Peri-operative Cardiac Morbidity: Prediction, Prevention And The Novel Role Of B-type Natriuretic Peptide

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Summary

Cardiovascular disease is the leading cause of death in surgical patients and because of this a number of strategies have been utilised to attempt to predict the cardiac risk of surgery. Theoretically, accurate pre-operative risk stratification would allow patients at low risk to have their surgery expedited efficiently, whilst those at higher risk could have a change made to their treatment plan such as peri-operative cardiac optimisation or in some cases, modification of the operative procedure. Despite this rationale, no guidelines currently exist in the United Kingdom for the management of the surgical patient at high cardiac risk. This may partly reflect the limited methods of risk stratification currently available. Clinical scoring systems are simple and inexpensive but limited by their predictive value. Trans-thoracic echocardiography provides prognostic information but is inconsistent, adding little to clinical information alone. The most accurate methods of pre-operative cardiac risk prediction at the present time are dobutamine stress echocardiography and dipyridamole thallium scanning. However they are expensive, time consuming and have shown poor positive predictive ability, even in high risk cohorts.

Few studies have studied the usefulness of biochemical markers in the prediction of post-operative cardiac events. In particular, no information was available in the literature regarding the role of B-type natriuretic peptide (BNP) in the prediction of cardiac events in non-cardiac surgical patients; despite the fact that its measurement has been shown to be an important prognostic tool in both non-surgical and cardiac surgical cohorts. In this thesis the aim was to determine whether pre-operative BNP concentration related to cardiac outcome following non-cardiac surgery; and also to

determine whether measurement of other markers such as C- reactive protein (CRP) and cardiac troponin I (CTnI) would be of benefit in pre-operative cardiac risk stratification.

To assess the effectiveness of plasma BNP measurement in the prediction of peri-operative cardiac morbidity a pilot study of 41 patients undergoing vascular surgery was conducted. To ensure that any post-operative rise in CTnI was due to operative stress, this was measured pre-operatively along with CRP. Median pre-operative BNP concentration was significantly higher in patients who suffered a post-operative cardiac event (cardiac death, non-fatal myocardial infarction (MI)) than in those who did not (210 (165-380) pg/ml vs. 34.5 (14-70) pg/ml, $p<0.001$). On the basis of these results a single-centre, prospective, observational cohort study was performed of all patients undergoing non-cardiac surgery. Of the 149 patients recruited to this study, 15 had a cardiac event. The median BNP in those patients having a cardiac event was more than ten-times higher than in those who did not (351 (127-1034) vs. 30.5 pg/ml (11-79.5), $p<0.001$). A BNP concentration of 108.5pg/ml was the best performing cut-off value having a sensitivity and a specificity of 87%.

Although CTnI had originally been measured to ensure that any post-operative rise was due to operative stress, 3 patients had a pre-operative elevation all of whom underwent lower extremity amputation. The amputation group, and in particular those patients who had a raised pre-operative cTnI were therefore analysed further. Amputation patients in general had a high cardiac event rate (23%); however the outcome in those patients who had a raised pre-operative cTnI was particularly poor with 2 suffering a cardiac death post-operatively and one suffering a non-fatal MI. A

pre-operative rise in CTnI was the only significant single predictor of peri-operative cardiac events in patients undergoing amputation (p= 0.009).

Pre-operative CRP concentration was measured routinely in vascular patients. The concentration in those who had a cardiac event was significantly higher than those who did not (69 (0-260) vs. 12 (0-285), (p=0.003). The cardiac event rate rose with each logarithmic increment in CRP concentration (0-10mg/l (5.7%); 11-100mg/l (22.4%), >100mg/l (55.6%) (p=0.002). Measurement of CRP was of most potential benefit in patients undergoing aortic aneurysm surgery.

In conclusion, this thesis has shown that pre-operative measurement of biochemical markers (BNP, CTnI, and CRP) can allow accurate peri-operative risk stratification. BNP concentration in particular was a sensitive and specific predictor of cardiac outcome. Careful case selection using a combination of clinical assessment and the results of these markers may lead to a reduction in the cardiac event rate.

Declaration

Biochemical tests were performed by Dr J Morton

and statistical analysis was conducted with the help of Professor I Ford, and the late Professor D Hole. Study design, patient recruitment and follow-up, data collection, analysis of data and preparation of the manuscript were performed by the author. In addition no work referred to in this thesis has been submitted in support of an application for another degree or qualification in this or any other university.

Signed

Dedication

To Christine and Lucy

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List of Publications

The predictive value of plasma brain natriuretic peptide for cardiac outcome after vascular surgery

Colin Berry, David Kingsmore, Simon Gibson, David Hole, James J Morton, Dominique S Byrne, and Henry J Dargie

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Should pre-operative troponin be a standard requirement in patients undergoing major lower extremity amputation?

Gibson SC**,** Marsh A, Berry C, Payne C, Byrne DS, Rogers PN, McKay AJ, Dargie H, Kingsmore DB

European Journal of vascular and endovascular surgery 2006 Jun; 31(6): 637-41

B-type natriuretic peptide predicts cardiac morbidity and mortality after major surgery.

Gibson SC, Payne CJ, Byrne DS, Berry C, Dargie HJ, Kingsmore DB.

British Journal of Surgery 2007; 94(7): 903-909

List of Presentations, Awards and Published Abstracts

Presentations and awards

Moynihan Prize, for best paper delivered at meeting, Association of Surgeons of Great Britain and Ireland, Edinburgh, 2006

B-type Natriuretic Peptide (BNP) predicts cardiac morbidity after major surgery: a prospective trial

SC. Gibson, A. Marsh, C Payne, C. Berry, JJ. Morton, D. Hole, H. Dargie, DS. Byrne, DB. Kingsmore

Prize for best Vascular Presentation, Association of Surgeons of Great Britain and Ireland, Edinburgh, 2006

C-reactive protein as a predictor of cardiac morbidity after vascular surgery.

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Can Brain Natriuretic Peptide Aid Cardiac Risk Assessment in Elective General Surgery?

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Should pre-operative troponin be a standard requirement in patients undergoing major lower extremity amputation?

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List of Abbreviations

ABPI-	Ankle brachial pressure index
BNP-	B-type natriuretic peptide
CABG-	Coronary artery bypass grafting
CAD-	Coronary artery disease
CCF-	Congestive cardiac failure
CCS-	Canadian Cardiovascular Society
CPX-	Cardio-pulmonary exercise testing
CRP-	C-reactive protein
CTnI-	Cardiac troponin I
CTnT-	Cardiac troponin T
CVA-	Cerebrovascular accident
DSE-	Dobutamine stress echocardiography
DTS-	Dipyridamole thallium scanning
ECG-	Electrocardiogram
LVD-	Left ventricular systolic dysfunction
LVEF-	Left ventricular ejection fraction
LVF-	Left ventricular failure
MI-	Myocardial infarction
NPV-	Negative predictive value
NWMAs-	New wall motion abnormalities
OR-	Odds ratio
PPV-	Positive predictive value
PTCA-	Percutaneous transluminal coronary angioplasty

RCRI- Revised cardiac risk index

ROC- Receiver-operating characteristics

RR- Relative risk

SPECT- Technetium-99m single photon emission computed tomography

TTE- Trans-thoracic echocardiography

VE/VCO_2- Ventilatory equivalent for carbon dioxide

1. Introduction

1.1 Peri-operative cardiac morbidity- the problem

Major general surgery and vascular surgery in particular, can carry considerable risk of cardiac morbidity. Cardiovascular disease is the leading cause of mortality in surgical patients and estimates suggest that 5% of the surgical population worldwide, (5 million patients annually) suffer some form of peri-operative cardiac morbidity (Mangano 1990). This is substantiated by a report from a surgical database of 83958 US male veterans which found that 4.5% suffered a peri-operative cardiac event (Khuri et al. 1995). The incidence of coronary artery disease is higher in Scotland than in many other countries, therefore it would be logical that cardiac complications post-operatively would also be higher in Scotland. Data from the Scottish Audit of Surgical Mortality illustrates the problem (Scottish audit of surgical mortality summary report, 2004). In Scotland in 2003 there were 370 myocardial infarctions in non-cardiac surgical patients. Of 1894 peri-operative deaths in that year, 578 were cardiac in origin, this being the commonest cause of mortality.

The impact of peri-operative myocardial infarction (MI) is substantial. It leads to increased short and long term mortality, a greater length of hospital stay, and increased costs (Khuri et al. 1995;L'Italien et al. 1995;McFalls et al. 1998). Accurate cardiac risk prediction with appropriate intervention could therefore be of considerable benefit.

1.2 The presentation and aetiology of peri-operative myocardial infarction

Peri-operative MI occurs most commonly on the first to third days post-operatively, with more recent studies of incidence reporting an increased frequency on the first day (Badner et al. 1998;Mangano et al. 1990;Raby et al. 1992). Peri-operative MI is

often clinically silent with as few as 17% of affected patients having symptoms of chest pain (Badner et al. 1998). This may be due to the residual effects of the anaesthetic and analgesia or competing incisional pain (Raby et al. 1992). Furthermore, non-q wave MI has a greater incidence post-operatively than in the general setting (Badner et al. 1998;Fleisher et al.1995;Goldberg et al. 1987). This may be because post-operative MI is more commonly due to prolonged ischaemia rather than sudden acute rupture of coronary atherosclerotic plaques.

Peri-operative MI represents an imbalance of oxygen supply and requirement. Decreased supply may result from rupture of a coronary atherosclerotic plaque, coronary vasoconstriction (secondary to catecholamine stimulation of ά1 adrenergic receptors), hypotension, anaemia or hypoxia (Breslow 1992). Increased demand results from post-operative tachycardia and hypertension secondary to withdrawal of anaesthesia, peri-operative pain and fluid shifts (Breslow 1992;Mangano et al. 1990;Raby et al. 1992). The aetiology and patho-physiology of peri-operative MI may differ from those in the general setting. The commonest cause in the non-surgical setting is from rupture of a coronary atherosclerotic plaque; often in haemodynamically insignificant lesions, leading to platelet aggregation and thrombus formation (Fuster et al. 1992, Fuster 1994)). In contrast, it has been suggested that up to half of peri-operative MIs are due to an imbalance in oxygen delivery and requirement caused by the stress of surgery in the setting of coronary heart disease (Grayburn & Hillis 2003). This view is supported by studies showing that deliberately increasing oxygen supply can reduce peri-operative cardiac morbidity (Boyd et al. 1992).

One such study, a randomised controlled trial of 107 high risk surgical patients, found that maximising the delivery of oxygen (to a target of 600ml/min/m^2) using dopexamine significantly reduced the overall morbidity (p= 0.015) and mortality (p=0.008) (Boyd et al. 1993). There were 8 (15.1%) cardiac events in the treatment group compared with 16 (29.6%) in the control group. However, the study had some weaknesses; there was no description of the surgical procedures performed, clinicians were not blinded to patients grouping, and 24 of 107 patients were entered into the study post-operatively. Furthermore, the extremely high 30-day mortality (22% in the control group) suggests that this study is not representative of normal clinical practice.

Wilson et al (1999) conducted a similar randomised controlled trial, again showing that increasing oxygen delivery to a target of 600ml/min/$m^{2)}$ with the use of dopexamine reduced both overall mortality and cardiac morbidity. In this study, the 138 patients received dopexamine, adrenaline or standard care. The mortality rate in those patients whose delivery of oxygen was optimised was 3% compared with 17% in the control groups (p=0.007). There were 14 (30.4%) cardiac events in the dopexamine group compared with 29 (63%) in the control group. Randomisation was carried out by a computer and patients were studied on an intention to treat basis. However the study was not blinded and there was a significant reduction in the critical care bed provision in the control group. Once again the 30-day mortality (in this case 17%) in the control group was higher than one would expect in normal practice, raising doubt about whether the findings are applicable to general use.

Two separate pathological studies have shown that half of fatal post-operative MIs are secondary to rupture of coronary atherosclerotic plaque. Dawood et al (1996)

retrospectively studied the coronary arteries and myocardium at autopsy of 42 patients who had suffered a fatal peri-operative MI and compared them with those of 25 patients who had suffered a fatal non-operative MI. Findings were similar in the two groups. Three vessel coronary artery disease was present in 59% of the operative group and 60% of the non operative group. There was evidence of plaque disruption in 55% of the operative group compared with 40% of the non-operative patients. In both groups the acute coronary lesion almost invariably correlated with the site of infarction, but the severity of pre-existing underlying stenosis did not predict the resulting infarct territory. Cohen and Aretz (1999) also studied autopsy specimens of patients suffering a peri-operative MI. Multi-vessel coronary artery disease was present in 88% of the 26 specimens included. 50% of patients showed evidence of plaque rupture and 35% had evidence of intra-coronary thrombus. There was a longer interval from surgery to death in those patients with plaque rupture. In 19% of patients the territory of MI had a circumferential distribution suggesting a diffuse lack of oxygen. Both studies were limited by small numbers, patient selection bias, and the fact that the groups represent only fatal peri-operative MI. Furthermore the coronary arteries were not fixed in distension and some of the observed narrowing could have resulted from post-mortem collapse. The studies may also have under-represented the incidence of intra-coronary thrombus due to spontaneous lysis after the event. However their findings are consistent, in that they show that ruptured atherosclerotic plaque is as important a cause of MI in the peri-operative setting as in the general one. Observations that a diffuse lack of oxygen plays a more significant role may therefore not be valid.

1.3 Predicting peri-operative cardiac morbidity

Various strategies have been proposed to improve the prediction of cardiac risk and thus allow clinicians a better means of assessing the risk/benefit ratio of a surgical procedure. Methods currently utilised include assessment by an experienced clinician, simple clinical scoring systems, blood tests, and more complex methods of assessing cardiac function. Accurate peri-operative cardiac risk stratification could allow surgery in low risk patients to be expedited efficiently, with moderate risk patients being appropriately pre-optimised. A more informed decision could be made about the need for surgery in high risk patients, with the management plan being changed if appropriate.

1.3.1 Patient factors

Patient factors that may be predictive of cardiac risk are numerous and include age, history of MI, angina pectoris, presence of congestive cardiac failure, diabetes, COPD, renal impairment, cerebrovascular disease, history of dysrhythmia and ischaemic ECG changes (Detsky et al. 1986;Eagle et al. 1989;Hollenberg et al. 1992;Lee 1999;Mamode et al. 2001;Poldermans et al. 1995;Raby et al 1992). The presence and severity of pre-existing ischaemic heart disease is particularly important in determining pre-operative co-morbidity and the Canadian Cardiovascular Society has developed an index of angina severity which offers a simple and useful means of risk stratification (Campeau 1976). This index has been shown to be as effective as some established risk indices in predicting peri-operative cardiac morbidity (Gilbert et al. 2000).

Definitions of what constitutes a history of ischaemic heart disease vary between studies; however Lee et al (1999b) prospectively studied 4315 surgical patients and identified the combination of variables describing pre-operative ischaemic heart disease which had the highest correlation with major cardiac complication. These are history of MI, 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. Using, in part, these variables they have developed an index of cardiac risk which is discussed later.

1.3.2 Operative factors

Operative factors are important in determining risk. The type of surgery has universally been found to correlate with the likelihood of a cardiac event, although there is varying consensus as to the risk associated with individual or groups of procedures. Detsky et al (1986) prospectively studied 455 surgical patients. They found patients undergoing vascular and orthopaedic surgery to have the highest incidence of cardiac events with rates of 13.2% and 13.6% respectively. Patients undergoing intraperitoneal or intrathoracic procedures were judged to be at moderate risk with 8% of patients suffering an event. Only 2.6% of head and neck patients suffered an event. Eagle et al (1997) retrospectively studied 3368 patients in the Coronary Artery Surgery Study population who had undergone non-cardiac surgery. Their categorisation of risk of procedure differed from that of Detsky et al. Patients undergoing vascular, abdominal, head and neck and thoracic procedures were grouped as high risk and had a combined cardiac event rate of greater than 4%, whereas orthopaedic, urology and breast patients were deemed low risk, with a combined event rate of less than 1%. However the heterogeneity of procedure within each group

is likely to confound the estimation of risk derived. Whilst Detsky et al solely reported arterial bypass surgery and amputation as vascular procedures, Eagle et al included aortic, femoral, renal and peripheral artery surgery as well as venous surgery. It is unlikely that the 4.2% of patients undergoing a venous procedure contributed to the post-operative cardiac events. Similarly, although urological procedures are categorised as low risk, few of the patients in this group underwent nephrectomy, the majority undergoing more minor procedures such as a transurethral resection of prostate or even dilatation and curettage. The study conducted by Eagle et al may also have overestimated the frequency of cardiac events as the definition of MI was subjective; all patients with ECG and enzyme abnormalities strongly suggestive of myocardial infarction were included. All post-operative deaths within 30 days were also judged positive, although not all such deaths would be of cardiac origin. In addition although the study was published in 1997, initial enrolment began in 1979 leading to a temporal effect.

Lee et al (1999b) studied 4315 patients undergoing major non-cardiac surgery and found vascular patients to have the highest risk of peri-operative cardiac morbidity with a relative risk (RR) of 3.9. Patients undergoing thoracic (RR of 1.1) and abdominal (RR of 0.8) surgery were at next highest risk. Orthopaedic patients were low risk (RR of 0.4). The prospective nature and large numbers analysed in this study add validity to these findings.

Although the cardiac morbidity associated with different groups varies between studies, most consistently find that major vascular surgery is of highest risk; although this may be as much to do with the co-morbidity of the patient population as to the

stress of surgery (Hertzer et al. 1984). Intra-abdominal and intra-thoracic procedures are generally categorised as moderate to high risk. However given the potential heterogeneity of these groups of procedure it would perhaps be more relevant to relate risk to the precise operation rather than the specialty of operating surgeon. This point is illustrated by those studies which have compared rates of cardiac events between individual procedures. Mamode et al (2001) found aortic surgery to have a significantly higher risk than peripheral vascular or extra-anatomical bypasses with 12 of the 92 (13%) patients in the aortic group suffering a primary event compared with 9 of 196 (4.6%) in the other groups (p=0.007) Similarly Fleischer et al (1999) found that aortic surgery patients (7.8%) had significantly greater 30 day mortality than infrainguinal bypass patients (5.8%). The categorisation of patients into "vascular" or "abdominal" groups may in some cases be too broad.

The urgency of surgery can also impact on the associated cardiac risk. O'Neill-Callaghan et al (2005) retrospectively studied 997 patients undergoing vascular surgery. Those patients whose procedure was classed as emergency had a 5 times greater risk of cardiac event. This is in agreement with the findings of Mangano (1990) who found emergency surgery to carry a three times higher cardiac risk.

Intra-operative factors are also important. Back et al (2003) found an operation duration of greater than 300 minutes to be a significant predictor of all cause mortality when they studied elective vascular patients and Park et al (2001) also showed that increased duration of procedure was a significant predictor of events post aortic surgery The occurrence of intra-operative hypotension has also been associated with

increased rates of cardiac morbidity and mortality (Cambria et al. 2002;Koness et al. 1990;Mangano, 1990;Monk et al. 2005).

It is clear that there are a number of operative factors, in addition to the type of surgery, which may impact on peri-operative cardiac risk. Whilst one must allow for these in any studies of cardiac risk, they may also prove important in interventions to reduce peri-operative cardiac morbidity.

1.3.4 Clinical Scoring Systems

Attempts to combine the most important patient and operative factors and allow some objectivity in peri-operative risk stratification have led to the development of clinical scoring systems. These systems allow patients to be put into categories of varying risk, and may identify those who would benefit from further testing or a change in treatment plan.

The American Society of Anaesthesiologists developed a classification of physical status in 1963 and found it to be a good predictor of peri-operative mortality (American Society of Anaesthesiologists, 1963). However whilst it has been shown to be useful in the prediction of all-cause mortality, further study has found it to be inaccurate in the prediction of post-operative cardiac complications (Eagle et al. 1971).

In 1977 Goldman et al (1977) developed their multi-factorial index of cardiac risk in non-cardiac surgical patients. Nine risk factors were identified from discriminate analysis of cardiac events in this prospective study of 1001 patients. However the

model was not validated and the index has performed poorly in studies other than the one from which it was derived (Charlson et al. 1987;Lee 1999b). The variable weighting given to different risk factors makes it difficult to use and the validity of this weighting has been questioned (Howell & Sear 2004). The index is largely of historical significance now but its development has led to the formulation of multiple scoring systems of varying complexity.

In 1989, Eagle et al (1989) retrospectively studied a cohort of 200 patients undergoing major vascular surgery who had been referred to a nuclear cardiology unit for pre-operative assessment. They produced a clinical scoring system dependent on five variables which were found to be significant after logistic regression, namely, age over 70, diabetes mellitus, history of angina, ventricular ectopics requiring treatment and Q-waves on ECG. The presence of none of these criteria places a patient in a low risk category, 1or 2 in a moderate risk category and 3 or more in a high risk category. In the original study, post-operative ischaemic events occurred in 3.1% of patients with no risk factors, 15.5% of patients with 1 or 2 risk factors, and 50% of patients with 3 or more risk factors. Failings of the study included the highly selected population and the lack of blinding to pre-operative evaluation which led to 44 patients having their surgery cancelled or postponed. Subjective end points such as unstable angina and ischaemic pulmonary oedema were also included. Despite these failings, various studies have found the Eagle criteria to be reliable in peri-operative cardiac risk stratification, particularly in identifying those patients at low likelihood of suffering an event. Poldermans et al (1995) found that an Eagle score of 0 had a negative predictive value (NPV) of 99% for cardiac events in their study of 302 patients undergoing major vascular surgery. They also found a significant difference

in cardiac event rates between patients whose scores placed them in the intermediate (11%) and high risk (29%) groups. A high Eagle score has also been shown to be predictive of adverse events. Back et al (2003) studied 425 consecutive patients undergoing elective vascular procedures and found an Eagle score of greater than 2 to be a significant predictor of cardiac events.

In 1989 Detsky et al (1999) studied 455 successive patients referred to a general medical consultation service prior to undergoing non-cardiac surgery. They found that the Goldman Index was not accurate at stratifying risk in this population, having an area under the receiver-operating characteristic (ROC) curve of 0.69. They therefore modified the original cardiac risk index by simplifying the point system and adding angina severity as a variable. This led to an improved area under the ROC curve of 0.76 and the development of the Detsky score. Whilst this system improved risk stratification in this particular cohort, there was concern about the applicability of the study given the highly selected population. In 1993 Poldermans et al (1993) found that although the Detsky score was significantly higher in patients with peri-operative complications, it was of little practical use in risk stratification. They confirmed this finding in 1995 in their study of 302 patients undergoing major vascular surgery (Poldermans et al. 1995). Despite the fact there was a significant difference in Detsky score between those patients having an event and those not, 22 (81%) of the 27 events occurred in the low risk group. In their more recent study of 297 patients, Mamode et al (2001) have also reported the Detsky score to be an inaccurate predictor of cardiac morbidity.

