University of Kwazulu-Natal

Peri-operative Studies of Hypertension

By

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ABSTRACT

Background:

The impact of a pre-operative history of hypertension on mortality and poor cardiac, renal, and neurological outcomes following non-cardiac surgical procedures in South African patients is not well described.

Aim:

The aim of this research was to study the impact of a pre-operative history of hypertension (classified as a physician-based diagnosis of hypertension made prior to surgery or any anti-hypertensive medication use prior to surgery) on mortality and poor cardiac, renal, and neurological outcomes following non-cardiac surgical procedures in South African patients.

Method:

This research involved the analysis of prospectively and retrospectively collected data obtained from adult patients undergoing non-cardiac and vascular surgery procedures at a tertiary South African hospital. Specifically, data related to patient factors (including comorbid conditions and medication use) and peri-operative outcomes (including in-hospital mortality, and cardiac, renal and neurological morbidity) were collected. Study designs employed in this research included prospective and retrospective cohort designs, and a case-control design. Data were analyzed by standard statistical methods. Results are presented within five manuscripts which have been published in peer-reviewed medical journals.

Results:

A pre-operative history of hypertension did not predict in-hospital mortality following non-cardiac surgery (Odds Ratio: 1.119, 95% Confidence Interval: 0.823-1.522), nor did it predict peri-operative major adverse cardiovascular events in vascular surgery patients (Odds Ratio: 0.740, 95% Confidence Interval: 0.416-1.315). Acute pre-operative β-blockade was independently associated with major adverse cardiovascular events in vascular surgery patients with a pre-operative history of hypertension (Odds Ratio: 3.496, 95% Confidence Interval: 1.948-6.273). Acute pre-operative β-blockade was also an independent predictor of post-operative acute kidney injury in non-suprainguinal vascular surgery patients with a pre-operative history of hypertension (Odds Ratio: 3.24, 95% Confidence Interval: 1.03-10.25). Extremes of pre-induction blood pressure were associated with a higher incidence of poor post-operative neurological outcomes in hypertensive carotid endarterectomy patients (p=0.003).

Conclusions:

In a South African setting, the relationship between a pre-operative history of hypertension and in-hospital mortality following non-cardiac surgery is unclear. The relationship between a pre-operative history of hypertension and poor peri-operative cardiac outcomes following vascular surgery is also unclear. It appears that pre-operative anti-hypertensive use, namely acute β-blockade, is an important driver of poor peri-operative cardiac and renal outcomes in vascular surgery patients with a pre-operative history of hypertension. There appears to be a crude association between extremes of pre-induction blood pressure and a higher incidence of poor neurological outcomes following carotid endarterectomy.

ATTESTATION

I declare that:

(i) The research reported in this thesis is my original research.

(ii) This thesis has not been submitted for any degree or examination at any other university.

(iii) This thesis does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

(iv) This thesis does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then their words have been re-written but the general information attributed to them has been referenced.

(v) This thesis does not contain text, graphics or tables copied and pasted from the Internet, unless specifically acknowledged, and the source being detailed in the thesis and in the References section.

My contribution to each manuscript includes:

(a) Conception or design of the work; and the acquisition, analysis, and interpretation of data for the work.

(b) Drafting the work or revising it critically for important intellectual content.

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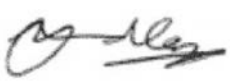
Signature:  **Date:** 02 February 2015

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Last but not least, I would like to thank my parents for their constant love and support during my scholarly journey.

LIST OF MANUSCRIPTS

LIST OF ABBREVIATIONS

Review of the Literature

ACEI	Angiotensin-Converting-Enzyme Inhibitors
AKI	Acute Kidney Injury
ALLHAT	Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ARB	Angiotensin Receptor Blockers
CAPPP	Captopril Prevention Project
CCB	Calcium Channel Blockers
RAS	Renin-Angiotensin System
UKPDS	United Kingdom Prospective Diabetes Study
VISION	Vascular events In non-cardiac Surgery patIents cOhort evaluatioN

Introduction

AKI	Acute Kidney Injury
DECREASE	Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography
GHS	General Household Survey
HIV	Human Immunodeficiency Virus
SADHS	South African Demographic and Health Survey

Manuscript 1

CIs	Confidence Intervals
IALCH	Inkosi Albert Luthuli Central Hospital
ICD-10	International Statistical Classification of Diseases and Related Health Problems (10th Edition)
IHM	In-Hospital Mortality
ORs	Odds Ratios
PAF	Population-Attributable Fraction
RCRI	Revised Cardiac Risk Index
SA	South African
SPSS	Statistical Package for the Social Sciences

