Maisel A. B-type natriuretic peptide measurements in diagnosing heart failure in the dyspnoeic emergency department patient. *Rev Cardiovasc Med* 2002;3:S10-7

329. Dr. P.J. Devereaux, McMaster University. Vascular Events In Noncardiac Surgery Patients Cohort Evaluation Study (VISION). Details at: http://clinicaltrials.gov/ct2/show/record/NCT00512109 accessed on 8th May 2011.

330. Sakai H, Tsutamoto T, Ishikawa C et al. Direct comparison of brain natriuretic peptide (BNP) and N-terminal pro-BNP secretion and extent of coronary artery stenosis in patients with stable coronary artery disease. *Circulation* 2007;71:499-505

331. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr. Plasma brain natriuretic peptide to detect preclinical ventricular systolic or diastolic dysfunction: a community-based study. *Circulation* 2004;109:3176-81