Gilbert et al (2000) compared the performance of the indices devised by Goldman, Detsky, the American Society of Anaesthesiologists and the Canadian Cardiovascular Society (CCS) in their prospective study of 2035 patients undergoing non-cardiac surgery. Area under the ROC curve was used to compare the accuracy of stratification of each index. No scoring system was found to be significantly better than the others and the predictive abilities of all were only moderately better than chance. The CCS index performed best with an area under the ROC curve of 0.654. Deficiencies of this comparative study included the use of all-cause mortality as an end point and lack of any screening for cardiac events.

In 1999, Lee derived and validated a simple modified scoring system for the prediction of cardiac risk in noncardiac surgical patients, the revised cardiac risk index (RCRI) (Lee et al. 1999b). In the derivation cohort of 2893 patients, 6 factors were found to be independently significant in predicting poor cardiac outcome. These were high risk of procedure, history of ischaemic heart disease, congestive heart failure, history of cerebrovascular disease, insulin therapy for diabetes and raised preoperative creatinine. The individual factors were clearly defined and each was given equal weighting as ROC analyses did not show any advantage in using the weighting derived from the logistic regression analyses. Four of the factors found to be independent predictors of outcome in the derivation cohort were confirmed to be univariate predictors in the validation cohort of 1422 patients. Diabetes and raised preoperative creatinine were not, although they did exhibit a trend to significance. Using the presence of these risk factors, patients in the derivation cohort were placed into 4 categories of increasing cardiac risk. In this cohort the cardiac risk was significantly different between each category. In the validation cohort, although the

cardiac risk did increase with each category, the difference only reached statistical significant between the second and third categories. The derived index was tested and also found to be of benefit in subgroup analysis with higher complication rates in the higher risk categories when individual procedures were analysed (with the exception of aortic aneurysm repair). The scoring system derived from this study was compared with other systems and was shown to significantly outperform the Goldman index and the Detsky score (Goldman et al. 1977; Detsky et al. 1986) in both the validation and derivation cohorts. Evidence from this study may seem compelling because of the large numbers analysed and because the system derived is simple and easy to use. However there was only a statistically significant difference in the cardiac event rate between classes two and three in the validation cohort; although the relative risks between classes one and two (2.2), and three and four (1.7) did show a trend to better prediction of outcome. Inclusion criteria for the study were also vague with patients being included if they had prospectively consented to the study, but also if they underwent post-operative cardiac marker sampling. This latter group which represented 14.5% of the population was found to have a significantly higher morbidity and this could have led to potential selection bias. High risk of procedure is also used as a variable in the revised cardiac index despite no information being available on how the group was derived. Furthermore, intra-peritoneal procedures are included in the high risk group despite the fact that on separate analysis abdominal operations carried a relative risk of 0.8. The model also performed poorly for aortic aneurysm procedures with patients in category 2 having a higher risk of cardiac event than those in category 3. Although the index has a good negative predictive ability, only 10% of patients in the highest risk category had an event leading to a significant

number of false positives. It would not be feasible for all these patients to have their operative plan modified.

Nevertheless, other investigators have found the revised cardiac risk index to have significant discriminatory ability (Boersma et al. 2001;Filipovic et al. 2003). Boersma et al (2001) retrospectively studied 1351 patients scheduled for vascular surgery. Some 611 patients had a score of 1, of whom 1.3% suffered an event. 509 had a score of 2, and 231 had scores of 3 or more with event rates of 3.1% and 9.1% respectively. Filipovic et al (2003) also found RCRI measurement to be useful in their study of peri-operative risk, with a score of 4 being an independent predictor of outcome.

The POSSUM scoring system was developed in 1991 and has been proposed as a tool for risk adjustment and comparative audit. It was developed from a multivariate discriminant analysis of factors measured in a broad group of general surgical patients (Copeland et al. 1991). It has been validated for use in general surgery but has been found to over-predict mortality, particularly in low risk groups (Whiteley et al. 1996). To address this, a revised equation for predicting death, the P-POSSUM was developed. This was shown to be a more accurate predictor of death (Whiteley et al. 1996) and has been validated in vascular, as well as in general surgical patients. Midwinter et al (1999) evaluated the predictive value of P-POSSUM in a population of 221 vascular surgical patients. They concluded that the methodology allowed satisfactory prediction of morbidity and mortality since there was no statistically significant difference between the predicted and observed morbidity and mortality. However given the small numbers analysed, the observed differences were large in some groups. For example in the 15 patients judged to have an estimated risk of death

of 20-40% P-POSSUM predicted 4 deaths and none were observed. In fact, in 5 of the 6 groups, P-POSSUM over predicted mortality albeit to a lesser extent than would have the original POSSUM equation. Although more useful than POSSUM it cannot be said that P-POSSUM is an accurate predictor of mortality as claimed. The lack of significant statistical difference between predicted and actual events in this study is likely to reflect a type 2 error. Moreover as P-POSSUM requires operative information to calculate a score it cannot be used in pre-operative risk stratification.

1.3.5 Serum Biochemical markers

Several biochemical markers have been proposed as potential predictors of peri-operative cardiac morbidity and thus as identifiers of patients at high risk. One such marker is cardiac troponin I (cTnI), a contractile protein which is released into the circulation after myocardial cell injury. It is not found in skeletal muscle and is therefore a sensitive and specific marker of myocardial necrosis and cardiac events (Adams, III et al. 1993;Apple et al. 1997). Hobbs et al (2005) have shown that as many as 38% of patients undergoing lower limb revascularisation for critical limb ischaemia have a raised cTnI post-operatively thus exhibiting myocardial injury. In this study of 29 patients there was no association between a raised post-operative cTnI and the late incidence of cardiac morbidity; however two patients with a raised pre-operative cTnI were identified. Although these patients were excluded from analyses, both were followed up and found to have post-operative morbidity and mortality (cardiac event and death).

Higham et al (2004) prospectively studied patients undergoing major vascular surgery or joint arthroplasty and demonstrated that an increase in peri-operative cTnI levels

was a significant predictor of adverse cardiac outcome at both 1 month and 1 year. Of 12 patients with a raised peri-operative troponin, 7 suffered a cardiac event post-operatively. The methods for the study were clear with well defined end points. A power calculation was used to determine the population size and the researchers would appear to have been blinded to troponin results although this is not clearly stated. However the significance of the conclusions is questionable as it is self-fulfilling that a raised peri-operative serum cTnI should predict short term events given that myocardial infarction (partly defined by a raised cTnI) was one of the study end points. Cerebrovascular accident (CVA) was also used as an end-point in the study despite carotid endarterectomy patients being included. In this case the surgery itself and not any factor predicted by a raised troponin may be responsible for the adverse event. Although there was a four-fold increase in cardiac mortality at 1 year in those patients who had raised post-operative cardiac enzymes, no single cardiac enzyme was a significant predictor of this, the only objective outcome. Furthermore the association between the raised enzymes and 1-year cardiac mortality is almost certainly accounted for by those patients who had early cardiac events as no patients developing late complications had a raised post-operative cTnI.

Kertai et al (2004) retrospectively studied the significance of cardiac troponin T (cTnT) measurement in 393 patients who had undergone aortic or infra-inguinal vascular surgery with a median follow up of four years. They excluded patients who had a confirmed myocardial infarction or cardiac death within 30 days of operation. They showed that an asymptomatic rise in cTnT peri-operatively was prognostically significant for all-cause mortality in the long term. A rise in cTnT was associated with an almost two-fold increased risk of mortality. The relationship remained significant

in multivariate analysis after correction for clinical and electrocardiographic findings. However, although the use of all-cause mortality as the primary end point prevents misclassification into cardiac or non-cardiac deaths, it leads to overestimation of the relevant end point, in this case cardiac complications. In addition, although only vascular procedures were included in the study, the population was heterogeneous since it contained patients undergoing both elective and emergency surgery. This was not accounted for in multivariate analyses. Furthermore, physicians had access to the cTnT results during the study which could have led to a treatment bias.

Kim et al (2002) prospectively studied cTnI levels in 229 patients post vascular surgery. CTnI levels were measured immediately after surgery and on the first three post-operative days. Clinicians were blinded to results. 98 patients had a detectable cTnI (>1.5ng/ml). The mortality at 6 months was 8%. A raised post-operative cTnI was an independently significant predictor of all-cause mortality with the difference first becoming apparent at 6 weeks. Mortality was higher in those patients with a greater cTnI rise: patients with an undetectable troponin had an odds ratio for death of 1.3, compared with 4.3 and 4.9 for patients with cTnI concentrations between 0.4 and 1.5mg/ml, and 1.6 and 3mg/ml respectively. However the study failed to exclude from analysis the 8 patients who had suffered a post-operative MI. The inclusion of these patients may have led to an overestimation of the influence of an isolated troponin rise with their mortality being secondary to the peri-operative MI. In addition no attempt was made to differentiate the cause of mortality in analyses and no account was taken of the stress of the procedure as a possible confounding factor.

A rise in peri-operative troponin would appear to be a prognostic indicator and its routine analysis may be of use to identify a high risk sub-group who would benefit from more intensive post operative care and follow up. A randomised study to assess any benefit from this may be beneficial.

D-dimer levels have been shown to correlate with the risk of coronary events in patients with peripheral arterial disease (Fowkes et al. 1993) and in 2001 Mamode et al (2001) found d-dimer levels to be a significant univariate and multivariate predictor of adverse cardiac events with odds ratios of 3.17 and 3.23 respectively. D-dimer level gave additional information to clinical assessment alone. However when only the objective end points of MI and cardiac death were considered, d-dimer level was no longer predictive of outcome. Furthermore there were weaknesses in the study design. Of a potential cohort of 608 patients undergoing surgery, only 297 were recruited raising the possibility of selection bias. In addition, results of pre-operative tests were available to clinicians, which in 19 cases led to the treatment plan being changed. This may have resulted in treatment bias and a possible reduction in the event rate. No researchers have provided further information on the prognostic value of d-dimers since this study's publication.

Evidence is accumulating that atherosclerosis is an inflammatory process (Libby 2002;Willerson & Ridker 2004) and raised circulating concentrations of the non-specific acute phase reactant c-reactive protein (CRP) have been shown to predict the occurrence of coronary events in patients with stable and unstable angina (Haverkate et al. 1997). In the Honolulu Heart Study patients with a raised CRP had increased odds of suffering an MI not only in the first few months of follow-up but as far as 20

years in the future (Sakkinen et al. 2002). Thus CRP concentration can predict cardiac outcome in the short and long term. CRP levels are also associated with the likelihood of developing peripheral vascular disease (Ridker et al. 1998) and show an inverse relationship with the ankle-brachial pressure index (Vainas et al. 2005).

Rossi et al (2002) found c-reactive protein (CRP) concentration to be an independent predictor of myocardial infarction in post-operative peripheral vascular disease patients. CRP levels in the upper tertiles predicted 60% of myocardial infarctions at 24 months. However only 51 patients were studied, 39 of whom underwent an endovascular procedure. Given that 1 patient underwent aortic bypass surgery this makes the population extremely heterogeneous in terms of operative stress. Despite this, the remainder of the study had a very exclusive design. Some 119 patients were excluded because of high baseline cardiac risk or the presence of infective, inflammatory or neoplastic disease. Even so, the cardiac event rate of 34% was high. When analysed, CRP concentration was only found to be predictive of MI at 24 months and not at 30 days. This is surprising given that it is an acute phase inflammatory marker. However this may be due to type 2 error as only one major event had occurred at a month. Alternatively it is possible that the surgery conducted was irrelevant and that CRP is instead a marker of base-line risk.

In a prospective observational study of 259 patients with critical limb ischaemia Barani et al (2005) found that raised inflammatory markers were associated with increased 1-year mortality. In the 61 patients who died, the mean CRP (mg/l) was 49.4 (+/-62.1) compared with 33.6(+/-56.5) in survivors. (p=0.02). However when the presence or absence of gangrene was taken into account the difference was no longer

statistically significant, suggesting that peripheral inflammation rather than generalised atherosclerosis accounted for the difference. However, levels of other markers of inflammation such as TNF, and IL-6 did remain significant predictors of outcome after logistic regression accounting for the presence of gangrene. Outcome was not significantly affected by surgical intervention although there was a trend to poorer prognosis in those patients who did not receive operative treatment.

Vainas et al (2005) conducted a study hypothesising that CRP was not only a marker of atherogenesis but actively participated in the process. Using reverse transcription–polymerase chain reaction analysis they showed that CRP was produced by, and found in femoral plaques but not in healthy brachial arteries. This particular study also analysed the association between CRP and various outcome measures. Some 136 of the 387 patients fulfilled the combined end-point of cardiovascular event (cerebral, coronary, peripheral) or death. Although CRP concentrations in the upper tertiles were not associated with any single end-point they were significantly associated with this combined end-point ($p=0.02$ using chi squared test for trend). CRP was also inversely associated with the ABPI. The study had an exclusive design with all patients having a CRP of greater than 10mg/l being excluded. However the association between CRP concentration and individual end-points was poor. In fact, patients with an intermediate CRP were more likely to suffer a coronary (12 vs.10) or peripheral (28 vs. 25) event. In addition there was only one more combined event in the high CRP group compared with the intermediate group (52 vs. 51). The novel finding that CRP is produced by femoral plaques is however noteworthy.

1.3.6 Transthoracic echocardiography (TTE) and resting left ventricular ejection fraction

TTE is commonly used in pre-operative cardiac risk assessment. It can deliver information on global and regional ventricular function as well as valvular abnormalities, and avoids the need for intravenous injections or exposure to radiation. It has been found to provide independent information about the risk of post-operative cardiac complications (Rohde et al. 2001) although the extent of its predictive ability has varied between studies. Halm et al (1996) studied a prospective cohort of 339 male veterans who underwent echocardiography prior to non-cardiac surgery. Clinicians were blinded to TTE results and patients were screened post-operatively for cardiac events. The best performing cut-off was a left ventricular ejection fraction (LVEF) of less than 40%. Some 65 patients had an adverse cardiac outcome and an LVEF of less than 40% was a significant predictor of cardiac events which were three times more likely in this group. However, the outcome measures of congestive cardiac failure (CCF) and in particular ventricular tachycardia (commonly unsustained) were subjective and of questionable clinical relevance. There were 10 ischaemic events (cardiac death, MI and unstable angina) and no echocardiographic measurement was predictive of these, the most objective and clinically important outcomes. On further analysis, adding echocardiographic variables to existing clinical models led to an improvement in positive predictive value (50%-73%) but no change in the negative predictive value for all cardiac events.

Other investigators have had similar results. McEnroe et al (1990) studied 59 patients undergoing abdominal aortic aneurysm repair. In this retrospective study all post operative ischaemic events occurred in patients with an ejection fraction of greater

than 50%. Takase et al (1993) studied 53 patients undergoing non-vascular surgery. Although reduced ejection fraction was predictive of peri-operative pulmonary oedema, it was not of benefit in the detection of myocardial infarction or cardiac death. Mamode et al (2001) also found ejection fraction to be a poor predictor of cardiac outcome in their study of 297 patients. More recently, in their study of 207 patients scheduled for aortic aneurysm surgery, Crow and colleagues found that reduced left-ventricular ejection fraction did not correlate with cardiac morbidity or mortality (Crow et al. 2004). The study also demonstrated that measurement of ejection fraction did not influence the decision of whether or not to proceed with the proposed surgery as in only one patient was the management plan altered as a result of TTE results.

In contrast some authors have found TTE to be a useful tool in predicting peri-operative cardiac risk. In 2001 Rohde et al (2001) studied 570 patients who had undergone TTE within three months of major non-cardiac surgery. The collection of pre-operative information and analysis of post-operative clinical data was conducted prospectively by clinicians blinded to echocardiographic data, however the information derived from echocardiography was retrospectively abstracted from letters sent to general practitioners. There were multiple study end-points (MI, pulmonary oedema, ventricular fibrillation, cardiopulmonary arrest, complete heart block) for which screening was conducted. The authors found that documentation of systolic dysfunction was a significant predictor of both MI and pulmonary oedema. In addition, systolic dysfunction and moderate to severe left ventricular hypertrophy were independent predictors of major cardiac events. Risk assessment models which included TTE data performed significantly better than those containing clinical

information alone (area under ROC curve, 0.73 vs. 0.68; $p<0.05$). However, although the presence of TTE-detected left ventricular systolic dysfunction had a negative predictive value (NPV) of 94% it only had a positive predictive value (PPV) of 13%. There were other limitations in the study protocol: TTE data may have been unreliable due to the retrospective data collection and source; the study population was highly selected (those patients in whom a pre-operative echo had been deemed clinically necessary); and treating clinicians had access to TTE data which could have resulted in treatment bias.

Kontos et al (1996) prospectively studied 87 patients who underwent TTE prior to major non-cardiac surgery. An ejection fraction of less than 50% had a PPV of 43% and an NPV of 97% for cardiac events, outperforming dipyridamole thallium scanning (DTS) which was also analysed in this study. In multivariate analysis a reduced ejection fraction was the only significant predictor of events. Despite the fact that the numbers analysed in this study were small, the population was highly selected and although clinicians were not blinded to TTE results, the study was well designed. It was prospective, the end points (MI, cardiac death, pre-operative revascularisation) were objective and post-operative screening was conducted. Rossi et al (1998) have also found reduced LVEF to be significantly predictive of early and late cardiac events. In this study a reduced LVEF had a PPV of 26% and an NPV of 93% for early cardiac events. However these results are difficult to interpret due to the small numbers involved (n= 97), the fact that the majority of patients did not undergo an open surgical procedure (73% underwent an endovascular procedure), and poor definition of end-points, which included myocardial ischaemia, pulmonary oedema and ventricular tachyarrhythmias.

1.3.7 Cardiac stress testing

In an effort to recreate the physiological burden placed on the body by surgery, cardiac stress testing has been utilized in peri-operative risk stratification. Dipyridamole-thallium scintigraphy (DTS) and dobutamine stress echocardiography (DSE) are the methods most commonly used.

Dipyridamole thallium scanning

DTS involves artificially increasing myocardial perfusion using dipyridamole, followed by thallium imaging which allows defects in the myocardial image to be detected. Reversible defects (those not present at rest) indicate myocardium at risk of ischaemia. Eagle et al (1989) were among the first to analyse its potential. They studied 200 patients referred to a nuclear cardiology unit prior to vascular surgery and found a reversible perfusion defect to be a significant predictor of the combined end point of cardiac death and MI. Thirteen of the 15 patients who suffered a post-operative MI or cardiac death had a positive thallium scan. The test was most discriminatory in the group considered at moderate risk clinically (those fulfilling 1 or 2 of Eagle's clinical variables). Flaws in the study included both referral and treatment bias. The population was highly selected and study results were available to treating physicians. Some 44 patients had their surgery either cancelled or postponed following evaluation. Although the end points considered were objective, the definition of cardiac death was non-specific, defined as any sudden post-operative death. More recently Mamode et al (2001) have found DTS to be an accurate predictor of cardiac events adding significant discriminatory information to clinical data alone. Although their study of 297 vascular surgical patients was flawed (with

the inclusion of non-consecutive patients and lack of blinding to DTS data) it showed after multivariate analysis that a reversible defect on DTS had an odds ratio (OR) of 13.6 (3.7-50.8) for the fulfilment of the combined end point of cardiac death and myocardial infarction. The test also had a sensitivity of 38% for the prediction of cardiac events.

Mangano et al (1991) conducted a study of 60 vascular surgical patients who had undergone DTS. They did not find any correlation between a perfusion defect on DTS and adverse outcome, and 7 of the 13 post-operative events occurred in patients with no perfusion defect. The study was prospective, triple blinded and the end points were clearly defined and objective. However it suffered from small numbers with only 60 patients and 13 adverse events. Consecutive patients were enrolled but the study design was highly exclusive with patients having unstable heart disease, pacemakers or ECG abnormalities being excluded.

Baron et al (1994) studied a cohort of 457 patients undergoing abdominal aortic surgery. They found that DTS was of little benefit in predicting peri-operative cardiac morbidity and that a definite history of ischaemic heart disease and age over 65 were the most important predictors of an event. A reversible perfusion defect on DTS was not a predictor of any cardiac event by either univariate or multivariate analysis, and only 31 of the 160 patients with a reversible perfusion defect experienced a post-operative cardiac event. Consecutive patients were enrolled; however clinicians were not blinded to DTS results with a consequent potential treatment bias. Although ventricular tachyarrhythmias and prolonged myocardial ischaemia were considered in

the combined end point, more objective end points such as cardiac death were analysed separately and also found not to correlate with DTS data.

Shaw et al (1996) conducted a systematic review of published reports on dipyridamole thallium scanning in the 10 years from 1985. Ten studies of appropriate quality were identified giving a total population of 1994 vascular surgery patients. Using the objective end points of cardiac death and MI, 1% of patients with no perfusion defect had an event compared with 9% of patients who had a reversible defect. This difference was statistically significant. The OR for prediction of a cardiac event was 3.9. Five studies included in the review utilised multivariate analysis and showed a reversible perfusion defect on DTS to be the single best predictor of events. However, only 4 of the studies were blinded which led to 6% of patients having surgery cancelled, 20% undergoing coronary angiography and 5% of patients undergoing pre-operative coronary revascularisation. The influence of publication bias may also have contributed to the number of papers citing positive results.

More recently, imaging has been performed using technetium-99m single photon emission computed tomography (SPECT) following dipyridamole infusion. Cohen et al (2003) retrospectively analysed its predictive potential in 153 patients undergoing elective vascular surgery. There were 16 post-operative events, and whilst none of these occurred in patients with a normal scan, neither fixed nor reversible defects were significantly predictive of outcome. In fact, no increased risk was conferred by the presence of a reversible defect (RR=1). However the study was limited by lack of blinding, poor definition of end-points, and a low event rate. Nine patients underwent coronary angiography and 1 proceeded to coronary angioplasty prior to surgery as a

result of SPECT data. Unstable angina and heart failure were used as end points and there was no differentiation of cardiac and non-cardiac death.

Dobutamine stress echocardiography (DSE)

In DSE, dobutamine is used to increase myocardial oxygen consumption, "stressing" the heart. The heart is imaged using TTE before and after the stress with wall motion defects being recorded. New wall motion abnormalities (NWMAs) indicate myocardium at risk of infarction. DSE is accurate in the detection of significant coronary artery disease (Cohen et al. 1991;Sawada et al. 1991) and has been advocated as a useful technique for pre-operative risk stratification. However it is expensive (although less so than thallium scanning), time-consuming and is not universally available in the United Kingdom.

Poldermans et al (1993) studied 131 consecutive patients undergoing vascular surgery and found DSE to be a practical and safe method of stratifying cardiac risk. It had an NPV of 100% and a PPV of 42% for the detection of cardiac events. Inducible ischaemia on DSE, and age over 70 were the only 2 independent predictors of an event. The study was prospective and blinded, however 10 of the 15 post-operative cardiac complications were subjective in definition (CCF and unstable angina). In an extension of this study published in 1995 involving a population of 302 patients, the value of DSE was further emphasised (Poldermans et al. 1995). All 27 patients suffering a cardiac event had NWMAs on TTE. A positive result on DSE had an OR of 124 and was the only factor found to be a significant predictor of post-operative cardiac events on multivariate analysis. The PPV was 38%. Interestingly neither ventricular dysrhythmias nor CCF were employed as end points in this study and a

greater proportion of patients (17 of 27) fulfilled the objective end points of cardiac death and non fatal MI.