Manuscript 2

ACC/AHA	American College of Cardiology/American Heart Association
ANOVA	Analysis of Variance
AUC	Area Under the Curve
CIs	Confidence Intervals
CVA	Cerebrovascular Accident
HIV	Human Immunodeficiency Virus
IALCH	Inkosi Albert Luthuli Central Hospital
IQR	Interquartile Range
MACEs	Major Adverse Cardiac Events
ORs	Odds Ratios
RCRI	Revised Cardiac Risk Index

ROC	Receiver-Operator Characteristic
SA	South African
SAVS-CRI	South African Vascular Surgical-Cardiac Risk Index
SD	Standard Deviation
VISION	Vascular events In non-cardiac Surgery patIents cOhort evaluatioN
VSG-CRI	Vascular Surgery Group of New England-Cardiac Risk Index

Manuscript 3

ACEI	Angiotensin-Converting-Enzyme Inhibitors
AKI	Acute Kidney Injury
BB	β-Blockers
CCB	Calcium Channel Blockers
CI	Confidence Interval
OR	Odds Ratio
POISE	Peri-operative Ischemic Evaluation
SPSS	Statistical Package for the Social Sciences

Manuscript 4

BP	Blood Pressure
CEA	Carotid Endarterectomy
DBP	Diastolic Blood Pressure
NASCET	North American Symptomatic Carotid Endarterectomy Trial

SBP	Systolic Blood Pressure
VISION	Vascular events In non-cardiac Surgery patIents cOhort evaluatioN

Manuscript 5

CI	Confidence Interval
MACEs	Major Adverse Cardiovascular Events
OR	Odds Ratio
SAVS-CRI	South African Vascular Surgical-Cardiac Risk Index
SPSS	Statistical Package for the Social Sciences
POISE	Peri-operative Ischemic Evaluation

Conclusions

GHS	General Household Survey
MACEs	Major Adverse Cardiovascular Events
SADHS	South African Demographic and Health Survey
VISION	Vascular events In non-cardiac Surgery patIents cOhort evaluatioN

LIST OF TABLES

Review of the Literature

Manuscript 1

Manuscript 2

Manuscript 3

Manuscript 4

Manuscript 5

LIST OF FIGURES

Manuscript 1

Manuscript 2

Manuscript 3

Manuscript 4

Manuscript 5

Not Applicable

TABLE OF CONTENTS

CHAPTER 1:

Review of the Literature

1. REVIEW OF THE LITERATURE

1.1 Definition of hypertension:

Several observational studies have demonstrated a direct relationship between high blood pressure and the development of cardiovascular and renal diseases.[1] A diagnosis of high blood pressure, or hypertension, is usually made following a physician-observed chronic elevation of systemic blood pressure above a defined threshold level.[2] The international threshold for defining hypertension has undergone several revisions. Initial medical guidelines published in the 1970's proposed that hypertension be defined as the average of consecutive systolic blood pressure measurements ≥160 mmHg or diastolic blood pressure measurements of ≥95 mmHg.[3] Following several modifications to this definition, the contemporary definition of hypertension is described as a chronic elevation in systolic/diastolic blood pressure measurement of ≥140/90 mmHg. Furthermore, the severity of hypertension can be classified into one of two groups (Table 1).[4]

Table 1. Classification of blood pressure measurements[4]

Blood Pressure Classification	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)
Normal	<120	and <80
Pre-hypertension	120–139	or 80–89
Stage 1 Hypertension	140–159	or 90–99
Stage 2 Hypertension	≥160	or ≥100

1.2 Epidemiology of hypertension:

Globally, hypertension is a major cause of cardiovascular disease, morbidity, and mortality.[5] An analysis of worldwide data by Kearney and colleagues found that nearly one billion adults had hypertension in 2000, with this number and likely to rise to approximately 1.5 billion by 2025. Developing countries are expected to be hardest hit by this predicted increased global burden of hypertension.[5] Ogah and Rayner estimated that there will be 125 million sub-Saharan Africans afflicted with hypertension by 2025.[6]

Whilst the conduct of epidemiological studies in Africa is challenging, there have been attempts to determine the burden of hypertension in this region. A review by Mensah which was published in 2013 estimated the prevalence of raised blood pressure in sub-Saharan Africa at between 16% and 40%.[7] A 2014 meta-analysis by Ogah and Rayner estimated the prevalence of hypertension in sub-Saharan Africa to be 16.2%.[6] Communicable diseases have long been associated with the highest levels of morbidity and mortality in Africa,[8] although many countries in Africa currently appear to be in a phase of epidemiological transition, which has seen the burden of non-communicable diseases nearing the burden of communicable diseases in these countries.[8] As such, there exists a need to shift public health focus towards the growing burden of chronic non-communicable diseases, in particular hypertension, on the African continent.