Das et al (2000) retrospectively studied 530 patients having non-vascular surgery who had previously undergone DSE without subsequent intervention. Inducible ischaemia had an NPV of 100% and a PPV of 15% for a cardiac event. An ischaemic threshold of less than 60% of age-predicted maximum heart rate added discriminatory information. DSE data provided incremental risk prediction at each level of the clinically based (Eagle's index) risk assessment. Although the end points in this study (non fatal MI and cardiac death) were objective, the study suffered from selection bias with the inclusion of only those patients thought to require DSE on clinical grounds. This resulted in an exceptionally high risk group, 30% of whom had suffered an MI in the past and only 29% of whom had a normal pre-operative ECG. There was no blinding; therefore treatment bias may have influenced results. In addition patients who had undergone coronary revascularisation as a result of a positive test were excluded from the retrospective analysis. Furthermore, post-operative screening for cardiac events was inconsistent with only 60% of patients undergoing routine testing following surgery.

In 1998, in their study of 103 patients undergoing lower limb revascularisation, Rossi et al (1998) found that combining resting and stress echocardiography achieved a NPV of 100% for the detection of cardiac events The PPV was 25%. Stress echocardiography alone had an NPV of 94% and a PPV of 25%. Reduced LVEF and positive stress echocardiography were the only significant predictors of peri-operative cardiac events. However 73% of patients in the study underwent endovascular

procedures and so were at low risk of peri-operative cardiac events. In addition only two patients fulfilled the objective end-points of cardiac death or MI; the remainder of the linked events being CCF, myocardial ischaemia and tachyarrhythmias; subjective end-points which were not defined and of limited prognostic significance. A continuous cohort of patients was not studied and physicians were not blinded to research data.

Boersma et al (2001) studied a cohort of 1351 patients undergoing major vascular surgery. Some 1097 underwent DSE preoperatively and 360 received beta blocker therapy. There were 31 cardiac deaths and 14 non-fatal MI's. The presence of NWMAs on DSE was predictive of peri-operative cardiac events (13.5% vs. 1.6%) and the extent of stress-induced ischaemia also added prognostic information. In multivariate analysis, the presence of NWMAs was the most important predictor of cardiac events. DSE data significantly improved the predictive ability of clinical data alone but were of most help in patients with a RCRI score of greater than 3. The study was well designed with objective end points and clear methodology but was limited by its retrospective nature; nonetheless it provides strong evidence supporting the use of DSE in peri-operative cardiac risk stratification. Kertai et al (2003b) later studied the same cohort of patients and showed that dobutamine-induced ischaemia was a significant predictor of late cardiac complications. In this retrospective study of the 1286 patients who had survived 30 days post-operatively after vascular surgery, 15.5% of patients with stress induced ischaemia suffered a cardiac event compared to 4.9% of those without. In multivariate analysis the presence of stress-induced ischaemia proved to be the most important factor in predicting cardiac events.

Furthermore the greater the extent of the stress- induced ischaemia the greater the likelihood there was of a cardiac event.

Pathological studies have analysed the usefulness of DSE. Poldermans et al (2001) studied 32 patients who died within 30 days of vascular surgery having undergone DSE prior to the procedure. Only 17 patients were suspected of having died from a cardiac cause yet autopsy showed evidence of recent MI in 21, 9 of whom had evidence of infarction in more than 1 coronary artery territory. All 16 patients who had a positive pre-operative DSE suffered a death confirmed to be of cardiac origin. However DSE would have failed to identify the remaining 5 patients with acute MI confirmed on autopsy. In addition 9 of the 16 patients had evidence of infarct in an area not shown to have NWMAs at DSE.

In meta-analysis DSE has outperformed 5 other diagnostic tests (ambulatory electrocardiography, exercise electrocardiography, radionuclide ventriculography, myocardial perfusion scintigraphy, dipyridamole stress echocardiograph) in predicting cardiac events, although the difference was only significant over DTS (Kertai et al. 2003a). Some 8119 patients participated in the studies selected and the comparison between tests took account of differing study and clinical characteristics.

The subgroup of patients in whom DSE and other pre-operative investigations should be used remains uncertain. To address this, the American College of Cardiology and the American Heart Association produced an algorithm for the use of DSE in peri-operative risk stratification (Eagle et al. 1996). The guidelines have been widely endorsed despite the fact that there was inadequate data in the literature to support

many of the recommendations. More recently the cost-effectiveness of the use of DSE according to these guidelines has been questioned. Morgan et al (2002) reviewed some 14855 patients scheduled for elective surgery. The guidelines led to 85 of these patients undergoing DSE. The positive predictive value for selecting a positive DSE was only 4.7 % and none of these patients suffered any cardiac morbidity. This would suggest that the appropriate place for DSE in peri-operative assessment is still unknown, a conclusion supported by other studies which have found that the ACC/AHA guidelines overestimate the requirement for cardiac investigation (Falcone et al. 2003;Farid et al. 2002).

However, appropriate use of the guidelines has been shown to be of benefit in peri-operative assessment. Back et al (2003) studied 425 consecutive vascular patients. Using the ACC/AHA guidelines, 200 patients underwent cardiac stress imaging leading to 78 patients undergoing coronary angiography. 15 patients underwent subsequent coronary intervention. Based on the results of the above investigations and interventions, the patients were placed into appropriate risk categories. The overall cardiac event rate was low (4.8%) at 30 days and those patients judged to be at high risk by the guidelines had a significantly higher event rate (11.9%) than those placed into lower risk categories (2.8% and 4%). The guidelines however were unable to differentiate between patients in the low (4% event rate) and intermediate (2.8% event rate) risk categories. The methodology of the study was clear and consecutive patients were enrolled. However multiple subjective end points (unstable angina, heart failure, arrhythmias) of limited prognostic value were studied. Despite this the study does show that a low event rate can be achieved in a relatively high risk population using the guidelines. However many patients underwent unnecessary investigation in the

process, again suggesting that the role of DSE in pre-operative assessment remains unclear.

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing (CPX) is a non-invasive test used for the assessment of cardiac and respiratory function. It measures oxygen uptake at increasing intensities of work and objectively determines cardiopulmonary performance. It is normally performed on a bicycle ergometer using respiratory gas analysis and an electrocardiogram. Both the exercise anaerobic threshold and the ventilatory equivalent for carbon dioxide (VE/VCO_2) can be determined at cardiopulmonary exercise testing.

In 2 separate studies Older et al. have demonstrated that an exercise anaerobic threshold of less than 11 ml/min/kg significantly predicts postoperative survival (Older et al. 1993;Older, Hall, & Hader 1999). The most recent publication, studied 548 patients undergoing major intra-abdominal surgery. Nine patients died of cardiopulmonary causes post-operatively and of these 7 had an anaerobic threshold of less than 11ml/min/kg.

Carlisle et al. evaluated CPX in 130 patients who underwent abdominal aortic aneurysm repair (Carlisle & Swart 2007). They demonstrated that both VE/VCO2 and anaerobic threshold were significantly predictive of long-term survival. At a median follow-up of 33 months, survival was 55 per cent for the 30 patients judged unfit by CPX, compared with 97 per cent for the 100 patients judged fit ($P < 0.001$).

However CPX is unsuitable for patients with critical limb ischaemia in whom claudication is likely to limit exercise capacity. Patients whose surgery is urgent rather than elective would also be unlikely to be able to access CPX due to logistics. Furthermore CPX has not proven beneficial in predicting post-operative cardiopulmonary morbidity in procedures such as oesophagectomy (Forshaw et al. 2008).

1.4 Preventing peri-operative cardiac morbidity: the benefit of perioperative risk stratification

The assignment of patients to different categories of peri-operative cardiac risk may be of benefit. Patients judged to be at low risk can have their surgery expedited with no requirement for further time-consuming or costly investigations. If patients are judged to be at high risk, various options exist. In some cases postponement or cancellation of the procedure may be appropriate. For example it may be inappropriate to operate on a 5.5cm aortic aneurysm in an elderly gentleman with unstable angina. However, in some cases, surgery may be deemed necessary. In this event, efforts should be directed at reducing the associated perceived cardiac risk. This could involve alterations in the pre-, intra- or post-operative management. Pre-operative coronary intervention (Eagle et al. 1997) and prescription of appropriate cardiac medications (Poldermans et al. 1999) have both been shown to influence cardiac risk. Anaesthetic techniques such as the use of thoracic epidurals can reduce morbidity (Beattie et al. 2003). In some cases it may even be possible to perform a surgical procedure with lower associated risk. Post-operatively, increased intensity of care such as in a high dependency unit might also be of benefit.

1.4.1 Coronary Revascularisation

Pre-operative coronary revascularisation can be conducted using both open and percutaneous methods. It may be done prophylactically or in selected patients. Eagle et al (1997) retrospectively studied 3368 patients who had undergone non-cardiac surgery in the Coronary Artery Surgery Study registry. Patients in this population had documented coronary artery disease and had received either best medical treatment or coronary revascularisation depending on physician and patient preference. Some 1961 patients who had undergone a high risk surgical procedure were included. Coronary revascularisation prior to surgery significantly reduced the rate of MI (0.8% vs. 2.7%) and of death (1.7% vs. 3.3%). Patients with more severe coronary disease were shown to derive most benefit. The effect of coronary surgery was maintained after adjustment for other risk factors with an OR of 2.5 (1.41-4.46). However, recruitment for the study began in 1974 so its applicability to present practice is questionable. In addition the demographics of the two groups were not compared and patients were not randomised to medical therapy or surgery. The main failing of the study however was its failure to take into account intention to treat. Cardiac surgery has significant morbidity and patients who suffered any complication of this surgery were invariably excluded from the analysis.

Fleischer et al (1999) studied a retrospective cohort of 6895 patients undergoing elective vascular surgery. In the subgroup of 2865 patients undergoing aortic surgery it was found that those who had undergone stress testing, with or without coronary revascularisation had significantly lower 30 day mortality (3.8% vs. 9%). Patients who had undergone coronary revascularisation following stress testing had the lowest peri-operative mortality (2.8%), although unfortunately no information was available

on mortality from the coronary artery revascularisation itself. Neither stress testing nor pre-operative revascularisation affected the peri-operative mortality in those patients undergoing infrainguinal procedures. Limitations of the study include the high overall 30 day mortality of 7.3%, disregard for potential clinical confounding factors and the retrospective nature which led to problems with data retrieval. In addition, no attempt was made to differentiate between cardiac and noncardiac causes of death.

Landesberg et al (2003) examined the efficacy of non-invasive testing and subsequent coronary revascularisation in patients undergoing major vascular surgery. All 407 patients included had undergone DTS preoperatively and patients with moderate – severe reversible defects or at high clinical risk were referred for coronary angiography and subsequent percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) as appropriate. For analysis, patients were placed into four groups: those with no defects or mild defects; those with fixed defects; those with reversible defects who did not undergo revascularisation and those with reversible defects who did undergo revascularisation. Patients who suffered morbidity from coronary revascularisation but did not undergo surgery were included in the final group. Patients were followed up for a period of 55 months (18-138). The presence of a moderate to severe reversible perfusion defect on DTS predicted poorer survival rates. Pre-operative coronary revascularisation independently improved long term survival, although the difference did not become significant until 5 years follow-up. Five year survival was 38% in those patients with reversible perfusion defects who had not undergone revascularisation compared with 62% in those who had. There was a trend towards better survival in the 36 patients who underwent CABG

compared with the 38 undergoing PTCA. The principal limitation of the study was its retrospective nature. The decision to revascularise patients with reversible ischaemia was made on clinical grounds and it is likely that the factors making patients unsuitable for revascularisation, for example the need for urgent surgery, may have had some impact on the reduced 5-year survival. The authors attempted to compensate for this using propensity analyses and although there was no significant difference between the two groups, it should be noted that only background factors included in the study were accounted for, with neither the type nor the urgency of surgery included.

In an attempt to clarify the issue of prophylactic coronary artery revascularisation a randomised controlled trial was conducted (McFalls et al. 2004). Patients scheduled for elective vascular surgery and judged to be at increased risk of a peri-operative cardiac event by a consultant cardiologist were referred for coronary angiography. Patients with coronary arteries suitable for intervention were randomised using a stratified process and underwent the planned vascular procedure with or without prior coronary revascularisation. Of the 258 patients assigned to coronary intervention, 99 underwent CABG, and 141 underwent PTCA. Eighteen did not undergo preoperative revascularisation due to patient choice (9), the need for urgent vascular surgery (8), or illness (1). Nine of the 252 patients scheduled to undergo surgery with no revascularisation required coronary intervention due to unstable cardiac disease. Seven of these subsequently underwent vascular surgery. Pre-operative revascularisation led to a significant delay in vascular surgery and in this group there were 10 deaths prior to vascular surgery compared with only 1 in the no-revascularisation group. There was no significant difference in the 30-day mortality,

or in the rate of peri-operative myocardial infarction of those patients who survived to undergo vascular surgery. At a median follow-up of 2.7 years, mortality in those patients assigned to revascularisation was 22% compared with 23% in those who were not. When actual treatment received was analysed, mortality was also 22% in the revascularisation group and 23% in the no-revascularisation group. The study was adequately powered and the end-points were objective. The committee validating all outcomes was blinded to coronary intervention. Although treating clinicians were not blinded, there were no obvious differences in peri-operative management. There were no significant differences in clinical variables between the groups; although 12% of those patients randomised to revascularisation had a previous history of heart failure compared with 7.5% of those who solely underwent vascular surgery. Heart failure is one of the most important predictors of peri-operative events and this difference may have influenced outcome. This however should not detract from the conclusion that prophylactic revascularisation showed no benefit prior to elective vascular surgery in this cohort of patients.

1.4.2 Beta Blockers

The beneficial role of beta blockers has previously been established in hypertension, acute coronary syndromes and heart failure, and it is believed that peri-operative beta-blockade may reduce the cardiac morbidity associated with surgery. Beta blockers increase diastolic perfusion time and reduce cardiac oxygen demand by decreasing heart rate and contractility. They have potent anti-arrhythmic effects, particularly in the setting of acute ischaemia and have been shown to have an anaesthetic sparing effect. They may also influence atherosclerotic plaque instability by reducing shear stress (London et al. 2004;Ohtsuka et al. 2001).

In 1996 Mangano et al (1996) published the findings of a randomised, double-blinded controlled trial of patients at risk of coronary artery disease undergoing non-cardiac surgery which found that the peri-operative prescription of atenolol significantly reduced post-operative ischaemia and mortality. Two hundred patients were prospectively enrolled and at two year follow-up there were 21 deaths and 32 cardiac events in the placebo group compared with 12 deaths and 16 cardiac events in the atenolol group. Event-free survival throughout the two-year study period was 68 percent in the placebo group and 83 percent in the atenolol group (P=0.008). The protective effect principally came from a reduction of cardiac events in the first 6 months after discharge. A statistician was consulted regarding numbers for the trial, the end-points were clear, and follow-up to two years was almost complete. However although the randomisation process was computerised, it was not stratified leading to some inequalities between group; for example the number of patients in the atenolol group prescribed anti-hypertensive agents was significantly greater than that in the placebo group suggesting that this group may have been better optimised. The incidence of definite coronary artery disease, previous MI and the presence of typical angina were also higher in the placebo group although not significantly so, making these patients more susceptible to cardiac morbidity. A further flaw was that those 6 patients who died in hospital were excluded from analysis. Four of these occurred in the atenolol group and although only one was of cardiac origin, if these results are included, the difference in all-cause mortality between the groups would no longer reach statistical significance. In addition some 8 patients in the placebo group regularly took beta blockers. This may have influenced the results as the withdrawal of established beta-blocker therapy is likely to have compromised the patient's

cardiac status. Nevertheless there was a 55% decrease in overall mortality and a 65% reduction in cardiac death in the atenolol group and this effect is unlikely to have solely been due to differences between the two populations, particularly as multivariate analysis revealed that the presence of diabetes and the prescription of atenolol were the only significant predictors of poor outcome.

The other early randomised controlled trial of peri-operative beta-blockade, in this case with bisoprolol, was conducted by Poldermans et al (1999). Included were 112 patients undergoing major vascular surgery with a positive result on DSE, and investigators found that those patients randomised to receive oral bisoprolol had a reduced peri-operative cardiac event rate. Some 35% of patients in the standard care group suffered either a cardiac death or a non fatal MI within 30 days of the procedure compared with 3.4 % in the bisoprolol group. Randomisation was carried out using a computer programme and this resulted in there being only minor differences between the groups. However the study design had some flaws: clinicians were not blinded to patients grouping; 4 patients in the placebo group received beta blockers; and the study was terminated after only 100 patients had been recruited despite an earlier power calculation recommending that 266 were required. The 35% event rate in the placebo group was also unusually high and the relevance of this highly selected study population to the general setting could be questioned. Despite these problems with the study protocol, the large difference in event rates would support the protective value of beta blockers suggested by Mangano and colleagues.

Boersma et al (2001) retrospectively studied 1351 patients undergoing major vascular surgery, 360 of whom were prescribed beta blockers. Of these, 301 were on long term

beta blockers, with the remaining 59 having been randomised to receive treatment as part of an earlier study (Poldermans et al. 1999). Patients receiving beta blockers generally had a worse risk profile, significantly more having a history of hypertension and ischaemic heart disease. Despite this they had a significantly lower 30 day cardiac event rate, although exact figures for the whole cohort are not available. The protective effect of beta blockers was most apparent in patients with NWMAs on DSE, with those prescribed beta-blockers having a cardiac event rate of 4.7% compared with 31.5% in those not. Although a difference was also seen in low risk patients it was not as marked. Problems with this study included the heterogeneous population (patients randomised to treatment, and those previously receiving beta blockers were all included), failure to blind physicians to DSE data or beta blocker usage, and the definition of end points. Although only cardiac death and non-fatal MI were considered, the number of deaths of cardiac origin was probably overestimated as all fatalities were included unless there was explicit evidence of a non-cardiac cause. Kertai et al (2003b) studied the same cohort of patients, following up those 1286 patients who had survived 30 days after vascular surgery to assess the long term benefits of beta blockade. In this group 370 (29%) patients received beta blockers. The median follow-up period was 23 months and patients receiving beta blockers had a marginally higher event rate than those not, although this was not significant. However the result may have been influenced by differences in clinical characteristics as patients on beta blockers had a greater incidence of ischaemic heart disease and of heart failure. In multivariate analysis, patients on beta blockers had a lower likelihood of events although again this was not significant. The only group of patients to have a significantly reduced cardiac event rate when prescribed beta blockers were those with stress-inducible ischaemia on DSE. However this observed influence could be

attributable to treatment bias as physicians were not blinded to beta blocker prescription. In fact patients on beta blockers received more intense follow-up being seen at clinic every 3 months for dosage monitoring. The study also had other problems with its methodology: 59 patients had been randomised to beta blockers whereas the remaining 301 were previously on long term treatment; 24 patients were only prescribed beta blockers post-operatively but were still included in the treatment group; and 12 patients who had undergone coronary revascularisation post-operatively were also included despite this potential influence on outcome. In their study, Lee et al (1999) found that patients taking beta blockers on admission to hospital had a similar cardiac event rate to those not. Some 13 of 533 (2.4%) patients on beta blockers suffered a cardiac event compared with 43 of 2360 (1.8%) who were not. Although it was not analysed, it is likely that those patients prescribed beta blockers were more likely to have risk factors for coronary artery disease which may have influenced results.

Stevens et al (2003) pooled data on eleven randomised-controlled trials assessing the myocardial protective effects of beta blockers in patients undergoing non-cardiac surgery. Inclusion criteria and strategy for literature review were clearly set out with the last search being conducted in November 2002. No data were analysed beyond a follow-up of 1 month after surgery. Beta blockers decreased ischaemic events during (7.6% vs. 20.2%), and after (15.2% vs. 27.9%) surgery. Their use reduced the risk of myocardial infarction (0.9% vs. 5.2%) and cardiac death (0.8% vs. 3.9%). There was a correlation between the pre-study prevalence of MI and the magnitude of risk reduction. However, the results were somewhat biased by the significant findings of a few papers. When the two studies involving the highest risk patients and highest event

rates were excluded, beta blockers no longer significantly reduced the risk of MI. When the study by Poldermans et al (1999) was excluded from the 8 studies reporting cardiac death, then the protective effect of beta blockers was also no longer significant. Bradycardia was the commonest adverse event related to beta blockers, occurring in 24.5% of treated patients compared with 9.1% of controls. Hypotension, atrio-ventricular block and pulmonary oedema were reported more frequently in patients on beta blockers but the differences were not significant. In quantitative terms, for every 100 patients prescribed beta blockers, 4 post-operative MIs and 3 cardiac deaths were prevented. However the studies included were heterogeneous in quality and different beta blockers and treatment regimens were used. Length of maintenance of the therapy also varied. There may also have been a temporal effect due to the inclusion of studies conducted as early as 1980. This is important since methods of anaesthesia and detection of post-operative events have changed over this period. In addition there was no standard definition of end points between the studies.

Despite the early evidence supporting the protective effects of beta blockers, there is still a reluctance to prescribe them in the peri-operative setting, as illustrated by a recent survey of Canadian anaesthetists (VanDenKerkhof et al. 2003). Although 95% of the 569 respondents were aware of the literature and 93% felt that beta blockers were of benefit in patients with CAD only 57% always or usually used beta blockers. The poor response rate (54%) and the selected study population (members of the Canadian Anaesthesiology Society) probably mean that actual figures are lower. In fact a recent meta-analysis has questioned the protective role of beta blockers, suggesting that the current evidence is too unreliable to allow any definite conclusions to be drawn (Devereaux et al. 2005). Despite this statement, the paper which included

data from 22 randomised control trials found a statistically significant beneficial relative risk of 0.44 (95% confidence interval 0.20 to 0.97) for the composite outcome of cardiovascular mortality, non-fatal myocardial infarction, and non-fatal cardiac arrest. No significant benefit was found for any individual end-point; however this could be attributed to the inclusion of all randomised controlled trials in non-cardiac surgery which led to an extremely heterogeneous population. Studies conducted as early as 1980 were included, as were those reporting on low risk populations such as those undergoing day case surgery or even dental extraction.

1.4.4 Statins

Inhibitors of the enzyme reductase of the hydroxymethylglutaryl-coenzyme A (HMG CoA) or "statins" decrease cardiac events and increase survival in patients with hypercholesterolaemia who have either established, or are at high risk for coronary artery disease (CAD). They are pleiotropic agents, which in addition to lowering cholesterol have a modulatory effect on endothelial function, inflammation and thrombosis (Vaughan et al. 2000). Poldermans et al (2003) performed a retrospective case-control study on 2816 patients undergoing major vascular surgery between 1991 and 2000. Case patients were the 160 who had died in hospital following surgery. Two controls for each case were chosen, one of whom had been operated upon immediately prior to the case and one of whom was operated on afterwards. There was a significant difference in statin usage between groups. 12 (8%) of cases received statins preoperatively compared with 81 (25%) of controls and the adjusted odds ratio for comparison of mortality between the groups was 0.22 (95% confidence interval 0.10-0.47). However, although the reduction in risk associated with statin use was maintained in sub-group analysis, confounding factors may have been responsible for

the significant difference noted as relevant clinical details such as a history of COPD were not included. In addition, beta blocker usage was significantly less common in cases than controls. This may be partly responsible for the case group's poor outcome given the potential protective effects of beta blockers. The study was also retrospective and the potential for observer bias may limit the significance of its findings.

Kertai et al (2004a) retrospectively studied 570 elective abdominal aortic aneurysm patients and found that the pre-operative prescription of statins independently reduced the risk of cardiac events and peri-operative mortality. Some 3.7% of patients prescribed statins had an event compared with 11% not prescribed the medication. The relationship was strongest in patients with a RCRI score of greater than two. Although the study was retrospective, researchers were blinded to outcome and multivariate analysis was conducted using the RCRI. However this does not take into account some of the important differences between the groups, for example, patients using statins were significantly younger and were more likely to have been prescribed other cardiac medications. Although they were also more likely to have suffered a previous MI, significantly more of the patients on statins had undergone prior coronary revascularisation. The effect of statins could therefore have been influenced by better pre-operative optimisation in these patients. In addition several different statins were used throughout the study and no information was available as to whether statin use had been continued throughout the peri-operative period.

In a retrospective study of 997 patients undergoing vascular surgery, O'Neill-Callaghan et al (2005) found that statins reduced the incidence of cardiac morbidity.

Some 9% of the 526 patients on statins had an event compared with 16.5% of patients not on statins (OR=0.56, p=0.001) and the propensity for a reduction in cardiac events remained after multivariate analysis. The study was well designed: a power calculation was used to determine the population size and there was quality control of the case-note review. However myocardial ischaemia, CCF and ventricular tachyarrhythmias were included as primary end points. When only objective end points such as death and acute MI were included, the benefit from statin usage was no longer statistically significant.

One randomised trial has been conducted assessing the effects of statins (in this case atorvastatin) on the occurrence of a 6-month composite of cardiovascular events (cardiac death, non-fatal MI, unstable angina, stroke) following vascular surgery (Durazzo et al. 2004). The study was double blinded and its design exclusive with 127 patients being judged ineligible. Some 50 patients were randomised to each group with 3 of those randomised to statin therapy being non-compliant. Data was analysed on an intention to treat basis. The atorvastatin group demonstrated a significantly lower cardiac event rate over the 6-month period with 4 events in this group compared with 13 in the placebo (p=0.022). There were no significant differences in the case-mix of the 2 groups and although only 90 of the patients subsequently underwent surgery the event rate remained significantly lower if patients were prescribed atorvastatin.

1.4.5 Method of Anaesthesia

Anaesthetic technique may influence the cardiac risk associated with surgery. The use of epidural anaesthesia and analgesia is thought to reduce cardiac stress through

systemic and coronary vasodilatation and a consequent reduction in cardiac pre-load. The improved post-operative analgesia provided reduces post-operative stress and hypertension.

Beattie et al (2003) conducted a meta-analysis investigating the effects of post-operative epidural analgesia on cardiac event rates. Eleven randomised controlled trials comparing post-operative epidural analgesia with other forms of parenteral analgesia were identified up until December 1998. A total of 1173 patients undergoing a variety of peripheral vascular and intra-abdominal procedures were studied. The group of patients receiving epidural analgesia had a significantly lower rate of post-operative myocardial infarction with a difference of 3.8% (p=0.049). The epidural group also had fewer deaths (rate difference 1.3%) although the difference was not statistically significant. (p=0.091). Sub-group analysis of those patients receiving post-operative thoracic epidural analgesia showed a post-operative MI rate reduction of 5.3% (p=0.04). There were no statistically significant differences in co-morbidity between groups; in fact more patients in the epidural group had a history of cardiac disease or COPD. However when a single study, that by Yeager et al (1987), is excluded the difference in peri-operative myocardial infarction between the groups is no longer significant although there remains a trend to a decrease in MI. The study by Yeager et al was terminated early because of the magnitude of the difference in outcome between the two groups. However the study methods were poorly designed: no blinding was employed and the control group may have received suboptimal analgesia. Beattie et al have recently updated the results of their meta-analysis to include further randomised controlled trials. The use of thoracic epidural analgesia

continues to significantly reduce the rate of peri-operative MI with an OR of 0.6 and a p value of 0.03.

Park et al (2001) conducted a randomised controlled trial comparing epidural anaesthesia and post-operative analgesia with general anaesthetic and systemic opioid analgesia. They included patients undergoing aortic, gastric, biliary and colonic procedures. There were multiple exclusions and a stratified randomisation technique was used. Some 18 (3.6%) of the 507 patients randomised to the epidural group suffered a myocardial infarction compared with 27 (5.3%) of 507 in the general anaesthesia group. The difference was not statistically significant (p=0.21). There were no cases of post-operative angina in the epidural group and 5 in the general group. This difference approached significance (p=0.07). When subgroups were analysed it became clear that differences between the two groups were most apparent in patients who had undergone aortic procedures. In the 184 such patients who had been randomised to the epidural group there were 5 events, compared with 15 events in the 190 general anaesthesia patients. The difference was statistically significant despite the fact that those patients who received epidural anaesthesia were more likely to have risk factors for ischaemic heart disease. The methodology for the study was clear and important pre- and intra- operative variables were taken into account. The stratified randomisation technique led to a good balance of prognostic factors between groups. However, no blinding was used in the study and no account was taken of beta-blocker or statin usage. In addition the study may have been underpowered due to the lower than expected event rate. The lack of significant effect of epidural anaesthesia in the reduction of events observed may therefore be secondary to a type 2 error.

1.5 B-type Natriuretic Peptide (BNP)

In 1981 de Bold and colleagues made the seminal observation that infusion of extracts of atrial tissue into rats caused a copious natriuresis (de Bold et al. 1981). This led to the subsequent isolation and cloning of atrial natriuretic peptide (ANP), a factor with potent natriuretic, diuretic and vasorelaxant properties. In 1988 a peptide with similar properties was identified in the porcine brain and therefore named brain natriuretic peptide (Sudoh et al. 1988). Although present in the human brain, highest concentrations are in fact found in the cardiac ventricles. Since then, C-type natriuretic peptide, a third compound with similar structure and pharmacological spectrum has also been discovered (Sudoh et al. 1990). Plasma levels of CNP are very low in humans. All 3 peptides share a common 17-amino acid ring structure and play an important physiological role in countering the effects of hypertension and plasma volume expansion with their natriuretic and vasodilatory actions.

BNP is initially synthesised as preproBNP. This is first cleaved to proBNP and then to N-terminal-proBNP (NT-proBNP) and BNP in cardiac myocytes in response to atrial or ventricular stretch. Elevated levels of angiotensin 2 also stimulate secretion of BNP. The ventricle is the main site of BNP secretion (Mukoyama et al. 1991).

Three natriuretic receptors have been identified in humans. Type A and type B are guanylate cyclase receptors and both are present in the lung, kidneys and adrenal glands. The A receptor has a greater affinity for ANP than BNP and is most abundant in large blood vessels. The B receptor primarily binds CNP and is predominately found in the brain (Nakao et al. 1992). The C receptor is mainly involved in the clearance of peptides.

In the cardiovascular system the natriuretic peptides reduce sympathetic tone in the peripheral vasculature causing fluid shifts by increasing the permeability of the vascular endothelium and increase venous capacitance. These actions lead to a decrease in pre-load and blood pressure. In the kidney the glomerular filtration rate (GFR) is increased through a combination of dilation of the afferent renal arterioles, constriction of the efferent renal arterioles, and relaxation of the tubular mesangial cells. The peptides have a direct natriuretic effect in the renal tubules, but also cause a reduction in plasma renin and aldosterone concentrations (Hunt et al. 1996). In the brain stem, the natriuretic peptides serve to decrease sympathetic tone (Steele et al. 1991) and inhibit vasopressin secretion. Centrally there is suppression of thirst and salt appetite (Burrell et al. 1991).

BNP has a plasma half-life of 22 minutes (McCullough & Sandberg 2003), and its plasma concentration has been shown to have a direct relationship with changes in pulmonary artery wedge pressure over 2 hours (Kazanegra et al. 2001). Its concentration increases with age and is higher in women than in men. BNP is less affected by age and renal function than its precursor pro-BNP which can also be measured in plasma (McDonagh et al. 2004).

Plasma BNP is most commonly assayed using immunoradiometric techniques however different assays will have different normal ranges of BNP meaning that absolute BNP concentrations between studies should not be directly compared unless the same assay has been used.

Plasma BNP concentration is a sensitive and specific predictor of left –ventricular systolic dysfunction (LVD) and has been shown to have an important diagnostic role in patients with heart failure. McDonagh et al (1998) randomly selected 2000 people from the North Glasgow population using a 2-stage process. The group were sent a questionnaire and the respondents were invited to attend for blood sampling, electrocardiography and echocardiography. Some 1252 participants had analysable electrocardiograms, echocardiograms and available blood samples and 37 of these were found to have left-ventricular systolic dysfunction (ejection fraction<30%). The BNP concentration was significantly higher in those patients with left-ventricular systolic dysfunction than in those with normal function (24 vs. 7.7 pg/ml). In patients over 55, a BNP concentration of >17.9pg/ml predicted heart failure with a sensitivity of 92% and a specificity of 72%. In multivariate analysis an increase in BNP concentration of 50% was a strong independent predictor of LVD. BNP was a more accurate predictor of LVD than NT-ANP and displaced it in the multivariate model.

Cowie et al reported similar findings in their study of 122 patients referred to a rapid-access heart-failure clinic (Cowie et al. 1997). Using clinical, radiological and echocardiographic parameters, 35 patients were given a diagnosis of heart failure. BNP samples were available for 29 of these. The median BNP concentration was significantly higher in those patients with heart failure than those with another diagnosis (63.9 vs. 13.9 pmol/l). A BNP level of 22.2pmol/l had a sensitivity of 97% and a specificity of 84% for the prediction of heart failure. Addition of ANP or NT-ANP levels to a logistic regression model containing BNP concentration alone did not give any added value.

Renal function has also been shown to be an important determinant of BNP concentration with levels being inversely related to GFR (Mark et al. 2006;Vickery et al. 2005). GFR has been shown to be an independent determinant of plasma BNP and NT-pro BNP levels in patients with kidney disease (Vickery et al. 2005) and in fact one study has demonstrated that in patients with chronic kidney disease, GFR is a more important determinant of BNP than ventricular function (Mark et al. 2006).

BNP has been shown to be an important prognostic indicator. Using the cohort of patients that had been recruited to assess the role of natriuretic peptides in the prediction of LVD (McDonagh et al. 1998) the same authors assessed the long-term prognostic role of BNP concentration (McDonagh et al. 2001). Patients were followed up for 4 years and all-cause mortality was 4.9%. The median BNP concentration in those patients who died was significantly higher than in survivors (16.9 vs 7.8 pg/ml) and a BNP level of greater than 17.9pg/ml was an independent predictor of mortality in sub-group analysis. Interestingly those patients with preserved left ventricular function and an elevated BNP concentration still had a poor prognosis.

In another study analysing the prognosis of natriuretic peptides, Wang et al (2004a) studied a cohort of patients from the Framingham offspring study, excluding patients with a history of heart failure or biochemical renal impairment. BNP and NT-pro BNP concentration were measured in 3346 patients who were regularly monitored for the occurrence of cardiovascular outcomes or death. Follow-up was prospective and investigators were blinded to plasma natriuretic peptide levels. Median follow-up was 5.2 years. In multivariate analysis, increasing plasma natriuretic peptide levels were significantly associated with an elevated risk of death, stroke, first cardiovascular

event, atrial fibrillation and heart failure, the association being strongest with the last two. BNP tended to outperform NT-pro BNP in the prediction of events. There was however no association between natriuretic peptide levels and coronary heart disease events (MI, unstable angina).

1.6 BNP as a predictor of perioperative cardiac morbidity

When the present thesis was initiated, no researchers had as yet analysed the predictive value of BNP for peri-operative cardiac morbidity in non-cardiac surgery. However given the association identified in the literature regarding BNP concentration and cardiac outcome it was felt by the collaborating team that its measurement might be of use in peri-operative risk stratification. Furthermore, as serum BNP concentration is an accurate predictor of LVD (McDonagh et al. 1998) and the presence of heart failure has consistently been associated with increased peri-operative risk it was logical that BNP levels could correlate with post-operative outcome. In Goldman's cardiac index, clinical signs of heart failure were the most significant predictor of fatal cardiac complications (Goldman et al. 1977) and in Lee's RCRI a history of heart failure was a significant predictor of cardiac morbidity in both derivation and validation cohorts (Lee et al. 1999). In a meta-analysis by Shaw et al (1996) a history of heart failure was the second most significant predictor of poor cardiac outcome after the presence of a reversible perfusion defect on DTS.

However BNP is not merely reflective of LVD. It has been described as a marker of cardio-renal distress and in those patients with a raised BNP and no evidence of LVD, some structural or functional cardiac or renal abnormality has often been found (McDonagh et al. 2004). This may enhance its use as a predictor of operative

morbidity. In fact, in a small pilot study BNP has also been shown to be a predictor of ischaemia during DSE (Asada et al. 2004).

One prospective study has investigated the role of pre-operative BNP measurement in the prediction of peri-operative complications in cardiac surgery (Hutfless et al. 2004). Of 98 male patients undergoing open heart surgery, 32 suffered a post-operative cardiac complication, the majority of these being new arrhythmias. Although pre-operative BNP concentration was not associated with increased post-operative cardiac events or 30 day mortality, it was significantly higher in patients who subsequently required the use of an intra-aortic balloon pump, and was associated with length of hospital stay and one-year mortality. A pre-operative concentration of 385pg/ml was the best predictor of these events. Although this level showed excellent accuracy (79%-86%) and specificity (90%) it was not sensitive (32%-50%) and positive predictive values although not documented in the published paper were low. Weaknesses of the study included lack of blinding, inadequate information on the influence of other risk factors, and insufficient sample size to allow detection of differences in BNP levels for some of the end-points.

In 2005 Yeh et al (2005) analysed the utility of plasma NT-pro BNP levels in the prediction of cardiac complications after non-cardiac surgery. 190 patients were retrospectively studied and pre-operative NT-pro BNP levels were significantly higher in those patients who had a complication compared with those who did not (1215 vs.95 ng/l). Pre-operative NT-pro BNP concentration was the only independent predictor of outcome after multivariate analysis and a level of greater than 450ng/l had a 100% sensitivity and an 82.9% specificity of for the prediction of cardiac

events. It should be noted that the study was flawed, in that the population studied was heterogeneous (32 patients underwent minor surgery, and the remainder a major procedure), screening was not conducted for cardiac events, and no firm statistical guidance was involved in the study design. Furthermore, the selected end points were mostly subjective with limited clinical relevance. Only 4 patients fulfilled the objective end points of MI or cardiac death, the remainder suffering heart failure post-operatively, the definition of which was open to interpretation. In the logistic regression model ASA grade was used despite the fact that other clinical models have been shown to be more accurate in the prediction of cardiac events. No information was available on intra-operative details nor of medications prescribed to patients and this may have influenced outcome.

1.6 Aims of this thesis

Currently, no method of pre-operative cardiac risk prediction is sufficiently effective or practical to be of routine use.

In this thesis the author has therefore set out the following objectives:

1. To recruit a single hospital pilot cohort of consecutive patients undergoing major vascular surgery over a six-month time-period and determine whether pre-operative plasma B-type natriuretic peptide (BNP) concentration is associated with the occurrence of peri-operative myocardial infarction and cardiac death in this population. (Chapter 3)

2. To study cardiac event rates and BNP levels in the pilot study and calculate the population size required for a validation cohort to allow determination of a BNP level at which cardiac risk increased. To then recruit a cohort of consecutive patients undergoing major non-cardiac surgery (vascular surgery, laparotomy, and thoracotomy) in a single centre in order to determine whether pre-operative serum BNP concentration predicts the occurrence of peri-operative myocardial infarction and cardiac death in this wider setting. (Chapter 4)

3. To determine whether cardiac troponin I levels are commonly raised prior to major vascular surgery and if so whether they are associated with the occurrence of peri-operative myocardial infarction and cardiac death. (Chapter 5)

4. To determine whether pre-operative serum C-reactive protein levels are associated with the occurrence of peri-operative myocardial infarction and cardiac death in patients undergoing major vascular surgery. (Chapter 6)

2. Patients and Methods

2.1 Recruitment

All patients undergoing major non-cardiac 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 major general, vascular or urological surgery which was expected to require a hospital-stay of more than 2 days. 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.

2.2 Clinical details

Patients' clinical details were gathered prospectively and recorded on the study data-sheet on the day prior to surgery (appendix 2). These included basic demographic data and factors relating to cardiac risk of surgery: age; sex; smoking history; medical diagnoses of angina, myocardial infarction, heart failure, hypertension, chronic obstructive airways disease cerebrovascular disease, hyperlipidaemia and medically treated diabetes. All patients' current medications were noted.

2.3 Pre-operative testing

2.3.1 Pre-operative observations

Pre-operative pulse and blood pressure were measured using a standard cardiac monitor.

2.3.2 Standard pre-operative investigations

All patients underwent chest radiography and a twelve lead-electrocardiogram.

2.3.3 Additional pre-operative investigations

Additional pre-operative investigations were conducted at the discretion of surgical and anaesthetic staff. These included resting trans-thoracic echocardiography, pulmonary function tests and CT scanning.

2.4 Venous blood sampling

The patient lay supine for 20 minutes and a venous blood sample was taken for the following:

2.4.1 Venous urea and electrolytes and plasma cholesterol

A 5ml sample was taken in a lithium/heparin tube and sent to the biochemistry laboratory for measurement of venous urea and electrolytes, plasma total cholesterol, triglycerides and the HDL fraction of cholesterol.

2.4.2 Full blood count and coagulation screen

A 5 ml sample was taken in an EDTA tube for analysis of haemoglobin concentration, white cell count and platelet count. A further 5mls was taken in a citrate tube for analysis of pro-thrombin time, activated pro-thromboplastin time and fibrinogen.

2.4.3 C-reactive protein (CRP)

A 5ml sample was taken in a lithium/heparin tube and sent to the biochemistry laboratory for measurement of serum CRP.

2.4.4 Cardiac troponin I (CTnI)

A 5ml sample was taken in a lithium/heparin tube and sent to the biochemistry laboratory for measurement of cTnI. Sample results were not available to clinicians.

2.4.5 B-type natriuretic peptide (BNP)

(a) Sample handling and plasma extraction

A 10ml sample of blood was placed into a pre-chilled tube containing potassium-EDTA (1mg/ml blood) and aprotonin (50 I.U./ml blood). The sample was stored on ice and centrifuged at 3000rpm for 10 minutes at 4°C immediately following collection. The plasma was then frozen and stored at -25°C until assay.

(b) BNP assay

BNP was assayed in unextracted plasma using a direct immunoradiometric assay kit (Shinoria BNP kit) supplied by Shinogi & Co, Ltd. (Osaka, Japan) (Kono et al 1993). This uses two monoclonal antibodies which recognise the carboxyl terminal sequence and the ring structure of human BNP, respectively, and measures it between the two antibodies without plasma extraction (Yasue et al 1994). The minimum detectable quantity of human BNP is 2pg/ml and the degree of cross reactivity with human ANP is less than 0.001% on a molar basis (Tsutamoto et al. 1997). The within-assay and between assay co-efficient of variation are both <5%.

2.5 Clinical Scoring

Using pre-operative information patients were attributed a clinical score using one and/or both of the following systems:

(a) The Revised Cardiac Risk Index (RCRI)

This is an objective scoring system of cardiac risk based on the presence of six clinical variables (high-risk surgery, history of ischaemic heart disease, history of congestive heart failure, history of cerebrovascular disease, pre-operative treatment with insulin and pre-operative creatinine>2.0mg/dl). It categorises patients 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. All patients were given an RCRI score.

(b) The Eagle score

This clinical scoring system is dependent on five variables: age over 70; diabetes; history of angina; ventricular ectopics requiring treatment; and Q-waves on ECG. The presence of none of the criteria puts a patient in a low risk category, 1or 2 in a moderate risk category and 3 or more in a high risk category. All patients undergoing vascular surgery were given an Eagle score.

2.6 Intra-operative details

Intra-operative details were prospectively documented and included:

2.6.1 Anaesthetic technique

The method of anaesthesia employed was recorded.

2.6.2 Duration of procedure

This was noted from anaesthetic charts.

2.6.3 Intra-operative blood loss

Intra-operative blood loss was estimated through measurement of losses in suction and the weighing of surgical swabs.

2.6.4 Intra-operative hypotension

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

2.7 Post-operative testing

All patients were screened for post-operative cardiac events. Other post-operative investigations were conducted at the discretion of the treating physicians.

2.7.1 Twelve lead electrocardiography (ECG)

This was conducted routinely on the mornings of the second and fifth post-operative days, the morning of discharge and at out-patient clinic six weeks following surgery. It was also conducted at other times as clinically indicated at the discretion of the treating physicians.

2.7.2 Cardiac troponin I sampling

Venous blood sampling for cardiac troponin I analysis was conducted routinely on the mornings of the second and fifth post-operative days, prior to discharge and at out-patient clinic six weeks following surgery. It was also conducted at other times as clinically indicated at the discretion of the treating physicians.

2.8 Study end points

The study end points were non-fatal myocardial infarction (MI), and cardiac death.

2.8.1 Timing

Patients were followed up for six weeks and any events occurring up to 6 weeks following surgery were included and analysed.

2.8.2 Non-fatal myocardial infarction

The definition of MI was that used by The Joint European Society of Cardiology/American College of Cardiology Committee, defined as “a typical rise and gradual fall of cTnI with at least one of the following: a) ischaemic symptoms; b)

development of pathological Q waves on the ECG; c) ECG changes indicative of ischaemia (ST segment elevation or depression); or d) coronary artery intervention."

2.8.3 Cardiac death

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

2.8.4 Interpretation of cardiac events

The decision of whether end points had been fulfilled was determined by a review of all post-operative data by 2 cardiologists who were blinded to pre-operative BNP levels.

2.9 Cardiac troponin I analysis

Serum cTnI was measured using the ADVIA Centaur® immunoassay (Bayer Diagnostics), which has a sensitivity and assay range of 0.1-50ng/ml.

2.10 Twelve lead electrocardiogram (ECG)

2.10.1 Recording

This was recorded in a standard fashion at a paper speed of 25mm/second by a qualified cardiac technician.

2.10.2 Analysis

All ECGs were interpreted by two experienced cardiologists blinded to patient and clinical details. They commented on the presence of an abnormal ECG preoperatively, and of electrocardiographic evidence of an MI. If there was any disagreement a third cardiologist was asked to make a determination.

2.11 Definitions

2.11.1 Ischaemic heart disease

Ischaemic heart disease was defined as the presence of one or more of: 1. history of myocardial infarction; 2. history of positive exercise test; 3. current complaint of chest pain considered to be secondary to myocardial ischaemia; 4. regular nitrate therapy; 5. ECG with pathological Q waves.

2.11.2 Heart Failure

Heart failure was defined as one or more of the following: 1.previous medical diagnosis of heart failure; 2. pulmonary oedema; 3. paroxysmal nocturnal dyspnoea; 4. physical examination showing bilateral rales or S3 gallop; 5. chest radiograph showing pulmonary vascular redistribution; 6. echocardiography showing reduced left ventricular ejection fraction (<40%).