1.3 Risk factors for the development of hypertension:

Risk factors for hypertension may be modifiable or non-modifiable.

1.3.1 Non-modifiable risk factors for hypertension:

1.3.1.1 Age:

Age is a well-established risk factor for hypertension.[9] The prevalence of hypertension has been shown to increase with age. It is estimated that more than 75% of the elderly population suffers from hypertension. The high prevalence of hypertension in this group may be explained by a number of age-associated trends. Amongst these trends are sodium sensitivity, frequent isolated systolic hypertension, increased arterial stiffness, and endothelial dysfunction.[9]

1.3.1.2 Gender:

The risk of hypertension is generally higher in men as compared to premenopausal women of similar age.[10] This is supported by findings from several studies which have shown higher mean ambulatory blood pressure measurements over a period of 24 hours in men in contrast to premenopausal women of similar age.[11] This trend appears to be reversed following menopause, as demonstrated by large American health surveys.[12,13] Although the exact mechanisms of how gender differences increase the risk of developing hypertension are still unclear, it is likely that sex hormones play an important role. Sex hormones are thought to modulate the renin-angiotensin system

(RAS), which itself is essential in the regulation of blood pressure.[14] Gender-related variations in the genes which control the RAS might also account for the observed difference in the epidemiology of hypertension between men and women.[13]

1.3.1.3 Genetics:

Genome wide association studies have demonstrated a potential link between genetics and a pre-disposition to elevated blood pressure.[15,16] Genes are thought to account for up to 60% of the variability in blood pressure in the general population.[17-19] In addition, behavioural patterns lead to the development of hypertension might also have a genetic basis.[20] Studies of genetic polymorphisms in a number of genes, including the genes which code for angiotensin, angiotensin-converting enzyme, angiotensinase C, adducin, renin binding proteins, β_2-adrenergic receptors, atrial natriuretic factor, the insulin receptor, and G-protein β_3 subunits, have suggested a possible role of mutations in these genes in the development of hypertension.

However, findings from these studies have been far from conclusive and many authors call for further research to validate these findings.[21] It is more likely that polymorphisms within a combination of genes rather than a single gene confers a higher risk of hypertension. Thus, environmental and patient-related factors appear to be the drivers of hypertension in most populations rather than genetics.

1.3.1.4 Race:

The impact of race/ethnicity on the development of hypertension is unclear. There are some studies which report that disproportionate rates of hypertension are often seen in racial and ethnic populations.[22] A systematic review by Kurian et al., provided an updated assessment of the relationship between race/ethnicity and hypertension.[23] The overall finding was that race/ethnicity was significantly associated with hypertension, with the majority of studies finding the burden of hypertension to be higher in African Americans as compared to Caucasian Americans.[23] However, an international comparative study conducted by Cooper et al.,[24] found that while there was a wide variation in hypertension prevalence amongst Caucasian and Black populations, the prevalence of hypertension amongst Blacks were not unusually high when viewed internationally. Furthermore, the authors suggested that environmental influences within population groups might be more important factors in predicting the development of hypertension rather than race/ethnicity.[24]

1.3.2 Modifiable risk factors for hypertension:

1.3.2.1 Obesity:

Obesity is an important risk factor contributing to the overall global burden of cardiovascular disease,[25] with the importance of obesity in the aetiology of hypertension being well established.[26] Obesity might account for almost two-thirds of prevalent hypertension.[27] Indeed, obese individuals exhibit higher mean levels of blood pressure than non-obese controls.[26] The mechanism involved in obesity-related

hypertension is still unclear, however it is likely that the mechanism is multifactorial.[25] There is often a marked release of adipokines and free fatty acids from the adipose tissue in obese individuals. The release of these molecules appears to trigger inflammatory pathways linked to RAS activity, resulting in hypertension.[28]

1.3.2.2 High sodium intake:

Increased sodium consumption is associated with elevated blood pressure.[29] Evidence suggests that the average worldwide consumption of sodium exceeds that required for physiological processes.[30] Both natural and processed foods contain sodium. However, processed foods often contain higher amounts of sodium than that present in natural sources.[31] It has therefore been suggested that a modern diet, of which a substantial portion consists of processed foods, would be high in sodium thereby increasing the risk of developing hypertension.[31] A large study which used estimated sodium excretion as a surrogate for sodium intake showed a nonlinear association between sodium excretion and blood pressure, which was most pronounced amongst persons consuming high-sodium diets, persons with hypertension, and older persons.[32] An estimated sodium intake of between 3 grams/day and 6 grams/day was associated with a lower risk of death and cardiovascular events than was either a higher or lower estimated level of intake.[33]

1.3.2.3 Low potassium intake:

Potassium is essential for electrolyte homeostasis.[31] Dietary potassium decreases blood pressure in a dose-dependent manner.[34] The effect of potassium-induced blood pressure

reduction in adults is pronounced, with several studies reporting significantly lower incidence rates of adverse cardiovascular events in the setting of increased dietary potassium.[35] A recent meta-analysis by Aburto and colleagues found that increasing potassium consumption reduced systolic blood pressure by almost 3.5 mmHg and diastolic blood pressure by almost 2 mmHg. However, the reduction in blood pressure was noted in hypertensives but not normotensives.[31] Considering the recent evidence detailed in the Aburto meta-analysis,[31] there may be a beneficial impact of a reduction in blood pressure through increased dietary potassium intake, particularly in hypertensive adults, potentially reducing adverse cardiovascular events in this high-risk group.

1.3.2.4 Alcohol consumption:

The estimated global attributable risk fraction for hypertension from alcohol consumption is 16%.[36] Although there have been two dated meta-analyses which have described the impact of alcohol consumption on blood pressure,[37,38] a more recent meta-analysis by Briasoulis et al. published in 2012,[39] found that men who consumed alcohol at 31-40 grams⁄day or >50 grams⁄day were at increased risk of developing hypertension. Women who consumed of 31-40 grams of alcohol per day were also at higher risk of developing hypertension.[39] The authors concluded by suggesting the importance of limiting alcohol intake in those with pre-existing hypertension. In addition, Briasoulis and colleagues recommended vigilant blood pressure monitoring, even in hypertensive patients who are light drinkers.[39]

1.3.2.5 Reduced physical activity:

Approximately 5–13% of all diagnosed cases of hypertension can be attributed to low levels of physical inactivity.[40] Conversely, observational data suggest that higher levels of physical activity reduce the risk of future cardiovascular disease.[41] As such, international treatment guidelines for the prevention of hypertension recommend increasing levels of physical activity as one of the lifestyle modifications which form first-line therapy.[42] Physical activity is also recommended as an important lifestyle intervention for the majority of hypertensive patients in Britain.[43] These recommendations appear vindicated following the results of several observational epidemiological studies which showed that the risk of developing high blood pressure was reduced by up to 53% in those who exercised regularly.[43]

1.3.2.6 Smoking:

Tobacco use is a well-established risk factor for cardiovascular disease. Smoking is associated with acute increases in blood pressure.[44] However, tobacco use is also closely linked to (but not always associated with) arterial stiffening which is a risk factor for hypertension. During arterial stiffening, arteries become considerably less compliant.[45] Smoking appears to result in an acute stiffening of the arteries.[46,47] Arterial stiffening and subsequent increases in aortic systolic blood pressure have been demonstrated in smokers.[48] This might reduce coronary and cerebral perfusion, thereby increasing the risk of ischaemic myocardial or cerebral injury.

1.4 Consequences of hypertension:

Hypertension is an important factor driving the burden of cardiovascular and renal disease, with the severity of cardiovascular (myocardial infarction and stroke/cerebrovascular accident) and renal disease (renal failure) correlated to the severity of hypertension-induced target organ damage.[49] The adverse clinical outcomes associated with hypertension, namely myocardial infarction, stroke, and renal failure are amongst the leading causes of mortality worldwide.[50]

1.4.1 Hypertension and the heart:

Initial hypertension-induced target organ damage in the heart manifests as left ventricular hypertrophy.[49] The pathophysiological mechanism of left ventricular hypertrophy in the hypertensive patient is the result of pressure overload. Hypertrophy of the ventricular myocardium without a corresponding increase in the volume of the left ventricle negatively impairs cardiac output, resulting in systolic/diastolic dysfunction and arrhythmia.[51] Another consequence of hypertension-induced left ventricular hypertrophy is myocardial ischaemia, which is highly correlated with myocardial infarction, particularly in patients with coronary stenosis. A combination of increased oxygen demand associated with high blood pressure as well as reduced oxygenation of the myocardium due to atherosclerosis appears to be the most likely explanation for this.[51] Interestingly, a number of myocardial infarctions are asymptomatic. Hypertension has been shown to moderately increase the risk of "silent myocardial infarction".[52] The prevalence of silent myocardial ischaemia in patients with arterial hypertension is estimated at 15-57%.[53] Mortality is increased following

myocardial infarction in the hypertensive patients, and can be attributed to an increased frequency of myocardial rupture or septal defects subsequent to the infarct.[54]