2.11.3 Diabetes Mellitus

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

2.11.4 Cerebrovascular Disease

Cerebrovascular disease was defined as previous medical diagnosis of cerebrovascular accident or transient ischaemic attack.

2.11.5 Hyperlipidaemia

Hyperlipidaemia was defined as a pre-operative cholesterol of >5.5mmol/l

2.11.6 Renal Impairment

Renal impairment was defined as a pre-operative creatinine of >130mmol/l.

2.11.7 Procedures

Patients undergoing emergency surgery (<24 hours from admission) were excluded. 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. The following procedures were included appropriate to each study's entry criteria.

(a) Aortic aneurysm repair

This was performed with either aortic tube or aortic bifurcation grafting as appropriate. No endovascular procedures were included in this study.

(b) Aorto-bifemoral bypass grafting

An onlay aortic graft was performed to appropriate infra-inguinal target vessels.

(c) Non-aortic vascular reconstruction

This included femoro-popliteal grafting, femoro-distal grafting, femoral endarterectomy, axillo-bifemoral grafting, and carotid-subclavian bypass surgery.

(d) Major lower extremity amputation

This included above-knee and below-knee amputation for critical limb ischaemia but excluded more distal procedures.

(e) Intra-abdominal non-vascular surgery (laparotomy)

This included total and sub-total gastrectomy for malignancy, Whipple's procedure for pancreatic/bilary malignancy and colorectal resection for malignant or inflammatory bowel disease. Laparoscopic procedures were not included.

(f) Nephrectomy

Total or partial nephrectomy for malignancy was included.

(g) Oesophago-gastrectomy

This was performed for oesophageal malignancy using the Ivor-Lewis technique, involving both intra-abdominal and intra-thoracic approaches.

2.12 Statistical analysis

Statistical analysis was conducted using SPSS® statistical software package (SPSS, Chicago, Illinois, USA). Univariate analyses between groups were conducted using Pearson's chi-squared test or a two tailed Fisher's exact test. Statistical analysis of continuous data was performed using a Mann-Whitney test. ROC curves were created to determine the association between BNP/CRP and cardiac outcome. A logistic regression model was fitted with cardiac events as outcome and the natural logarithm of BNP ($\log_e$BNP) as covariate. A probability value of less than 0.05 was considered statistically significant.

2.12 Ethics

The study was approved by West Glasgow Ethics Committee. All patients gave their written consent to the study on admission to hospital.

3. A Pilot Study to Evaluate the Value of B-type Natriuretic Peptide (BNP) In Predicting Cardiac Morbidity after Vascular Surgery

3.1 Introduction

Vascular surgery is associated with substantial risk of cardiovascular events and death (Kim et al. 2002). Currently, there is no effective method of determining cardiac risk pre-operatively: validated risk prediction instruments are limited by their complexity and poor predictive value (Detsky et al. 1986;Lee et al. 1999b), whilst other cardiac investigations such as nuclear stress testing and coronary angiography are limited by time and resources. For these reasons, alternative methods that could predict outcome in at-risk patients would represent an important advance.

Plasma BNP has counter-regulatory vasodilator and natriuretic properties (Hunt et al. 1996) and its concentrations are increased and relate to prognosis in cardiac disorders, such as angina and heart failure (McDonagh et al. 1998;Wang et al. 2004b). Many of these cardiovascular disorders occur in patients with peripheral vascular disease.

The aim of this study was to investigate the predictive value of pre-operative plasma BNP concentration for the occurrence of peri-operative fatal or non-fatal myocardial infarction (MI) in a high-risk cohort of vascular surgical patients. Results from this study would then be used to help calculate a sample size for a study examining a more general population.

3.2 Patients and Methods

3.2.1 Study population

Consecutive patients undergoing major surgery for aortic or peripheral arterial occlusive disease in Gartnavel General Hospital were screened between April and September 2004. A sample size (n=40) had been calculated based on i) an anticipated rate of fatal or non-fatal MI of 10%, and ii) median (interquartile range) BNP concentrations in patients with or without cardiovascular disease who had participated in the North Glasgow MONICA study.

3.2.2 Preoperative testing

All patients underwent conventional pre-operative preparation, which included routine blood tests, an ECG and a chest radiograph. Additional tests, such as echocardiography, were performed at the discretion of the surgical team. BNP samples were collected and analysed using the techniques described in section 2.4.5. Batch analysis of the BNP samples was performed at the conclusion of the study by a biochemist blinded to clinical detail. In addition, to detect if any patient had asymptomatic cardiac disease, cardiac troponin I (cTnI) was measured pre-operatively (ADVIA Centaur assay, Bayer Diagnostics). The result of this was not available to clinicians.

3.2.3 Study end-points

The study end points that were used were non-fatal myocardial infarction, and cardiac death. The definition of myocardial infarction was that of The Joint European Society

of Cardiology/American College of Cardiology Committee as described in section 2.8.2 (Alpert et al. 2000). Cardiac death was defined as death secondary to myocardial infarction, cardiogenic shock or intractable dysrhythmia and was determined by a review of all post-operative data by 2 cardiologists blinded to pre-operative BNP levels. Patients were followed up for six weeks after surgery.

3.2.4 Post-operative screening for cardiac events

Post-operative screening for cardiac events consisted of daily clinical assessment, serial ECGs and cTnI measurement (post-operative days 2 and 5, prior to discharge and at out-patient follow-up around day 42). Other investigations were conducted as clinically indicated. ECG analysis was performed by 2 cardiologists blinded to all other data and patient details, in a batch at the end of the study period. Ten percent of all ECGs, clinical notes and data entry was analysed separately to ensure quality control.

3.2.5 Statistical analysis

Statistical analysis of continuous data was performed using a Mann-Whitney test. Categorical data was analysed using a Pearson's chi-squared test or a two-tailed Fishers' exact test. Values are reported as median (interquartile range). As a BNP concentration of 100pg/ml had previously been shown to be predictive of heart failure this value was initially used to compare BNP with other factors.

Local research and development, and ethics approval was obtained and a statistician consulted for study design and data analysis.

3.4 Results

Forty-one patients were included (Table 3.1). Of these, 17 underwent lower limb bypass surgery, 11 had aortic surgery, and 13 underwent major lower limb amputation. Post-operatively, 4 patients died from an acute MI and 7 other patients experienced a non-fatal MI, 3 of which were clinically silent. Events were most common in the first 48 hours (7), but did occur from 48 hours to 1 week (3), and up to 6 weeks post-operatively (1).

Patients with pre-existing cardiac disease, renal impairment or who suffered intra-operative hypotension were more likely have a cardiac event. Patients prescribed beta blockers had a lower cardiac event rate. The Eagle score but not the RCRI was a significant predictor of cardiac outcome (Table 3.1).

BNP concentration correlated with operative risk factors with higher levels in patients with cardiac disease, diabetes mellitus and renal impairment (Table 3.1).

Table 3.1: The case mix and cardiac event rate

Case Mix		BNP* (pg/ml)	Cardiac Event Rate n†	%	p
Sex	Male	60 (16-148)	7/25	28.0	
	Female	58 (32-132)	4/16	25.0	1.000
IHD	Absent	37 (12-111)	5/23	21.7	
	Present	88 (32-203)	6/18	33.0	0.489
Heart failure	Absent	43 (15-111)	6/31	19.3	
	Present	138 (25-203)	5/10	50.0	0.098
β-blockers	Used	36 (15-121)	1/7	14.3	
	Not Used	65 (20-146)	10/34	29.4	0.651
Diabetes	Absent	37 (16-118)	7/29	24.1	
	Present	101 (48-240)	4/12	33.0	0.701
Renal impairment	Absent	52 (20-123)	9/37	24.3	
	Present	225 (19-532)	2/4	50.0	0.288
COPD	Absent	70 (19-146)	10/34	29.4	
	Present	27 (13-93)	1/7	14.3	0.651
Intraoperative hypotension	Absent	42 (16-119)	8/36	22.2	
	Present	139 (85-206)	3/5	60.0	0.110
Eagle	0	16 (10-30)	0/12	0.0	
	1	69 (18-174)	6/14	42.9	
	2	88 (67-169)	2/10	20.0	
	3	172 (96-321)	3/5	60.0	0.026‡
RCRI	0	71 (17-124)	3/11	27.3	
	1	36 (13-57)	3/17	17.6	
	2	81 (50-236)	1/6	16.7	
	3+	172 (85-210)	4/7	57.1	0.229‡

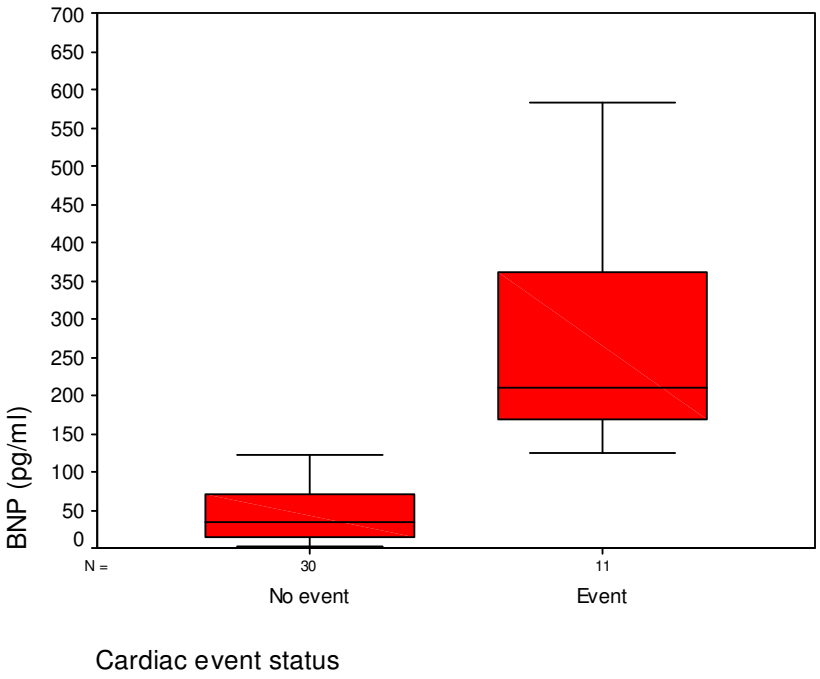
BNP*= Median pre-operative BNP concentration (interquartile range)

†The numerator indicates the number of subjects who experienced a cardiac event and the denominator indicates the total number of subjects who share an attribute ie 7 out of 27 men experienced a cardiac event. p values derived from two-tailed Fishers' exact test.

‡ p value derived from χ^2

The median (interquartile range) plasma BNP concentration in patients who experienced a fatal or non-fatal MI (n=11) was 210 (165-380) pg/ml, compared to 34.5 (14-70) pg/ml in those who did not (n=30), p<0.001 (Figure 3.1). All patients who experienced an event had a preoperative BNP concentration greater than >123 pg/ml. All patients who were event free had a BNP of <122pg/ml.

Figure 3.1 BNP and cardiac events



3.4 Discussion

This study has shown that pre-operative plasma BNP concentrations are elevated in patients who subsequently experience a peri-operative fatal or non-fatal MI. In fact there was no cross-over in BNP concentrations between those patients who did and those who did not suffer a cardiac event; a BNP level of 123pg/ml being completely discriminatory.

In this study no single clinical variable (other than BNP concentration) was significantly predictive of outcome, although patients with pre-existing cardiac or renal disease were more likely to suffer a cardiac event. Patients' whose operation involved a period of hypotension had a higher cardiac event rate and if beta blockers were prescribed the likelihood of a cardiac event was halved, in keeping with the cardio-protective role of these drugs. The Eagle clinical scoring system (Eagle et al. 1989) was a significant predictor of outcome, however the RCRI (Lee et al. 1999b) was not, in keeping with the fact that the former but not the latter was derived in a cohort of vascular patients.

In the recent Coronary Artery Revascularization Prophylaxis trial, 510 patients with obstructive coronary artery disease and an indication for vascular surgery were randomised to coronary revascularisation before surgery or to conventional management (McFalls et al. 2004). Perhaps surprisingly, coronary revascularisation did not confer any survival advantage. This result illustrates the complexity of risk management in high-risk surgical patients and underscores the need for further investigations in this area.

Results from this study suggest that a single pre-operative blood BNP measurement may predict risk in this, and potentially other, surgical settings. BNP concentration measured prior to surgery may lead to a change in the management plan. This thesis requires validation in a larger population of patients. If reproduced, these findings could enhance the cost-effectiveness of interventions in patients with surgical disease.

4. B-type Natriuretic Peptide (BNP) Predicts Cardiac Morbidity and Mortality after Major Surgery: A Prospective Study

4.1 Introduction

Cardiovascular disease is the leading cause of mortality in surgical patients (Mangano 1990). Despite this, current methods of peri-operative cardiac risk stratification remain flawed: clinical scoring systems, although simple to use, are limited by their predictive value (Lee et al. 1999b), whilst other cardiac investigations such as nuclear stress testing are highly sensitive (Poldermans et al. 1993), but limited in practice by time and resource implications. A simple, practical and accurate method of predicting cardiac morbidity would therefore be of great benefit.

B-type natriuretic peptide (BNP) was originally identified in the porcine brain (Sudoh et al. 1988), although its main site of secretion is from atrial, and in particular ventricular myocytes in response to cardiac wall stress (Mukoyama et al. 1991). It has potent natriuretic, diuretic and vasorelaxant properties, and inhibits the release of aldosterone via the renin-angiotensin system (Hunt et al. 1988). Recent studies have demonstrated that the concentration of BNP in plasma has many clinical applications: it is a sensitive and specific predictor of left–ventricular systolic dysfunction (McDonagh et al. 1998), and predicts first cardiovascular event and mortality in the general population (McDonagh et al. 2004a).

Few studies have evaluated pre-operative BNP concentration as a method of predicting cardiac complications in surgical patients. The only prospective study to do so correlated pre-operative BNP concentration with outcome following cardiac surgery (Hutfless et al. 2004). No study has evaluated BNP concentration as a predictor of cardiac risk in non-cardiac surgical patients, although one recent

retrospective study did predict the occurrence of cardiac failure following non-cardiac surgery using the BNP precursor, plasma N-terminal pro-BNP (Yeh et al. 2005).

The previous section of this thesis found pre-operative BNP concentration to be a significant predictor of cardiac outcome following vascular surgery with a value of 123pg/ml being completely discriminatory for the occurrence of cardiac events. The aim of this study was to validate the proposal that pre-operative BNP concentration predicted post-operative cardiac outcome, but this time in a larger heterogeneous group of patients undergoing major non-cardiac surgery.

4.2 Patients and Methods

4.2.1 Study Design

A prospective, observational, single centre cohort study was conducted on the basis of the findings of the pilot study (chapter 3). Using the BNP concentrations in the group of high-risk patients who underwent major vascular surgery, and an expected cardiac event rate of 5% in the patients undergoing non-vascular surgery a sample-size (n=140) was determined. The initial cohort of patients (chapter 3) had been chosen to ensure that the numbers of patients at risk of cardiac events was sufficient to show a significant difference should one exist; this second cohort was chosen to determine the widespread applicability of the initial findings to the general surgical population, a group in which a lower cardiac event rate is to be anticipated. The methods used in this validation study were consistent with those employed in the pilot study (see chapter 3).

4.2.2 Patients

Patients undergoing non-cardiac surgery with an estimated cardiac complication rate of greater than 5% (vascular surgery, laparotomy, and thoracotomy) were prospectively recruited over a period of one year. Patients were excluded if surgery was emergency (surgery being required within 24 hours), or if informed consent was not obtainable.

Basic demographic data and factors relating to the cardiac risk of surgery were prospectively gathered for each patient. These included: clinical variables (history of cardiovascular, renovascular, cerebrovascular and pulmonary disease), medications prescribed, and intra-operative details (length of operation, intra-operative

hypotension, operative blood loss). Ischaemic heart disease (IHD) and heart failure were classified using established definitions (Lee et al. 1999b). Renal impairment was defined as a pre-operative creatinine of greater than 130µmol/l and intra-operative hypotension as a systolic blood pressure of less than 90mmHg for more than 5 minutes during surgery.

The risk of cardiac events was objectively calculated using the revised cardiac risk index (RCRI), (Lee et al. 1999b) with the cumulative scoring system allowing categorisation of patients into 4 groups of increasing cardiac risk.

4.2.3 Preoperative assessment

Pre-operative assessment and investigation were at the discretion of the surgical and anaesthetic teams and included routine blood tests, an ECG and a chest radiograph. BNP samples were collected and analysed using the techniques described in section 2.4.5. Batch analysis of the BNP samples was performed at the conclusion of the study by a biochemist blinded to clinical detail. In addition, to detect if any patient had asymptomatic cardiac disease, cardiac troponin I (cTnI) was measured pre-operatively (ADVIA Centaur assay, Bayer Diagnostics). These results were not available to clinicians.

4.2.4 Study end-points

The study end points were non-fatal myocardial infarction (MI), and cardiac death. The definition of myocardial infarction was that of The Joint European Society of Cardiology/American College of Cardiology Committee (Alpert et al. 2000). Cardiac death was defined as death secondary to myocardial infarction, cardiogenic shock or

intractable dysrhythmia, and was determined by a review of post-operative data by 2 cardiologists who were blinded to pre-operative BNP levels. Patients were followed up for six weeks after surgery.

4.2.5 Post-operative screening

Post-operative screening for cardiac events consisted of daily clinical assessment, serial ECGs and cTnI measurement (post-operative days 2, 5, prior to discharge and day 42). Other investigations were conducted as clinically indicated. ECG analysis was performed by 2 cardiologists blinded to all other data and patient details, in a batch at the end of the study period. In a random sample of 10% of patients, ECGs, clinical notes and data entry were analysed separately in order to ensure quality control.

4.2.6 Statistical analysis

Statistical analysis was conducted using SPSS® statistical software package (SPSS, Chicago, Illinois, USA). BNP values are reported as median (interquartile range). Univariate analyses between groups were conducted using Pearson's chi-squared test or a two-tailed Fisher's exact test. Continuous variables were compared using a Mann-Whitney test. A logistic regression model was fitted with cardiac events as outcome and the natural logarithm of BNP ($\log_e$BNP) as covariate. The odds ratio (OR) for a one unit change in $\log_e$BNP and its 95% confidence interval (CI) were calculated.

Local research and development and ethical approval were obtained and a medical statistician consulted for study design and data analysis.

4.3 Results

4.3.1 Study Population

One hundred and forty-nine patients were prospectively recruited over a one-year period. As in the pilot study, the median age was 68 years (60-76). Other than this, the two cohorts were not similar (Table 4.1). Ischaemic heart disease (21% vs. 44%) and heart failure (17% vs. 24%) were less prevalent and while all patients in the derivation cohort had undergone major vascular surgery, the validation cohort was composed of patients undergoing major non-cardiac surgery (laparotomy-49, peripheral bypass-39, amputation-25, aortic procedure-24, nephrectomy-7, oesophago-gastrectomy-5). The cardiac event rate was lower in this cohort (10% vs. 27%), as was the percentage of patients with a BNP of greater than 100 pg/ml (23% vs. 34%). As previously noted, BNP concentrations correlated with cardiac risk factors, higher levels being observed in patients with heart failure, ischaemic heart disease, diabetes mellitus and renal impairment (Tables 4.2).

Table 4.1 The case mix of derivation and validation cohorts.

Case Mix Cohort:		Derivation n (%)	Validation n (%)	p
Male Sex		25 (61)	99 (66)	0.579
Ischaemic Heart Disease		18 (44)	32 (21)	0.008
Heart Failure		10 (24)	25 (17)	0.264
β-blocker prescribed		7 (17)	30 (20)	0.824
Diabetes Mellitus		12 (29)	30 (20)	0.211
Renal Impairment		4 (10)	21 (14)	0.606
Cerebrovascular disease		1 (2)	17 (11)	0.129
Chronic Obstructive Lung Disease		7 (17)	25 (17)	1.000
Intraoperative hypotension		5 (12)	30 (20)	0.362
Revised cardiac index	0	11 (27)	26 (17)	0.267
	1	17 (41)	85 (57)	0.081
	2	6 (15)	21 (15)	1.000
	>2	7 (17)	17 (11)	0.424
BNP 100+		14 (34)	35 (23)	0.226
Cardiac events		11 (27)	15 (10)	0.010
Total		41 (100)	149 (100)	

p values derived from two-tailed Fishers' exact test.

4.3.2 Cardiac Events

A total of 149 patients (99 males, 50 females) were recruited to the validation study and underwent major non-cardiac surgery (Table 4.1). There were 15 cardiac events: 8 non-fatal myocardial infarctions (amputation-3, laparotomy-2, aortic surgery-2, peripheral bypass surgery-1); and 7 cardiac deaths (amputation-3, laparotomy-2, aortic surgery-1, peripheral bypass surgery-1). Three of the non-fatal myocardial infarctions were silent and detected by post-operative screening at 48 hours. As in the pilot study, events were most common in the first 48 hours (9), but did occur from 48 hours to 1 week (3), and up to 6 weeks post-operatively (3).

Cardiac events were more common in patients with ischaemic heart disease (15.6% vs. 8.5%), cerebrovascular disease (17.6% vs.9.1%), or pre-operative renal impairment (19% vs. 8.6%), (Table 4.2). Patients who underwent a vascular procedure (12.5% vs. 6.6%) or whose procedure involved a period of hypotension (16.7% vs. 8.4%) were also more likely to have a cardiac event. Although the RCRI was not discriminatory between the event rates in the lowest two risk categories, patients in the three highest risk categories had an increasing likelihood of suffering a cardiac event (8.2%, 9.5% and 17.6%). When only the 61 non-vascular patients were considered, the RCRI was again inconsistent in its predictive ability: 3 of the 51 patients (5.9%) with an RCRI of 1 had an event; and 1 of 6 patients (16.7%) with an RCRI of 2 had an event however none of the 4 patients with an RCRI of 3 suffered a cardiac event.

Table 4.2 Validation cohort: the case mix and cardiac event rate.