1.4.2 Hypertension and the kidney:

Hypertension has been identified as an independent predictor of renal injury, and has been shown to hasten the progression of chronic kidney disease.[55,56] It is estimated that hypertension accounts for 21-29% of newly treated patients with end stage renal disease in several developed world countries.[57,58] Essential hypertension is associated with detrimental effects on the renal vascular bed, such as arteriolar thickening, fibrinoid deposition in the glomeruli, and proteinuria. Renal injury occurs when the pre-glomerular autoregulatory mechanism cannot maintain renal haemodynamic stability.[59] There are several mechanisms associated with hypertensive nephropathies. The inflammatory component of hypertension is thought to reduce nephron numbers, thereby limiting sodium filtration. Hypertension may also affect glomerular permeability, resulting in protein infiltration and nephrotoxicity.[59] Essential hypertension manifests itself as nephrosclerosis characterized by sclerosis of the arteries, arterioles, and glomeruli, as well as interstitial fibrosis.[60] These lesions may promote renal failure in the long term, however it is difficult to differentiate between lesions associated with nephrosclerosis and renal lesions that develop with advanced age.[61] Chronic administration of certain anti-hypertensive drugs, namely angiotensin-converting-enzyme inhibitors (ACEI), may also negatively influence renal autoregulation, resulting in kidney injury.[62]

1.4.3 Hypertension and the brain:

Stroke/cerebrovascular accident, defined as "rapidly developing signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours, or leading to death with no apparent cause other than that of vascular origin",[63] is amongst the leading causes of death worldwide,[50] with stroke resulting from neurological ischemia being the most common subtype.[64] Hypertension appears to be one of the most important risk factors for the development of stroke, with more than an half the global burden of stroke being attributed to comorbid hypertension.[65] In some instances, the risk of stroke might be increased four-fold in patients who have hypertension.[66]

Importantly, the progression of hypertensive disease to stroke in most cases appears to be a gradual process, with a series of pathological changes ensuing prior to the onset of a stroke. In a similar mechanism as observed in the occlusion of the coronary arteries in myocardial infarction, hypertension appears to be associated with atheroma formation in vital blood vessels providing oxygen to the brain, namely the carotid arteries.[67] It is estimated that carotid artery stenosis accounts for one-fifth of strokes which occur in adult populations.[68] Atheroma formation is linked to an inflammatory process, in which hypertension appears to play a role.[69] Rupture of the atheroma can also lead to thromboembolism and subsequent neurological injury.[68] In addition to its modulating effects on atheroma formation in the cerebral circulatory system, hypertension is associated with increased vascular stiffening and higher pulse pressure, which itself is correlated with a higher risk of stroke.[67] Hypertension is also associated with the less common haemorrhagic stroke,[70] whereby uncontrolled hypertension results in

degenerative changes in the structure of cerebral arterioles and subsequent haemorrhage.[71]

1.5 Treatment of hypertension:

1.5.1 Lifestyle modification therapy:

Several lifestyle interventions have been shown to lower blood pressure. The most compelling evidence comes from a comprehensive meta-analysis of randomized controlled trials of interventions to reduce elevated blood pressure.[72] This meta-analysis found that improved diet, aerobic exercise, alcohol and sodium restriction resulted in mean reductions in systolic blood pressure of between 3.6 mmHg and 5.0 mmHg, with corresponding reductions in diastolic blood pressure.[72] However, the reduction in blood pressure in response to lifestyle modifications may not be sufficient, in which case hypertensive patients are required to commence anti-hypertensive medications in addition to continuing with lifestyle modification therapy.[73]

1.5.2 Anti-hypertensive drug therapy:

A recent survey of International Society of Hypertension affiliates suggests that ACEI, angiotensin receptor blockers (ARB), calcium channel blockers (CCB) and diuretics appear to be the most commonly prescribed pharmacological agents for the management of hypertension, whilst the current use of β-blockers remains restricted to hypertensive patients with ischaemic heart disease.[74]

1.5.2.1 Angiotensin-Converting-Enzyme Inhibitors (ACEI):

The angiotensin-converting-enzyme (ACE) is required for the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. ACEI are anti-hypertensive drugs which inhibit the ACE. Precursors of ACEI were first isolated from snake venom, and ACEI have since been shown to effectively reduce high blood pressure, as evidenced by several large clinical studies.[75] Although ACEI are effective in reducing blood pressure in patients with uncomplicated hypertension, ACEI do not reduce the risk of adverse cardiovascular events in these patients when compared with conventional therapies. Three important randomized controlled trials compared ACEI with CCB (Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial - ALLHAT), ACEI with a β-blocker or diuretic (The Captopril Prevention Project - CAPPP), and ACEI with a β-blocker alone (United Kingdom Prospective Diabetes Study - UKPDS) and did not report a reduction in the risk of myocardial infarction, stroke, or cardiac death in patients receiving ACEI when compared with patients receiving conventional therapy.[76] Hence, ACEI are just one component in an approach to managing uncomplicated hypertension which may also involve other anti-hypertensive drug classes. Common adverse effects of ACEI include cough, angioedema, and hypotension. Hyperkalaemia might occur in patients with reduced renal function. In addition, ACEI use during pregnancy has been linked to foetal defects.[75,77]

1.5.2.2 Angiotensin Receptor Blockers (ARB):

Although the majority of angiotensin II is thought to be derived via the ACE pathway, it is estimated that close to 30% of angiotensin II might also be produced in reactions

catalysed by cathepsins, chymases, or serine proteases.[78] As with ACEI, ARB have targets within the RAS, specifically receptors which bind angiotensin. Competitive inhibition of these angiotensin receptors increases vasodilation allowing more efficient renal excretion of sodium ultimately resulting in lower blood pressure by reducing cardiac preload and afterload.[77] ARB appear to be more tolerable than ACEI. However, like ACEI, ARB use is contraindicated during pregnancy. ARB use does not appear to overtly affect patient laboratory parameters, although elevations in the levels of liver enzymes and urinary uric acid in patients using ARB have been reported.[79]

1.5.2.3 Calcium Channel Blockers (CCB):

CCB reduce blood pressure by blocking calcium channels in the membranes of vascular endothelial cells, thereby inducing vasodilation. CCB have been shown to be effective blood pressure lowering agents across a multitude of patient groups, especially when prescribed as part of a multi-drug treatment regimen.[80] Although CCB use reduces the risk of stroke, with the exception of heart failure, several randomized controlled trials of initial calcium antagonist administration suggest that CCB reduce the risk of most forms of cardiovascular disease.[80] CCBs are contraindicated in patients present with a heart block or heart failure.[81] Adverse drug effects usually associated with CCB use include nausea, headache, rash and oedema.[81]

1.5.2.4 Diuretics:

Diuretics have been widely used in the treatment of hypertension for almost 50 years, owing to their high levels of efficacy in reducing blood pressure, as well as their ability

to reduce the burden of adverse clinical outcomes associated with hypertensive disease.[82] There are two commonly used classes of diuretics: thiazides and loop diuretics. Hydrochlorothiazide is the most commonly prescribed thiazide, whilst furosemide is the most widely used loop diuretic.[83] Diuretics can be co-administered with most other anti-hypertensive agents.[84] Diuretics reduce blood pressure through natriuresis. During this process, urinary sodium excretion is increased, reducing plasma volume. This inevitably results in a reduction in cardiac output.[82] Overall, diuretics are well-tolerated. Most reported adverse drug effects involve electrolyte changes or metabolic abnormalities.[83]

1.5.2.5 β-Blockers:

β-blockers were first introduced for the treatment of hypertension in the 1970's. Since then, considerable doubts have been raised regarding the use β-blockers as a primary tool to treat hypertension.[85] Although β-blockers reduce the risk of future adverse cardiovascular events in patients with cardiac disease, β-blockers were found to be of no benefit in preventing future adverse cardiovascular events in patients without cardiac disease.[86] As such, β-blockers are now usually recommended as fourth-line treatment options in hypertensive patients.[85] β-blockers effectively reduce blood pressure through a number of proposed mechanisms including: reducing heart rate and cardiac output, inhibiting renin release, inhibiting central nervous sympathetic overflow, reducing venous return and plasma volume, generating nitric oxide, reducing vasomotor and vascular tone, improving vascular compliance, resetting baroreceptor levels, and attenuating the pressor response to catecholamines with exercise and stress.[86] A

common side effect of β-blocker therapy, particularly older β-blockers which do not induce vasodilation, is impaired glycaemic control.[87]

1.6 Hypertension and peri-operative outcomes:

1.6.1 Peri-operative outcomes in the non-cardiac surgery patient:

1.6.1.1 Peri-operative mortality:

The Vascular events In non-cardiac Surgery patIents cOhort evaluatioN (VISION) study reported the contemporary relationship between hypertension and peri-operative mortality in non-cardiac surgery patients.[88] The incidence of peri-operative mortality (defined as death within 30 days following non-cardiac surgery) was estimated at 2.3% in patients with hypertension versus 1.4% in normotensive patients. Ultimately however, hypertension was not found to be an independent predictor of peri-operative mortality in patients undergoing non-cardiac surgery (Odds Ratio: 1.05, 95% Confidence Interval: 0.80-1.38).[88]