Case Mix		Cardiac Event Rate BNP*	n†	%	p
Sex	Male	33 (13-88)	10/99	10.1	
	Female	41 (11-104)	5/50	10.0	1.000
Ischaemic heart disease	Absent	28 (10-80)	10/117	8.5	
	Present	83 (23-149)	5/32	15.6	0.316
Heart failure	Absent	30 (11-81)	12/124	9.7	
	Present	91 (38-351)	3/25	12.0	0.718
β-blockers	Used	82 (37-170)	7/30	23.3	
	Not Used	30 (11-81)	8/119	6.7	0.014
Statin	Used	39 (16-115)	9/62	14.5	
	Not Used	30 (11-85)	6/87	6.9	0.168
Diabetes	Absent	32 (13-82)	11/119	9.2	
	Present	74 (12-146)	4/30	13.3	0.504
Cerebrovascular disease	Absent	33 (12-90)	12/132	9.1	
	Present	38 (17-164)	3/17	17.6	0.382
COPD	Absent	36 (12-103)	13/124	10.5	
	Present	32 (14-87)	2/25	8.0	1.000
Renal impairment	Absent	32 (11-85)	11/128	8.6	
	Present	63 (23-362)	4/21	19.0	0.230
Operation	Vascular	39 (15-102)	11/88	12.5	
	Non-vascular	28 (10-78)	4/61	6.6	0.279
Intra-operative hypotension	Absent	40 (12-95)	10/119	8.4	
	Present	34 (13-93)	5/30	16.7	0.185
Blood loss (mls)	<500	31 (10-93)	11/112	9.8	
	500+	40 (29-99)	4/37	10.8	1.000
Operation length (hrs)	<2	37 (13-110)	8/86	9.3	
	2+	34 (11-88)	7/63	11.1	0.786
RCRI	0	46 (15-90)	3/26	11.5	
	1	28 (10-63)	7/85	8.2	
	2	69 (34-154)	2/21	9.5	
	3+	91 (31-150)	3/17	17.6	0.691‡

BNP* = Median BNP (interquartile range)

† The number of subjects who experienced a cardiac event over the total number

p values derived from two-tailed Fishers' exact test, ‡ p value derived from χ^2

4.3.4 BNP concentration and outcome

The median (interquartile range) pre-operative BNP concentration was significantly higher in patients who had a cardiac event than in those who did not (351 (127-1034) vs. 30.5 pg/ml (11-79.5), p<0.001, Figure 4.1). For each increment in $\log_e$BNP the OR was 3.85, 95% CI (2.19- 6.78) (figure 4.2). The median (interquartile range) BNP level in patients who suffered a fatal event was higher than in those who suffered a non-fatal myocardial infarction (743 (184-1034) vs. 247.5 pg/ml (63-1046), p=0.463).

Figure 4.1 BNP concentration and cardiac events

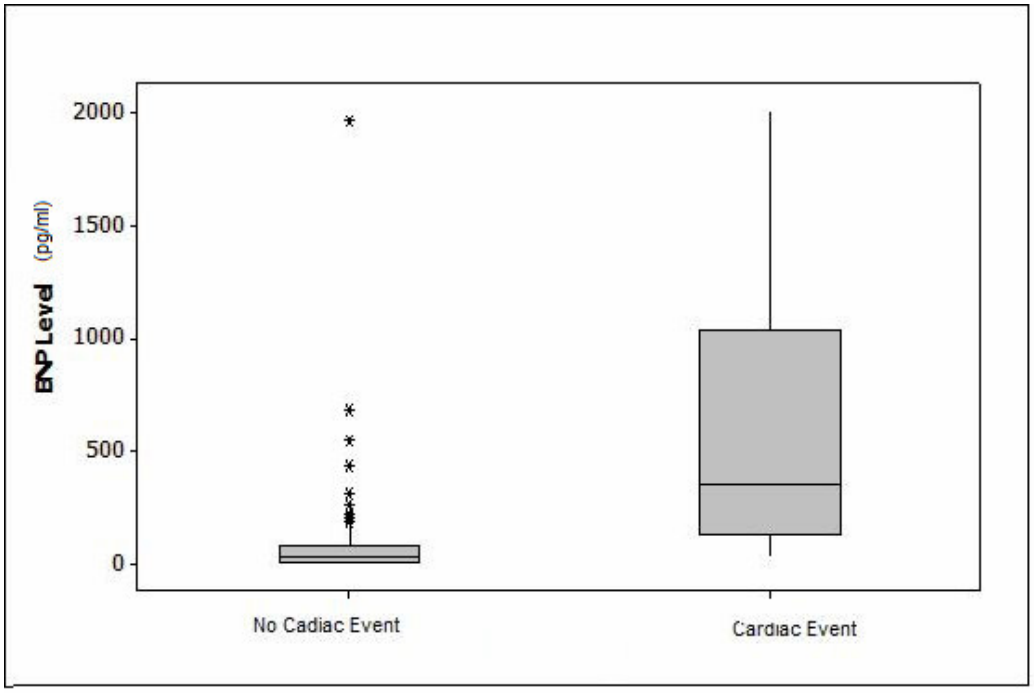
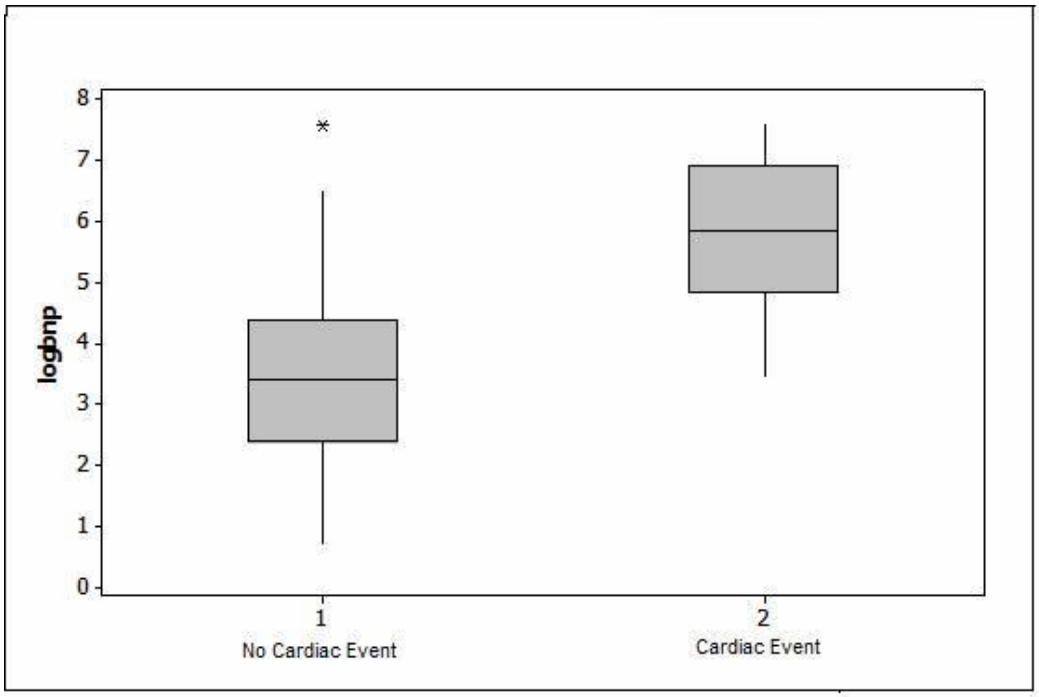


Figure 4.2 Log$_e$BNP concentration and cardiac events



A logistic regression model was fitted with cardiac events as outcome and the natural logarithm of BNP as covariate. The OR for a one unit change in log$_e$BNP and its 95% CI was calculated. The logistic regression model demonstrated a highly significant association between log$_e$BNP and the risk of a cardiac outcome (OR= 13.69, 95%CI (3.62-51.83), P<0.001). Adjustment for additional risk factors was explored (Table 4.3). This had no effect on reducing the statistical significance of log$_e$BNP as a predictor of events. However, there was evidence that the statistical model was becoming unstable, with the OR for log$_e$BNP increasing dramatically (as did its 95% CI) and other terms having very large or very small ORs with wide confidence intervals.

Table 4.3 Logistic Regression Table

Predictor	Coef	SE Coef	Z	P	Odds Ratio	95% CI Lower	95% CI Upper
Constant	-9.13180	4.17241	-2.19	0.029			
logbnp	2.61678	0.679192	3.85	0.000	13.69	3.62	51.83
SEX	-0.575739	1.00572	-0.57	0.567	0.56	0.08	4.04
IHD2	-0.310073	1.08579	-0.29	0.775	0.73	0.09	6.16
HF2	-4.91978	2.11415	-2.33	0.020	0.01	0.00	0.46
CVA2	0.416425	1.28320	0.32	0.746	1.52	0.12	18.76
RF2	-0.749416	1.17093	-0.64	0.522	0.47	0.05	4.69
OpVasc	-0.0152394	1.12753	-0.01	0.989	0.98	0.11	8.98
betab	0.709553	0.998672	0.71	0.477	2.03	0.29	14.40
stat	1.27782	1.05039	1.22	0.224	3.59	0.46	28.12
hypotension	2.90674	1.22955	2.36	0.018	18.30	1.64	203.70

Log-Likelihood = -20.085
Test that all slopes are zero: G = 57.144, DF = 10, P-Value = 0.000

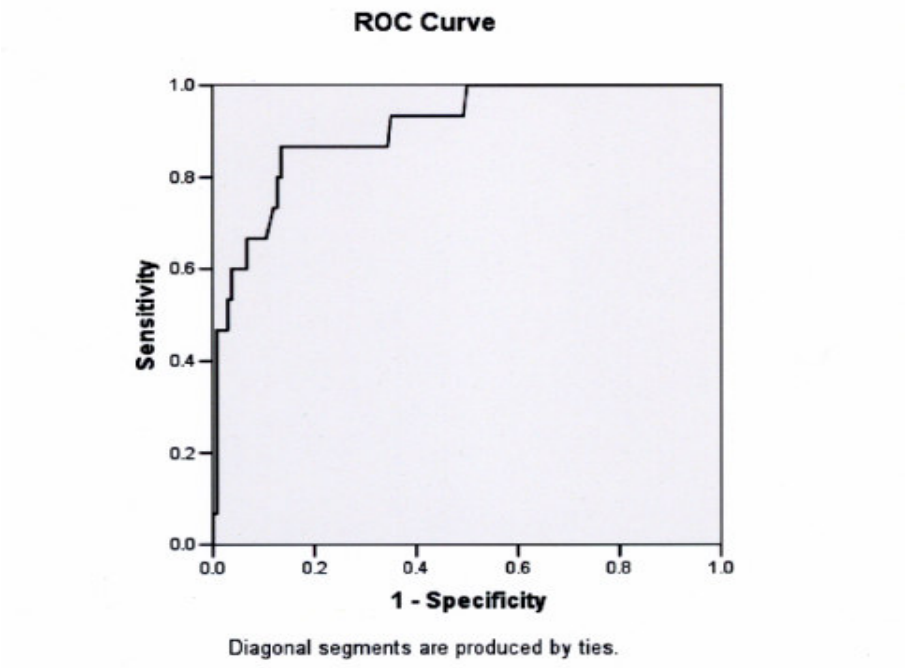
For all categories of the revised cardiac risk index, the median BNP level was higher in patients who had a cardiac event than those who did not (RCRI=0 (895 vs. 32 (13-81) pg/ml) p=0.001, RCRI=1 (184 (127-351) vs. 25 (9-50) pg/ml) p<0.001, RCRI= 2 (1060 vs. 46 (31-144) pg/ml) p=0.152, RCRI 3+ (1034 vs. 77 (31-169) pg/ml) p=0.24.

The median BNP concentration was higher in patients who had a cardiac event whether patients underwent vascular surgery (850 (144-1111) vs. 37 (13-84) pg/ml, p<0.001) or non-vascular surgery (211 (115-337) vs. 26 (9-52) pg/ml, p=0.001).

Receiver operating characteristic (ROC) curve analysis was performed to identify the BNP concentration that best predicted cardiac events (figure 4.3). The area under the ROC curve was 0.907. A BNP concentration of 108.5 pg/ml had the best combined sensitivity (87%) and specificity (87%). Some 31(20.8%) of patients had a pre-operative BNP concentration of greater than this value which had a positive predictive value of 42% and a negative predictive value of 98%. To substantially increase the

positive predictive value it was necessary to increase the threshold BNP concentration to 180pg/ml. This level of BNP had a sensitivity of 67%, a specificity of 93%, a positive predictive value of 53% and a negative predictive value of 96%.

Figure 4.3 ROC curve: BNP concentration and cardiac events



A BNP concentration of 108.5pg/ml predicted outcome whether ischaemic heart disease was present or not, and in all classes of the RCRI, although this was only significant in the lowest 2 categories due to the fewer numbers analysed in the higher risk categories (Table 4.4). A BNP concentration of greater than 108.5pg/ml also remained predictive irrespective of the type of surgery. In fact, no cardiac events occurred in patients undergoing non-vascular surgery with a BNP of less than 108.5pg/ml (Table 4.4).

Table 4.4 The cardiac event rate by risk factors and BNP levels in the validation cohort

Risk Factor		BNP (pg/ml)	Cardiac Event Rate n†	%	p
Ischaemic Heart Disease	Absent	<108.5	1/97	1.0	
		108.5+	9/20	45.0	0.000
	Present	<108.5	1/21	4.8	
		108.5+	4/11	36.4	0.037
Revised Cardiac Index	0	<108.5	0/21	0.0	
		108.5+	3/5	60.0	0.004
	1	<108.5	1/73	1.4	
		108.5+	6/12	50.0	0.000
	2	<108.5	0/13	0.0	
		108.5+	2/8	25.0	0.133
	3+	<108.5	1/11	9.1	
		108.5+	2/6	33.3	0.515
Operation	Non-vascular	<108.5	0/51	0.0	
		108.5+	4/10	40.0	0.000
	Vascular	<108.5	2/67	3.0	
		108.5+	9/21	42.9	0.000

†The number of subjects who experienced a cardiac event over the total number

p values derived from two-tailed Fishers' exact test

ROC curve analysis was performed separately in the non-vascular and vascular cohorts. In the non-vascular cohort the area under the curve was 0.939, with a BNP of 108.5pg/ml having the best combined sensitivity (100%) and specificity (89%), (figure 4.4). In the vascular cohort the area under the curve was 0.884 with a level of 140.5pg/ml having the best combined sensitivity (82%) and specificity (86%), (figure 4.5).

Figure 4.4

ROC curve: BNP concentration and cardiac events in non-vascular patients

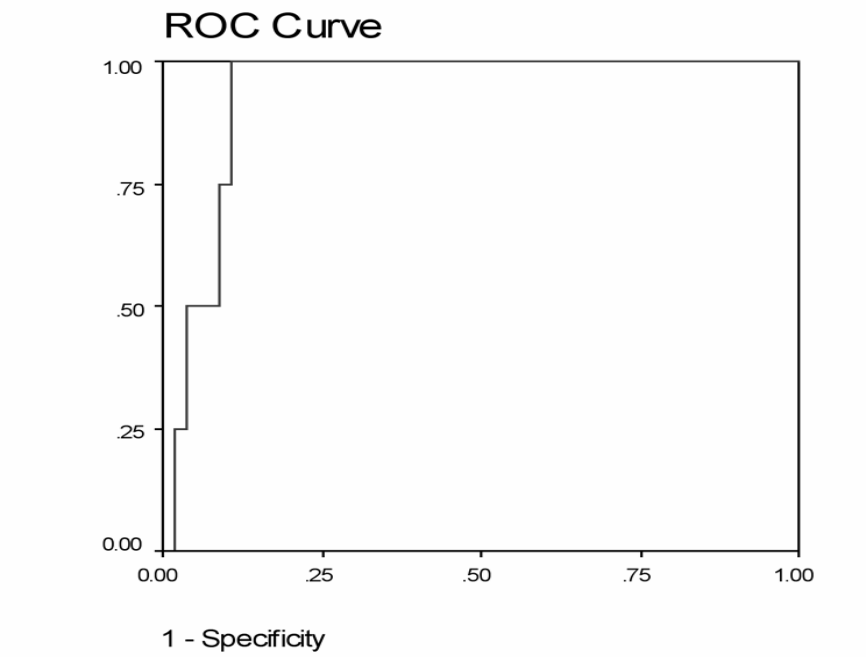
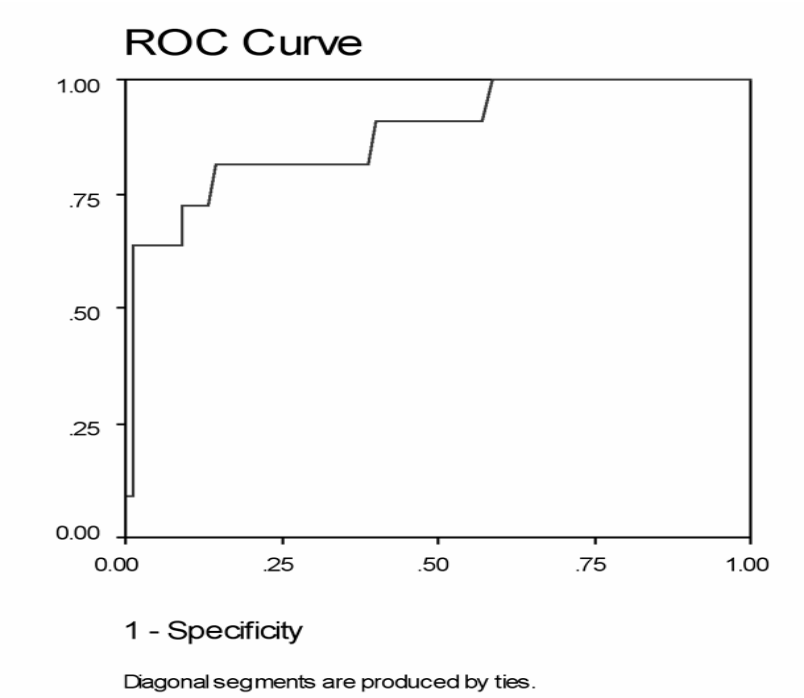


Figure 4.5

ROC curve: BNP concentration and cardiac events in vascular patients



4.3.5 Application of best performing BNP concentration to the pilot cohort

These best performing BNP concentrations were then applied to the cohort of patients studied in chapter 3. In this group a BNP of 108.5 pg/ml had a sensitivity of 100% and a specificity of 90% and a BNP of 140.5pg/ml had a sensitivity of 82% and a specificity of 100%.

4.3.6 BNP concentration and 6 week all cause mortality

The median pre-operative BNP level (pg/ml) was significantly higher in those patients who died within 6 weeks of surgery (155.5 (46-781) vs. 32 (11-82) (p=0.001).

A BNP level of greater than 108.5pg/ml was a good predictor of all cause mortality (sensitivity- 57.1%, specificity- 82.2%, ppv- 25.8%, npv- 94.9%); however a level of 86.5 had the best combined sensitivity and specificity (sensitivity- 71.4%, specificity- 77.8%, ppv- 25.0%, npv- 96.3%).

4.3.7 Cardiac events in patients with a "low" BNP concentration (<108.5pg/ml)

Only 2 of the patients who suffered a cardiac event had a "low" BNP (31 and 47pg/ml). Both had non-fatal events, one occurring at 48hrs (following aortic tube graft) and one at 4 weeks (following amputation). Although both had risk factors for ischaemic heart disease, there were few similarities to explain the occurrence of an event in the presence of a "low" BNP. One patient suffered from ischaemic heart disease, cerebrovascular disease and experienced intra-operative hypotension (RCRI- 3, Eagle- 1). The other had non-insulin dependent diabetes mellitus, hypertension, hyperlipidaemia and documented heart failure (RCRI- 1, Eagle- 2).

4.3.8 Resting echocardiography and outcome

10 patients underwent resting echocardiography (up to 6 months) pre-operatively. These were not requested as part of the study protocol. Left ventricular function was described as poor in 1 patient who suffered a cardiac event (BNP=1217). Three patients had

moderate left ventricular function and 6 had good ventricular function. None of these 9 patients suffered a cardiac event.

4.4 Discussion

This is the first prospective study to have demonstrated a clear correlation between pre-operative plasma BNP concentration and cardiac risk employing strict, objective and clinically relevant end-points. It has shown that the pre-operative BNP concentration is consistently a sensitive and specific predictor of cardiac events which predicts outcome irrespective of clinical risk factors, and also discriminates between fatal and non-fatal events.

Using ROC curve analysis in the validation cohort, a BNP level of 108.5pg/ml was identified as being the optimal cut-off point for the prediction of cardiac events. This level was also highly predictive of outcome in the derivation (pilot) cohort and levels above this may predict a poor cardiac outcome necessitating a change in the treatment plan. The majority (79%) of patients in the study had a pre-operative BNP concentration of less than 108.5pg/ml and therefore could proceed to surgery without any change in their treatment plan. Although the threshold concentration of BNP at which management should be changed is still not absolutely clear, and may vary depending on the population, our results would suggest that below 108.5pg/ml the likelihood of a cardiac event is low whereas above this level there is substantial risk. Above 180pg/ml the likelihood of a cardiac event increases further, being greater than 50% in this study.

In this cohort, BNP concentration was also found to be a significant predictor of all cause 6-weekly mortality. It is interesting that the best performing cut-off value for this end-point was a BNP level of 86.5pg/ml, which is lower than that which best predicted the

occurrence of cardiac events. Patients with a low BNP concentration suffering a non-cardiac death probably explain this phenomenon.

BNP is a sensitive and specific predictor of left ventricular systolic dysfunction (McDonagh et al. 1998) and a level of 100 pg/ml has been shown to have a diagnostic accuracy of 83.4 % for the diagnosis of heart failure (Maisel et al. 2002). Heart failure is an important predictor of poor post-operative cardiac outcome (Shaw et al. 1996), and this may partly explain the predictive ability of the assay. Although pre-operative BNP concentration unsurprisingly reflected the presence of heart failure, heart failure itself was not found to be a significant predictor of cardiac outcome.

BNP levels have been shown to predict both death and cardiovascular events in the community (McDonagh et al. 2004;Wang et al. 2004b). The BNP concentration that was predictive of poor outcome in those cohorts (17.9pg/ml and 20pg/ml) was much lower than the critical values found in this study and those used in the diagnosis of heart failure, however this is partly explained by the use of a different BNP assay. One other study has prospectively evaluated the relationship between BNP concentration and outcome. This was conducted in patients scheduled for cardiac surgery (Hutfless et al. 2004). They found a BNP concentration of >385pg/ml to be associated with complications and death, reflecting the unstable cardiac status of this population. Only one study has analysed the value of BNP measurement in the prediction of cardiac events following non-cardiac surgery (Yeh et al. 2005). This retrospective study of the BNP precursor, N-terminal proBNP, found that all patients suffering a cardiac complication had a serum

concentration greater than 450ng/l, with this concentration having a sensitivity of 100% and a specificity of 82.9% for the prediction of events. However the study was limited by the retrospective design, its use of subjective outcome measures and failure to screen for cardiac events (Gibson, Berry, & Kingsmore 2005).

A number of different methods have been used to aid pre-operative cardiac risk stratification. Clinical scoring systems such as those devised by Eagle (Eagle et al. 1989) and Lee (Lee 1999b) allow some objectivity but lack predictive ability for the individual patient. In the present study the RCRI showed some discriminatory ability, however a disproportionate number of patients with a score of 0 had an event. This may be related to the definition of lower extremity amputation as "infra-inguinal vascular surgery" which is considered as low risk of surgery in the RCRI. Other modalities such as trans-thoracic echocardiography (TTE) are commonly employed as an aid to pre-operative decision-making. TTE delivers information on global and regional ventricular function as well as valvular abnormalities, and has been found to provide independent information about the risk of postoperative cardiac complications (Rohde et al. 2001). However some investigators have found that echocardiographic data adds little to clinical information alone, particularly when only objective end-points are studied (Halm et al. 1996). In addition, BNP has been found to be superior to resting echocardiography in the diagnosis of congestive heart failure (Steg et al. 2005). Cardiac stress testing has consistently identified those patients who will be free from cardiac events with high negative predictive values (Das et al. 2000;Poldermans et al. 1993). However it is expensive, time consuming and has shown poor positive predictive ability, even in high risk cohorts (Das

et al. 2000). Despite guidelines on its use being produced (Eagle et al. 1996b), the appropriate role of cardiac stress testing in this setting is still unknown (Morgan et al. 2002).