1.6.1.2 Peri-operative cardiac outcomes:

The overall impact of hypertensive disease on peri-operative cardiac outcomes in patients undergoing non-cardiac surgery was described in a 2004 systematic review and meta-analysis. Following a systematic review of the published literature, Howell et al., included thirty studies involving 12995 non-cardiac surgery patients in their meta-analysis.[89] The odds ratios describing the impact of hypertension on adverse peri-

operative cardiac events in non-cardiac surgery patients varied amongst studies included in the meta-analysis, ranging between 0.3 and 8.6.[89] Overall, hypertensive disease was associated with an increased risk of adverse cardiac events in non-cardiac surgery patients (Odds Ratio: 1.35, 95% Confidence Interval: 1.17-1.56). This finding was however, interpreted with caution as significant heterogeneity was observed between the studies included in the meta-analysis.[89] Ultimately, the authors concluded that although there was a statistically significant independent association between hypertensive disease and poor peri-operative cardiac outcomes in their study, the clinical significance of this association remained unclear.[89]

The VISION study was a prospective cohort study which recruited 40000 patients worldwide.[90] One of the objectives of the VISION study was to describe the incidence of poor peri-operative outcomes (including cardiac outcomes) and risk factors for these outcomes in non-cardiac surgery patients.[88,90] When adjusted for other clinical comorbidities and patient demographic factors, a pre-operative history of hypertension was found to be an independent predictor of myocardial injury following non-cardiac surgery (Odds Ratio: 1.34, 95% Confidence Interval: 1.14-1.54),[90] a finding which appears to validate the meta-analysis of Howell and colleagues.[89]

1.6.1.3 Peri-operative renal outcomes:

Several studies have sought to determine the role of hypertension, along with other comorbid conditions, in the development of poor peri-operative renal outcomes in non-cardiac surgery patients. A study of 75952 general surgery procedures from the American College of Surgeons National Quality Improvement Program database by

Kheterpal and colleagues found patients who were hypertensive were at higher risk of peri-operative acute kidney injury (AKI) than patients who were normotensive (Odds Ratio: 1.50, 95% Confidence Interval: 1.20-1.90).[91] However, other studies by Abelha et al.,[92] and Biteker et al.,[93] did not find hypertension to be an independent predictor of poor peri-operative renal outcomes in non-cardiac surgery populations. Furthermore, whilst chronic treatment with ACEI is associated with a reduction in functional nephrons,[94] ACEI use did not predict AKI in the study by Biteker et al.[93] Therefore, the contribution of chronic hypertension toward the development of poor peri-operative renal outcomes in non-cardiac surgery patients remains unclear.

1.6.1.4 Peri-operative neurological outcomes:

Systematic reviews of the published literature by Ng et al.,[95] and Macellari et al.,[96] cite hypertension as an important risk factor for peri-operative stroke following non-cardiac, non-neurosurgical surgery and general surgical procedures, respectively. Since the publication of these reviews there have been two important studies of peri-operative stroke in non-cardiac surgery patients.

In the first study, Mashour and colleagues attempted to describe the incidence and predictors of peri-operative stroke and its role in mortality in a broad range of non-cardiac, non-neurosurgical cases using a large, prospectively gathered clinical data set derived from the American College of Surgeons National Surgical Quality Improvement Program.[97] In this study, the authors found that hypertension which required treatment with anti-hypertensive medications was an independent predictor of peri-operative stroke (Odds Ratio: 2.0, 95% Confidence Interval: 1.6-2.6).[97]

In a subsequent study, Sharifpour and colleagues attempted to describe the incidence, predictors, and outcomes of peri-operative stroke in patients undergoing non-carotid major vascular surgery, also through the use of the American College of Surgeons National Quality Improvement Program database.[98] Although no independent association between hypertension and peri-operative stroke was observed in a mixed vascular surgery population, when the authors performed a sub-analysis of a surgical group with traditionally high levels of peri-operative morbidity and mortality (patients undergoing abdominal aortic aneurysm repair), hypertension was associated with an almost four-fold increased risk of peri-operative stroke (Odds Ratio: 3.73, 95% Confidence Interval: 1.36-10.25).[98] Carotid artery surgery patients represent a non-cardiac surgical population with a high risk of developing peri-operative stroke.[99] In these patients, hypertension is an established risk factor for poor peri-operative neurological outcomes as evidenced by a systematic review conducted by Rothwell et al., which found that a pre-operative systolic blood pressure of >180 mmHg was associated with an almost two-fold increased risk of developing peri-operative stroke in carotid endarterectomy patients (Odds Ratio: 1.82, 95% Confidence Interval: 1.37-2.41).[100]

1.7 Concluding Remarks:

Hypertension is an important risk factor for cardiovascular and renal disease worldwide. Although the burden of hypertension appears to have plateaued in the developed world, the burden of hypertension is increasing in developing countries. It is likely that in these countries the burden of cardiovascular disorders, including hypertension, will in time surpass the burden of communicable disease. Although a multitude of

interventions to treat hypertension exist, it is important that these interventions are appropriately and adequately implemented in populations with hypertension or populations with a high risk of developing hypertension. Whilst there is literature suggesting a possible role for hypertension in the development of poor peri-operative outcomes following non-cardiac surgery, the strength and clinical significance of these associations remain unclear in many instances. Therefore, further research is still required to unequivocally establish the impact of hypertension on peri-operative outcomes in the non-cardiac surgery patient.