A variety of options exist for the surgical patient judged at high risk. In some cases, such as in elective aortic aneurysm repair, the surgery may be cancelled or postponed. In other cases where surgery is deemed essential, patients' cardiac status should be optimised. The benefits of coronary intervention in this group have been questioned (McFalls et al. 2004); however the prescription of beta-blockers, statins and the use of appropriate anaesthetic techniques such as thoracic epidurals may reduce morbidity (Kertai et al. 2004a;Yeager et al. 1987).

In conclusion, BNP measurement is a simple, practical test that provides important prognostic information in the pre-operative population. It outperforms conventional clinical risk scoring strategies and has a similar predictive ability to more complex, time consuming and expensive tests (Das et al. 2000;Poldermans et al. 1993). BNP shows great promise in identifying patients at high risk of cardiac complications in whom consideration should be given to a modified treatment plan.

5. Should pre-operative troponin be a standard requirement in patients undergoing major lower extremity amputation?

5.1 Introduction

Patients requiring lower extremity amputation have a high associated peri-operative risk, with reported 30 day mortality rates of up to 17% (Cruz et al. 2003). The most common cause of death after surgery is MI (Aulivola et al. 2004), supporting the results of pathological studies which report that up to 92% of patients with peripheral arterial disease significant enough to warrant amputation have diffuse and severe coronary artery atherosclerosis (Mautner et al. 1992).

Cardiac troponin I (cTnI) is a contractile protein that is released into the circulation after myocardial cell injury. It is not found in skeletal muscle and is therefore a sensitive and specific marker of myocardial necrosis and cardiac events (Adams et al. 1993;Apple et al. 1997). Whilst a raised post-operative level of cTnI has been found to correlate with all cause mortality in vascular surgical patients (Higham et al. 2004;Kertai et al. 2004a;Kim et al. 2002;Tambyraja et al. 2005), there are only isolated reports of an association between elevated pre-operative cTnI and the risk of cardiac events or death (Hobbs et al. 2005). Most studies of outcome specifically exclude patients on the basis of an elevated pre-operative cTnI (Higham et al. 2004) or do not include its measurement in their protocol (Kertai et al. 2004a;Kim et al. 2002). The aim of this study was to ascertain the benefit of routine pre-operative cTnI measurement in vascular surgery, in particular in lower extremity amputation patients.

5.2 Patients and Methods

5.2.1 Patients

Initially, all patients undergoing major vascular surgery in a single vascular surgery department were considered for inclusion in the study, however in the pilot cohort of 41 patients there was only one case of an elevated pre-operative cTnI. This was in a patient scheduled for lower extremity amputation. A decision was therefore made to focus on this particularly high-risk group of patients with patients from the pilot study being included.

All patients scheduled for major lower extremity amputation were therefore prospectively identified between April 2004 and April 2005. Clinical variables and medications prescribed were recorded, and the Eagle score calculated for each patient (Eagle et al. 1989). Procedures were classed urgent if they were conducted on the same admission as a referral from the emergency department or another source. Procedures were considered elective if patients were admitted from home for treatment. Patients were excluded if there was clinical evidence of unstable coronary artery disease (cardiac chest pain or ischaemic ECG changes) at the time of pre-operative evaluation, if the surgery was performed as an emergency (<24 hours) or if informed consent could not be obtained. Local research ethics committee approval was obtained for this study.

5.2.2 Sample collection and analysis

Pre-operative venous blood samples were collected on the evening prior to surgery in sterile lithium heparin tubes. Serum cTnI was measured using the ADVIA Centaur® immunoassay (Bayer Diagnostics), which has a sensitivity and assay range of 0.1-50ng/ml. Results of the cTnI assay, performed exclusively as part of this study and not requested by clinicians, were not released to treating clinicians. Routine pre-operative investigations were conducted at the discretion of anaesthetic and surgical staff.

5.2.3 Study end points

The study end points were non-fatal MI, and cardiac death. The definition of MI was that of The Joint European Society of Cardiology/American College of Cardiology Committee. Cardiac death was determined by a review of all post-operative data by 2 cardiologists who were blinded to pre-operative cTnI levels. Patients were followed up for six weeks after surgery.

5.2.4 Post-operative detection and interpretation of cardiac events

Post-operative screening for cardiac events consisted of daily clinical assessment, serial electrocardiography and cTnI measurement (postoperative days 2, 5 and 42). The results of these tests were circulated to the responsible clinicians. Other investigations were conducted as clinically indicated. ECG analysis was performed, in a batch at the end of the study period, by 2 cardiologists blinded to all other data and patient details. A separate independent clinician reviewed 10% of all ECGs, clinical notes and data analysis to ensure quality control.

5.2.5 Statistical analysis

Statistical analysis was conducted using SPSS® statistical software package (SPSS, Chicago, Illinois, USA). Values are reported as median (range). Univariate analyses between groups were conducted using a two tailed Fisher's exact test. Continuous variables were compared using a Mann-Whitney test. A probability value of less than 0.05 was considered statistically significant.

5.3 Results

5.3.1 Population

During the 1-year period, a total of 44 patients underwent major lower extremity amputation and were included in the study. The indication for operation in all cases was critical lower limb ischaemia. Of the forty-four patients included, 28 were male and 16 were female. The median age was 71 (41-91) years (Table 1). Thirty-two patients underwent a below knee amputation and twelve an above knee amputation, all as primary procedures. Co-morbidity was common: ischaemic heart disease (15); medically treated diabetes mellitus (19); chronic obstructive airways disease (9); cerebrovascular disease (10); renal impairment (pre-operative creatinine >130mmol/l) (12); hyperlipidaemia (24); hypertension (33). Some twenty-four patients were prescribed statins and 9 were prescribed beta-blockers peri-operatively. The median Eagle score was 2 (range 0-4). Twelve procedures were urgent and 32 were elective.

In total there were 2 amputation stump infections and one traumatic haematoma. One patient suffered a chest infection and one a transient ischaemic attack post-operatively.

5.3.2 Post-operative cardiac events

There were 10 post-operative cardiac events: 5 non-fatal MIs and 5 cardiac deaths. Three of the non-fatal MIs were symptomatic and occurred within 48 hours of the procedure. Two were clinically silent and were diagnosed by screening (days 2 and 5 post-operatively). Of the 5 cardiac deaths, one followed an intra-operative cardiac arrest, the

other 4 being secondary to myocardial infarction. Two of the fatal MIs were diagnosed clinically and both patients died within 2 weeks of the procedure. Two were detected by screening on day 5, and these patients died following progression of heart failure in weeks 4 and 5 respectively.

The median age of those patients having an event was 76.5 (41-91) compared with 71 (54-86) in those who were event free (p=0.503). Post-operative cardiac events were more common in patients who had renal impairment, underwent an urgent procedure or had an Eagle score of greater than 1. Events were less likely in patients prescribed statins or beta-blockers. There was no difference in post-operative cardiac event rates in patients with a history of ischaemic heart disease (Table 5.1).

Table 5.1 Post-operative cardiac outcome by risk factors

Risk Factor		n	Cardiac Event n (%)	No Cardiac Event n (%)	p*
Sex	Male	28	6 (21%)	22 (79%)	1.000
	Female	16	4 (25%)	12 (75%)	
Ischaemic Heart Disease	Yes	15	3 (20%)	12 (80%)	1.000
	No	29	7 (24%)	22 (76%)	
Diabetes Mellitus	Yes	19	5 (26%)	14 (74%)	0.723
	No	25	5 (20%)	20 (80%)	
COPD	Yes	9	2 (22%)	7 (78%)	1.000
	No	35	8 (23%)	27 (77%)	
Cerebrovascular Disease	Yes	10	2 (20%)	8 (80%)	1.000
	No	34	8 (24%)	26 (76%)	
Renal Impairment	Yes	12	4 (33%)	8 (67%)	0.422
	No	32	6 (19%)	26 (81%)	
Beta Blocker	Yes	9	1 (11%)	8 (89%)	0.659
	No	35	9 (26%)	26 (74%)	
Statin	Yes	24	3 (12%)	21 (88%)	0.147
	No	20	7 (35%)	13 (65%)	
Urgent Procedure	Yes	12	4 (33%)	8 (67%)	0.422
	No	32	6 (19%)	26 (81%)	
Eagle > 1	Yes	24	7 (29%)	17 (71%)	0.306
	No	20	3 (15%)	17 (85%)	
Amputation level	BKA	32	6 (19%)	26 (81%)	0.422
	AKA	12	4 (33%)	8 (67%)	
Elevated cTnI	Yes	3	3 (100%)	0 (0%)	0.009
	No	41	7 (17%)	34 (83%)	
Total		44	10	34	

p*- Fisher's exact test
cTnI – Cardiac troponin I

5.3.4 Raised pre-operative troponin

Pre-operative cTnI was raised in three patients (0.8, 0.3, 14.8ng/ml), all of whom underwent an urgent procedure (Table 5.2). In no patients was the pre-operative ECG identified as indicating acute myocardial injury. Whilst none of the patients were prescribed statins pre-operatively, there were no other consistent clinical variables. All 3 patients had post-operative cardiac events with 2 deaths and 1 non-fatal MI. There was no correlation between cTnI level and severity of event. Patient 1 (pre-operative cTnI=0.8ng/ml) suffered a fatal MI, dying on day 10 post-operatively. Patient 2 (pre-operative cTnI=0.3ng/ml) suffered a fatal intra-operative cardiac arrest. Patient 3 (pre-operative cTnI=14.8ng/ml) suffered an MI on day 2 post-operatively, diagnosed using clinical and ECG criteria. This patient was discharged home 4 weeks post-operatively.

Although there were few clinical variables consistent between the 3 patients, when other markers were analysed there was an association, as all 3 patients, in addition to having a raised cTnI, had high BNP and CRP concentrations.

Table 5.2 Co-morbidity and outcome in patients with a raised pre-operative cardiac troponin I

Patient	**1**	**2**	**3**
Pre-op Troponin (ng/ml)	0.8	0.3	14.8
Pre-op Creatinine (µmol/l)	126	172	50
Pre-op BNP (pg/ml)	263	1034	1111
Pre-op CRP (mg/l)	260	102	204
Ischaemic Heart Disease	Yes	Yes	No
Diabetes Mellitus	Yes	Yes	No
COPD	No	Yes	No
Cerebrovascular Disease	Yes	No	Yes
Beta-Blocker	No	Yes	No
Statin	No	No	No
Urgent Procedure	Yes	Yes	Yes
Eagle Score	3	4	0
Outcome	Cardiac death	Cardiac death	Non-fatal MI

5.4 Discussion

In this study of patients undergoing major lower extremity amputation for critical limb ischaemia, pre-operative cTnI was elevated in 7% of cases and was associated with a very poor outcome. Whilst the absolute number of patients recruited was small, the rigid entry criteria ensured a homogeneous, stable population with consistent surgical and anaesthetic techniques, without selection bias, and whose follow up was complete. The study also employed objective end-points that were clinically relevant.

Previous studies of patients undergoing amputation have found high associated co-morbidity and a high cardiac complication rate (Cruz et al. 2003). In this study of 44 patients, there were 9 post-operative MIs, 4 of which were silent and only detected by the post-operative screening protocol. Five patients died of cardiac causes within 6 weeks of the procedure. Major lower extremity amputation patients therefore represent a particularly high-risk group. Knowledge of the pre-operative cTnI might influence peri-operative support and anaesthetic techniques.

The number of patients in this study prescribed beta blockers and statins was disappointingly low given the published evidence concerning their role in the prevention of peri-operative cardiac events (Kertai et al. 2004b;Poldermans, Boersma et al. 1999). However this lower than expected prescription rate is consistent with other published evidence such as a recent survey of Canadian anaesthetists (VanDenKerkhof et al. 2003). Whilst the numbers in the present study were small, it is interesting to note that the cardiac event rate was 50% lower in patients prescribed statins or beta-blockers. This

may relate to the effect of the drugs, more aggressive investigation in this group, or may reflect more stable coronary artery disease in these patients.

The most important clinical risk factors in determining the occurrence of post-operative cardiac events were an urgent procedure and the presence of renal impairment. Patients with an Eagle score of greater than 1 were also more likely to suffer an event. Although none of these factors reached statistical significance, this probably reflects the small numbers in each group. Interestingly there was no correlation between a history of ischaemic heart disease and outcome despite the use of the definition established by Lee et al (Lee et al. 1999a). This finding may be explained by the high frequency of occult coronary artery disease in patients with peripheral vascular disease (Mautner et al. 1992). The simplistic allocation of cardiac disease into symptomatic and asymptomatic may not be valid in this cohort.

Myocardial infarction after surgery is more often silent than symptomatic (Badner et al. 1998). In this study, one-half of post-operative MIs were clinically asymptomatic. Post-operative MI is associated with a poor prognosis and those patients with an asymptomatic rise in post-operative troponin have been shown to have a poorer outcome at 1 year (Kertai et al. 2004a). Therefore, routine post-operative screening for cardiac events may be beneficial to identify these high-risk patients, allowing appropriate cardiac assessment.

Pre-operative cTnI was raised in 3 patients in whom it was a universally poor prognostic marker (2 cardiac deaths, 1 non-fatal MI). Interestingly there was no correlation between

the level of cTnI rise and severity of outcome. Few studies have reported the role of pre-operative cTnI measurement, and those that have done so confirmed these findings. Hobbs et al (2005) studied peri-operative cTnI in patients with critical limb ischaemia and described 2 patients who had an elevated pre-operative level: one sustained a fatal intra-operative cardio-pulmonary arrest while the other had a markedly raised post-operative troponin and developed acute congestive heart failure. The only common factors amongst the three patients with a raised preoperative cTnI in this study were the urgency of their procedure, the failure of prescription of statins and high levels of both BNP and CRP.

In summary, this study confirms that routine preoperative cTnI testing could be used to identify patients in whom a poor outcome is likely. For these patients it may be preferable to defer surgery allowing cardiac investigation and optimisation (Kertai et al. 2004b). In some cases, surgery cannot be delayed since the tissue ischaemia and necrosis is the cause of the cardiac stress. In this event the presence of a senior anaesthetist and surgeon as well as high dependency care, cardiac optimisation and haemodynamic monitoring post operatively may reduce risk.

6. C-reactive Protein (CRP) As A Prognostic Marker In Patients Undergoing Major Vascular Surgery

6.1 Introduction

Cardiac morbidity remains a major problem associated with vascular surgery despite measures to reduce risk (Kertai et al. 2003b). As atherosclerosis is a systemic disease, patients scheduled for vascular surgery are predisposed to having coronary artery disease with haemodynamically significant lesions present in up to 36% of patients (Hertzer et al. 1984).

Atherosclerosis is also now thought to be an inflammatory process, with inflammation coupling dyslipidaemia to atherogenesis. (Libby 2002;Willerson & Ridker 2004) As a consequence, of this inflammatory markers have been investigated as predictors of cardiac outcome. The non-specific acute-phase reactant C-reactive protein (CRP) has shown particular promise in this regard with raised serum concentrations increasing the odds of patients suffering a myocardial infarction in the short and long term (Haverkate et al. 1997;Sakkinen et al. 2002). CRP levels have been analysed specifically in critical limb ischaemia patients and have predicted cardiac morbidity and mortality at 1 year follow-up in both surgical and non-surgical cohorts (Barani et al. 2005;Rossi et al. 2002).

The aim of this study was to determine if there was an association between pre-operative CRP concentration and short-medium term cardiac outcome in patients undergoing major vascular surgery.

6.2 Patients and Methods

6.2.1 Patients

All patients scheduled for major vascular surgery in a single centre over an 18 month period were eligible for inclusion. Patients in this study had participated in the studies assessing the predictive value of BNP concentration. Patients were excluded if they were unable to give informed consent or if their surgery was emergency (<24 hours of admission). Local research and ethics committee approval was obtained for this study.

6.2.2 Sample collection and analysis

Serum CRP was collected and analysed along with routine pre-operative bloods on the day prior to surgery. CRP was determined with the Abbott assay (Abbott diagnostics) which has a sensitivity of 0.5mg/l. Routine pre-operative investigations were conducted at the discretion of surgical and anaesthetic staff.

6.2.3 Data Collection

Basic demographic data and factors relating to the cardiac risk of surgery were prospectively gathered for each patient. These included: clinical variables, medications prescribed, and intra-operative details. Ischaemic heart disease (IHD) and heart failure were classified using established definitions (Lee et al. 1999b;Swedberg et al. 2005). Renal impairment was defined as a pre-operative creatinine of greater than 130µmol/l and intra-operative hypotension as a systolic blood pressure of less than 90mmHg for more than 5 minutes during surgery.

6.2.4 Study end-points

The end-points for the study were non-fatal myocardial infarction and cardiac death. The definition of myocardial infarction was that of The Joint European Society of Cardiology/American College of Cardiology Committee. Cardiac death was defined as death secondary to myocardial infarction, cardiogenic shock or intractable dysrhythmia, and was determined by a review of post-operative data by 2 cardiologists who were blinded to pre-operative CRP levels. Patients were followed up for six weeks after surgery.

6.2.5 Post-operative detection and interpretation of cardiac events

Post-operative screening for cardiac events consisted of daily clinical assessment, serial electrocardiography and cardiac troponin I measurement on post-operative days 2, 5 and 42. Other investigations were conducted as clinically indicated. ECG analysis was performed by 2 cardiologists blinded to all other data and patient details, in a batch at the end of the study period. In a random sample of 10% of patients, ECGs, clinical notes and data entry was analysed separately in order to ensure quality control.

6.2.6 Statistical analysis

Statistical analysis was conducted using SPSS® statistical software package (SPSS, Chicago, Illinois, USA). Univariate analysis between groups was conducted using Pearson's chi-square test or a two-tailed Fisher's exact test. Continuous variables were compared using a Mann-Whitney test. Values are reported as median (interquartile

range). ROC curves were created to determine the relationship between CRP and cardiac events.

6.3 Results

6.3.1 Population

124 patients (86 males and 38 females) were recruited to the study over the 18 month period. Cardiac co-morbidity was common: ischaemic heart disease (44); heart failure (30). Some 55 patients were prescribed a statin and 22 a beta blocker. The case-mix is shown in table 6.1. Patients underwent aortic surgery (36), peripheral bypass surgery (51) and lower extremity amputation (37). Further operative factors are shown in table 6.1

6.3.2 Cardiac events

Some 21 patients (17%) suffered a cardiac event. These consisted of 12 non fatal myocardial infarctions and 9 cardiac deaths. Thirteen events (62%) occurred in the first 48 hours, 5 from 48 hours to 1 week (24%) and 3 (14%) between 1 and 6 weeks. Cardiac events were more common in patients with a history of cardiovascular, cerebrovascular or renovascular disease, although none of these were significant predictors of outcome. The event rate was lower in patients prescribed statins but not beta-blockers. Urgency of procedure (within the same stay as an emergency admission/referral) and type of procedure were the only operative factors which significantly impacted on outcome, although the cardiac event rate was higher if patients had sustained intra-operative hypotension (Table 6.1).

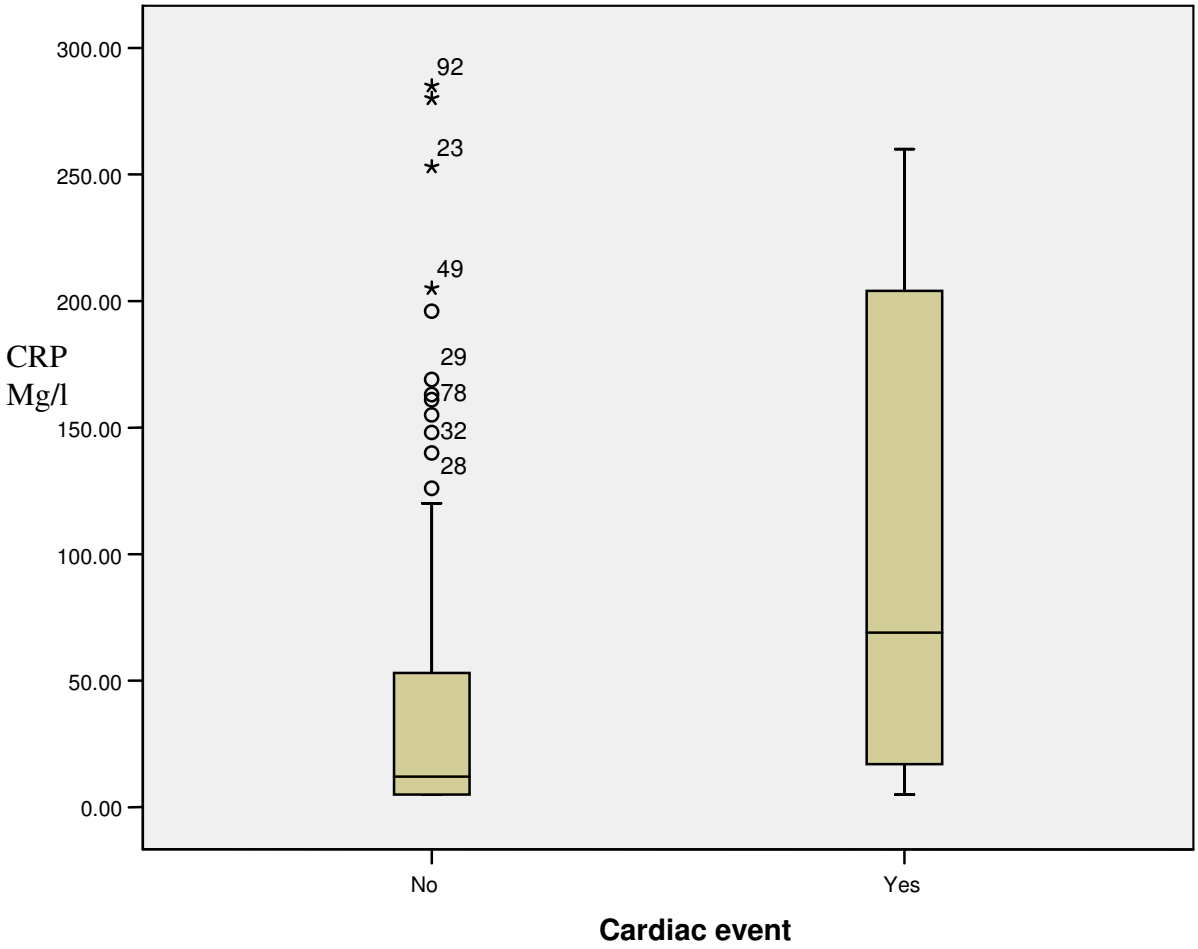
Table 6.1 Risk factors and the cardiac event rate

Risk Factor		n	Cardiac Event n	No Cardiac Event (%)	p
Sex	Male	86	15 (17.4)	71 (82.6)	1
	Female	38	6 (15.8)	32 (84.2)	
Ischaemic Heart Disease	Yes	44	10 (22.7)	34 (77.3)	0.219
	No	80	11 (13.8)	69 (86.2)	
Heart Failure	Yes	30	8 (26.7)	22 (73.3)	0.159
	No	94	13 (13.8)	81 (86.2)	
Diabetes Mellitus	Yes	32	8 (25.0)	24 (75.0)	0.177
	No	92	13 (14.1)	79 (85.9)	
COPD	Yes	27	3 (11.1)	24 (88.9)	0.562
	No	97	18 (18.6)	79 (81.4)	
Cerebrovascular Disease	Yes	14	4 (28.6)	10 (71.4)	0.254
	No	110	17 (15.5)	93 (84.5)	
Renal Impairment	Yes	17	4 (23.5)	13 (76.5)	0.487
	No	107	17 (15.9)	90 (84.1)	
Beta Blocker	Yes	22	5 (22.7)	17 (77.3)	0.530
	No	102	16 (15.7)	86 (84.3)	
Statin	Yes	55	9 (16.4)	46 (83.6)	0.815
	No	69	13 (18.8)	56 (81.2)	
Urgent Procedure	Yes	11	6 (54.5)	5 (45.5)	0.028
	No	113	15 (21.1)	98 (78.9)	
Surgery	Aortic	36	5 (13.8)	31 (86.2)	0.008
	Bypass	51	4 (7.8)	47 (92.2)	
	Amputation	37	12 (32.4)	25 (67.6)	
Intraop hypotension	Yes	27	7 (25.9)	20 (74.1)	0.243
	No	97	14 (14.4)	83 (85.6)	
Blood Loss	<500mls	93	18 (19.4)	75 (80.6)	0.276
	500+mls	31	3 (9.7)	28 (90.3)	
Operation time	<2hrs	61	12 (19.7)	49 (80.3)	0.479
	2+hrs	63	9 (14.3)	54 (85.7)	
Eagle score	0	57	3 (5.3)	54 (94.7)	
	1-2	58	13 (22.4)	45 (77.6)	
	3+	9	5 (55.6)	4 (44.4)	<0.001

6.3.3 Inflammatory markers and cardiac outcome

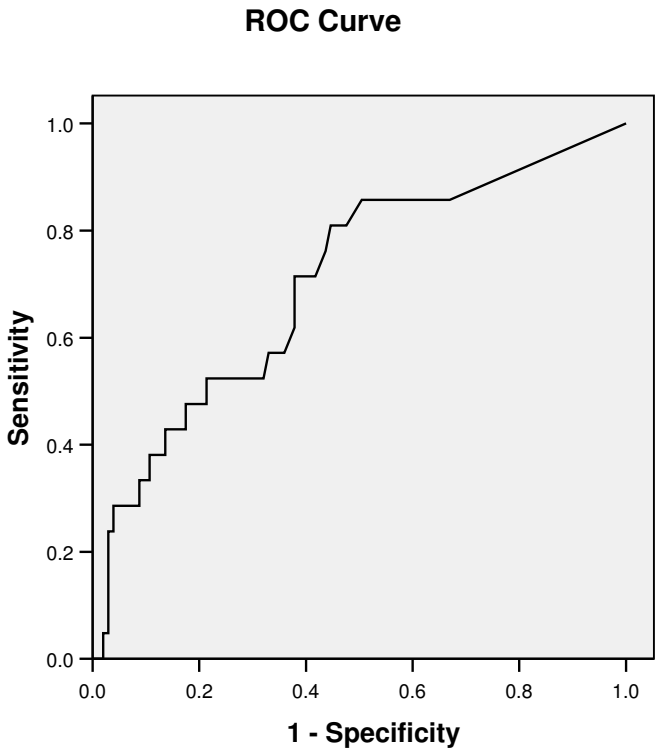
The median CRP (mg/l) was 16 (5-75). The median CRP in those patients who had a cardiac event was significantly higher than those who did not: 69 (17-205) vs. 12 (5-55), (p=0.003) (Figure 6.1).

Figure 6.1 CRP and the cardiac event rate



ROC curve analysis was conducted (figure 6.2) with the area under the curve being 0.704. A CRP of 20mg/l was the best performing cut-off having a sensitivity of 71.4% and a specificity of 62.1%

Figure 6.2 ROC curve: CRP and cardiac events



The cardiac event rate rose between each CRP tertile, although there was only a trend to significance (p= 0.057) (Table 6.2). However with each logarithmic increment in CRP the cardiac event rate changed significantly: 0-10mg/l (5.7%); 11-100mg/l (22.4%), >100mg/l (55.6%) (p=0.002), (Figure 6.3, Table 6.3).

The median white cell count (WCC) was 9.4 (7.4-12.0). The median WCC in those patients who had an event was higher than in those who did not: 10.9 (9.9-12.0) vs. 8.7 (7.1-12.0) (p=0.008). Some 15 of 92 (16.3%) patients with a WCC of less than 12 had a cardiac event compared with 6 of 32 (18.8%) patients whose WCC was 12 or greater (p=0.787), (Table 6.2).

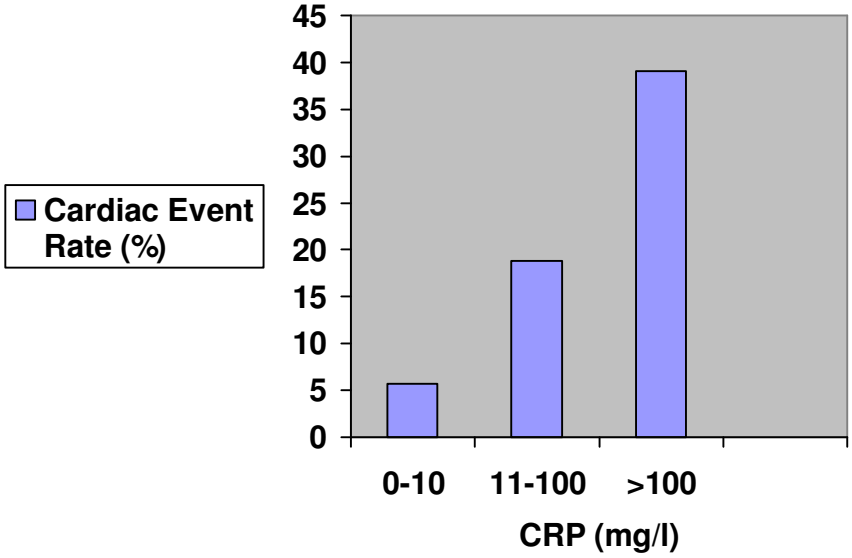
Table 6.2 CRP tertiles and the cardiac event rate

Inflammatory marker		n	Cardiac Event		No Cardiac Event		p
CRP tertile	0-6	42	3	(7.1)	39	(92.9)	
	7-44	41	7	(17.1)	34	(82.9)	
	>44	41	11	(26.8)	30	(73.2)	0.057
WCC (10^9)	4-12	92	15	(16.3)	77	(83.7)	
	>12	32	6	(18.8)	26	(81.3)	0.787
Total		124					

Table 6.3 CRP and the cardiac event rate

Inflammatory marker		n	Cardiac Event		No Cardiac Event		p
CRP (mg/l)	0-10	53	3	(5.7)	50	(94.3)	
	11-100	48	9	(18.8)	39	(81.2)	
	>100	23	9	(39.1)	14	(60.9)	0.002
Total		124					

Figure 6.3 CRP and the cardiac event rate by logarithmic increment



The correlation between CRP and cardiac outcome varied depending on the category of vascular procedure conducted. In patients who underwent an aortic operation the cardiac event rate rose with each increment in CRP concentration. However this relationship did not hold in the amputation and peripheral revascularisation groups. Although in peripheral bypass patients the event rate rose markedly between the first 2 categories, none of the 4 patients with a CRP (mg/l) of greater than 100 had an event. Similarly, in the amputation group, although patients with a CRP (mg/l) of greater than 100 had a much higher event rate than those with a level of 11-100, 1 of the 3 patients with a CRP of less than 10 did suffer a cardiac event (Table 6.4).

CRP concentration was associated with cardiac outcome irrespective of the presence of ischaemic heart disease. The cardiac event rate rose with each increment in CRP whether IHD was present or absent (Table 6.4).

Table 6.4 CRP and cardiac events by procedure

	CRP(mg/l)	Cardiac Events	%	p
Aortic Procedure	0-10	1/18	5.6	
	11-100	3/16	18.8	
	>100	1/2	50.0	0.170
Peripheral bypass	0-10	1/32	3.1	
	11-100	3/15	20.0	
	>100	0/4	0.0	0.111
Amputation	0-10	1/3	33.3	
	11-100	3/17	17.6	
	>100	8/17	47.1	0.187
IHD present	0-10	1/34	2.9	
	11-100	4/29	13.8	
	>100	6/17	35.3	0.007
IHD absent	0-10	2/19	10.5	
	11-100	5/19	26.3	
	>100	3/6	50.0	0.117

6.4 Discussion

This study confirms the high incidence of cardiac complications in patients undergoing vascular surgery consistent with the systemic nature of atherosclerosis. Cardiac events occurred more commonly in patients with a history of cardiac, renal or cerebrovascular disease, although the only clinical factors which were significant predictors of cardiac outcome were urgency and type of procedure. The clinical scoring system developed by Eagle (Eagle et al. 1989), which incorporates 5 clinical factors was highly predictive of cardiac events consistent with previous studies (Back et al. 2003;Poldermans et al. 1995).

C-reactive protein concentration was significantly predictive of outcome, with increasing cardiac event rates with each logarithmic increment. A trend to significance was demonstrated between CRP tertiles. Both CRP concentration and WCC were significantly higher in those patients who suffered a cardiac event compared with those who did not. The cardiac event rose with each increment in CRP whether ischaemic heart disease was present or absent. When different procedures were considered, the correlation between CRP concentration and cardiac events was most consistent in the aortic group, possibly because in this group the CRP concentration was least likely to be raised as a consequence of peripheral sepsis. A raised level in these patients may have been more likely to represent systemic atherosclerosis.

CRP concentration has been shown to predict coronary events in patients with pre-existing cardiac disease in the medium and long term (Sakkinen et al. 2002). Levels have been associated with the likelihood of developing peripheral vascular disease (Ridker et

al. 1998) and found to be inversely proportional to the ABPI (Vainas et al. 2005). Furthermore femoral plaques have been demonstrated to produce CRP (Vainas et al. 2005). CRP concentration has been correlated with cardiac outcome at 24 months following vascular surgery, with concentrations in the upper tertile predicting 60% of myocardial infarctions (Rossi et al.2002). In addition, in their study of 259 patients with critical limb ischaemia, Barani et al found the mean CRP in those patients who suffered a fatal event was significantly higher than those who survived (49.4 vs. 33.6, p= 0.02), although when the presence or absence of gangrene was taken into account the difference was no longer significant (Barani et al. 2005). No studies to date have correlated CRP concentration with peri-operative cardiac complications.

This study has demonstrated a correlation between CRP concentration and cardiac outcome following vascular surgery. Whilst this may reflect systemic inflammation, raised levels due to coronary atherosclerosis would also explain the relationship. Furthermore the correlation between CRP and cardiac outcome was most noticeable in aortic surgery patients, the group in whom peripheral sepsis was least likely.
CRP is a relatively inexpensive and routine test. Measurement prior to vascular surgery may be of benefit in predicting the likelihood of peri-operative cardiac events, but may also be of use as a target for reducing the event rate by modulating the inflammatory response.

7- Discussion

7.1 Limitations of the thesis

An attempt was made to make the work in this thesis as robust and comprehensive as possible, however there were limitations. Although adequately powered to demonstrate significant differences between the primary variables studied, the small sample-size was an issue and precluded multivariate analysis in all but chapter 4. Even in this study however, the statistical model became unstable as additional factors were adjusted for, thus limiting the information gained.

A differing approach to statistical analysis may also have been appropriate. Creatinine concentrations were dichotomised when they could have been better analysed as continuous variables. This may have led to a more accurate demonstration of the effect of pre-operative renal function on outcome. Furthermore the same cut-off values were used to discriminate an abnormal creatinine in males and females when ideally differing values for each sex would have been more appropriate.

The predominant role of renal function in determining BNP levels could also have been better accounted for. In addition to the use of creatinine as a continuous variable in analysis, glomerular filtration rate could have been employed as a variable and would have been superior to the methods used. Unfortunately on initiation of the studies conducted in this thesis the current techniques for estimating GFR were not available.

7.2 Cardiac morbidity associated with surgery

The findings of this thesis confirm that cardiac morbidity is still a major problem associated with general surgery and with vascular surgery in particular. Cardiac event rates were 6.6% in general surgical patients and ranged from 12.5% to 26.8% in vascular patients. Lower extremity amputation carried a particularly high risk consistent with the extreme nature of the atherosclerosis in these patients. Attempts to predict the occurrence of cardiac events in these cohorts and therefore improve the outcome post-surgery therefore continue to be relevant.

This thesis does not deal with the nature of peri-operative myocardial infarction, but the prevalence of silent myocardial infarction (20-27% of events) was surprising although consistent with some studies (Badner et al. 1998;Raby et al. 1992). Screening for cardiac events detected silent myocardial infarctions and this almost certainly contributed to the higher event rates in the studies within this thesis.

7.3 Timing of cardiac events

The likelihood of a cardiac event was inversely proportional to the length of time from the operative stress. Peri-operative cardiac events occurred most commonly in the first 48 hours (60-64%), with events from 48 hours to 6 weeks (20-27%) and from 1 week onwards (9-20%) being less likely. Screening for cardiac events would therefore be most useful immediately following surgery but if confined to this period would fail to detect some events. Screening may therefore also be of benefit for a period beyond the immediate post-operative phase.

7.4 Clinical and operative factors and the cardiac event rate

The cardiac event rate was universally higher in patients with established clinical risk factors. Heart failure, ischaemic heart disease, renal impairment, cerebrovascular disease and diabetes mellitus were consistently associated with poor cardiac outcome although none was a significant single predictor of cardiac events in any of the cohorts.

Patients undergoing vascular surgery, particularly those scheduled for amputation were at highest risk of cardiac events reflecting the systemic nature of their atherosclerosis. This has been a consistent finding in studies assessing the risk of individual procedures (Detsky et al. 1986;Lee et al. 1999b). The single most important operative factor relating to outcome was the presence of intra-operative hypotension. Although not a significant predictor of outcome, its occurrence was consistently related to an increased cardiac event rate. This finding would support the theory that peri-operative myocardial infarctions are due to an imbalance in the supply and demand of oxygen related to the stress of surgery in the presence of coronary artery disease (Grayburn & Hillis 2003).

Patients undergoing procedures classed as urgent were also at higher risk of a cardiac event. This may relate to the physiological condition of the patient, but also to the lack of opportunity for optimisation prior to the procedure. Surprisingly neither increased procedure time nor increased blood loss consistently affected the cardiac event rate in any of the studies described in this thesis.

7.5 Cardiac medications

This thesis has not specifically addressed the benefits of beta-blockers or statins, however it is interesting that in the pilot BNP study (chapter 3), the cardiac event rate was lower in patients prescribed beta-blockers. This finding was however not replicated in the larger studies. This is perhaps unsurprising since those patients in whom beta blocker therapy was thought necessary by treating physicians would be more likely to have associated co-morbidities predisposing them to cardiac events. The benefits of statin prescription are similarly difficult to interpret. In the validation BNP study, which analysed both general and vascular surgical patients (chapter 4), the cardiac event rate was higher in patients prescribed statins. However in the purely vascular cohorts and in particular when only amputation patients were considered, the event rate was lower in patients prescribed statins consistent with those studies reporting their cardio-protective role (Kertai et al. 2004a;Poldermans et al. 2003). It may be that statin therapy is of most benefit in these higher risk patients.

7.6 Clinical scoring systems

The two main scoring systems studied and employed in this thesis are the Eagle score (Eagle et al. 1989) and the RCRI (Lee et al. 1999b). The Eagle score was consistently predictive of cardiac outcome in patients undergoing vascular surgery, being a significant predictor of outcome in both cohorts in which it was evaluated (chapters 3 and 6). Although it was not a significant predictor of outcome in the study analysing purely amputation patients (chapter 5) this may reflect the fewer numbers analysed. Despite being devised some years ago the Eagle score may be of benefit in pre-operative decision

making strategies. As it was not designed to do so, the effectiveness of the Eagle score was not evaluated in non-vascular patients.

The revised cardiac risk index has been validated in non-cardiac surgical patients (Lee et al. 1999b), however in the studies included in this thesis it was not discriminatory between the event rates in the lowest two risk categories, with a disproportionate number of patients with a score of 0 suffering an event. The likelihood of suffering a cardiac event did however increase between the three highest risk categories (8.2%, 9.5% and 17.6%). In the original paper the RCRI performed better in those patients who underwent non-vascular surgery. However, when only non-vascular patients were considered in this thesis the predictive ability of the RCRI did not improve. This could be attributed to the smaller numbers analysed as only 4 patients were found to have an RCRI of 3 or more. Although the RCRI can provide additional prognostic information, on the evidence of this thesis it could not be used to determine a treatment plan for individual patients.

7.7 B-type natriuretic peptide

BNP concentration was consistently found to be a predictor of cardiac events, and mortality, although the optimal cut-off point varied depending on the cohort and the type of surgery conducted. In the pilot study (chapter 3), a BNP concentration of 123pg/ml was completely discriminatory for the prediction of cardiac events, whereas in the validation study, ROC analysis identified a BNP concentration of 108.5pg/ml as being the best cut-off, having the best combined sensitivity (87%) and specificity (87%) for the prediction of cardiac events. Whilst the optimal cut-off BNP concentration for patients

undergoing a non-vascular procedure in the validation study was also 108.5pg/ml, it was somewhat higher in the vascular patients with a level of 140.5pg/ml having a sensitivity of 82% and a specificity of 86%.

The majority of patients in the studies in this thesis had a BNP concentration of less than 108.5pg/ml and could therefore have their surgery expedited with no further intervention required. As only 21% of patients had a BNP concentration of greater than 108.5pg/ml (in the validation cohort, chapter 4) it is feasible that these patients could be more thoroughly investigated and better optimised prior to the proposed surgical procedure. This may be of benefit, particularly given the high cardiac event rate observed in these patients in the validation study. In patients with a BNP concentration of greater than 180pg/ml the cardiac event rate exceeded 50%. This group therefore carry a significant risk of a cardiac event and a change in their treatment pathway is likely to be appropriate.

The prognostic ability of BNP cannot be attributed to any other factor, as in a logistic regression model, $\log_e$BNP remained a highly significant predictor of cardiac events. Furthermore, in each category of the RCRI, BNP levels were higher in those patients who had a cardiac event. BNP concentration was highly predictive for cardiac events irrespective of the surgery performed and its measurement is therefore applicable to both vascular and general surgery populations. Measurement of BNP is a simple and practical test, with newer assays yielding results in 21 minutes. It outperforms conventional scoring systems (Lee 1999b) and has a similar predictive ability to more complex, time consuming and expensive tests such as DSE (Poldermans 1995).

Some 20% of patients in this study had a BNP concentration of greater than 108.5pg/ml and results from this study would suggest that in these patients it may be appropriate to consider a change in the treatment plan. Only 2 patients with a "low" BNP had a cardiac event and although both patients would be considered as at moderate or severe risk of a cardiac event by virtue of their other clinical factors, there were few similarities between the two. This reflects the multifactorial nature of peri-operative cardiac morbidity.

Cardiac troponin I

A pre-operative rise in cTnI is a rare phenomenon, both in this study and in those studies available in the literature (Higham et al. 2004;Hobbs et al. 2005). In the patients analysed in this thesis a rise occurred exclusively in patients scheduled for lower extremity amputation. Nonetheless it is a useful observation since these patients had a universally poor outcome (significant cardiac event or death). It may therefore be preferable to defer surgery in this group thus allowing the opportunity for cardiac optimisation. At the very least it should be ensured that operative stress is at a minimum with an experienced team being involved. Post-operatively, high dependency care for these patients may also be of benefit.

C-reactive protein

Consistent with previous studies, pre-operative CRP concentration correlated with cardiac outcome following vascular surgery (Barani et al. 2005;Rossi et al. 2002). The percentage of patients having a cardiac event increased with each logarithmic increment

in CRP (p=0.002) and also between tertiles (p=0.057). Whilst peripheral sepsis may have contributed to the elevated CRP level observed in some patients; coronary and systemic atherosclerosis is also likely to have influenced levels. It is particularly interesting that in the aortic surgery group (those patients least likely to have peripheral gangrene/sepsis) the observed relationship between cardiac events and CRP remained, suggesting that this particular group may benefit from further study. Measurement of CRP prior to vascular surgery may be of benefit in predicting the likelihood of peri-operative cardiac events, although its value may be limited by its non-specific nature. However it could also be of use as a marker in attempts to reduce the cardiac event rate by modulating the inflammatory response.

Conclusion

It has been suggested that the paradigm has shifted from predicting peri-operative cardiac events to their prevention (Grayburn, 2003). However with some doubt being cast over the initially promising measures to reduce the cardiac event rate (Devereaux et al. 2005), perhaps it is necessary to reconsider this. By careful case selection it may be possible to reduce the cardiac event rate and therefore the morbidity and mortality associated with surgery. Clinical scoring systems and biochemical markers such as CRP can give a guide to the likelihood of a cardiac event, but are not sufficiently predictive to alter the treatment plan. However pre-operative BNP concentration is a sensitive and specific predictor of outcome with predictive values sufficiently high to suggest that a change in the management plan for patients with raised level may be appropriate. Based on the

findings of this thesis BNP measurement is likely to become an integral part of pre-operative assessment in the future.

Further work

Whilst the findings of this thesis are promising, further work is necessary to accurately determine the cut-off BNP concentration at which a particular patient's treatment plan should be altered. This may vary depending on the patients' co-morbidities but of particular interest would be identifying cut-off values for specific types of surgery. Therefore, following up from the work conducted in this thesis, a study is currently being conducted assessing the predictive ability of BNP (and other biochemical marker) concentrations specifically in patients scheduled for abdominal aortic aneurysm repair.

Each biomarker (BNP, CRP, CTnI) has been assessed individually in this thesis however potential exists to undertake a multi-marker approach and determine whether this would improve the prediction of cardiac events. This could form the basis for further work in a larger cohort.

This thesis has dealt with the predictive value of BNP and other biochemical markers in predicting cardiac outcome up to 6 weeks post-surgery. It would also be of benefit to know whether the predictive ability of BNP was maintained over a longer period. To this end the cohorts studied in this thesis are currently being followed up to determine the predictive value of BNP and other biochemical markers at 1 year.

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Appendix 1: Information sheet/consent form

THIS SHEET HAS BEEN APPROVED BY THE WEST ETHICS COMMITTEE

INFORMATION SHEET FOR PATEINTS/VOLUNTEERS IN CLINICAL RESEARCH PROJECT

Brief Title of Project

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

Patient's Summary (Purpose of study, nature of procedure, discomfort and possible risks in terms which the patient or volunteer can understand).

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, and also 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: Data sheet

B.N.P. Study

Name
Hospital Number
Date of Birth

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 disease 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

Lipids - cholesterol LDL
Triglycerides HDL

Magnesium

Troponin

ECG done normal abnormal

Sats on air

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

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

1 week

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