CHAPTER 2:

Introduction

2. INTRODUCTION

2.1 Epidemiological transition in South Africa

South Africa is experiencing an epidemiological transition in its national burden of disease, whereby the current communicable disease burden will soon be surpassed by a rapidly growing non-communicable disease burden. The burden of many communicable diseases in South Africa appears to have gradually plateaued, and in some cases decreased.[101] The decreased burden of communicable disease can be attributed to well-coordinated prevention and treatment programmes implemented by the South African government as well as non-governmental organizations.[102] Vaccination programmes have also contributed significantly to lowering the burden of infectious disease in South Africa.[103] Furthermore, along with successful efforts which aim to reduce the burden of communicable disease, it appears that the rapid urbanization of the South African population has resulted in a growing burden of non-communicable disease.[104]

2.2 Urbanization and non-communicable disease in South Africa

Urbanization has prompted lifestyle changes in South Africans. A western diet combined with reduced physical activity has increased the burden of risk factors for non-communicable, lifestyle-associated diseases in South Africa.[105] The prevalence of hypertension, considered a disease of lifestyle, has noticeably increased post-1994 in South Africa.[106] Furthermore, this has also coincided with an increase in the prevalence of comorbid conditions associated with a higher risk for developing hypertension in

future, such as obesity.[107] Urbanization has also lead to the increased availability of tobacco products and alcohol, which are also risk factors for the development of hypertension.[108]

2.3 The aging South African population

Urbanization has also afforded access to improved healthcare services for many South Africans, including access to treatment for HIV infection which is estimated to affect almost 10% of the population.[109,110] As such, the average life expectancy in South Africa has increased.[110] An increasingly elderly population has been matched by an increase in the national burden of non-communicable disease. Older age is also a risk factor for the development of hypertension.[8] The older South African population might require non-cardiac surgical procedures for many health conditions, such as cancer, when conservative methods of treatment have failed. The importance of diseases associated with older age, such as cancer, in the setting of non-cardiac surgery has been demonstrated by the Vascular events In non-cardiac Surgery patIents cOhort evaluatioN (VISION) study, wherein 26.5% of non-cardiac surgery patients ≥45 years old had undergone surgical intervention for cancer.[90]

Although literature describing the epidemiology of non-cardiac surgery in the South African population is scarce, it is likely that similar trends would be observed between South African hospitals and those in other developing countries such as Brazil, where the burden of non-cardiac surgery had increased between 1995 and 2007.[111]

2.4 Hypertension in the South African population

Two South African surveys provide the best description of the burden of hypertension in the South African population post-1994.

The first survey to describe the epidemiology of hypertension in the general South African population was the South African Demographic and Health Survey (SADHS),[106] conducted in 1998. The survey presented the prevalence of hypertension using the World Health Organisation blood pressure measurement threshold (Systolic/Diastolic blood pressure ≥140/90 mmHg), as well as the threshold recommended by the South African national hypertension guidelines at the time (Systolic/Diastolic blood pressure ≥160/95 mmHg).[106] When a threshold of Systolic/Diastolic blood pressure ≥140/90 mmHg was used, it was estimated that 25% of South African men and 26% of South African women were hypertensive. When the threshold of Systolic/Diastolic blood pressure ≥160/95 mmHg was used, the prevalence of hypertension in South African men and women was 11% and 14%, respectively.[106] Data from the SADHS also showed that only 18% of women and 10% of men had controlled hypertension when a threshold of <140/90 mmHg was used.[106]

A sub-analysis of questionnaires administered during the 2010 South African General Household Survey (GHS),[112] which was a nationally representative study of private households and workers' hostels, found that approximately 10% of South African adults self-reported a diagnosis of hypertension. This finding appeared to be age-dependant, and is of importance when one considers the growing elderly population in South

Africa. The findings of the GHS also suggest that the true burden of hypertension in the South African population might well be underestimated.[112]

2.5 The hypertensive South African non-cardiac surgery patient

A meta-analysis of non-South African studies found a pre-operative history of hypertension to be statistically associated with poor cardiovascular peri-operative outcomes in non-cardiac surgery patients, although the authors of the meta-analysis conceded that the clinical significance of this association was difficult to interpret.[89] However, this finding might not be applicable to South African non-cardiac surgery patients. Whilst peri-operative studies of South African non-cardiac surgery patients are limited, some of the findings of these studies suggest that the South African non-cardiac surgery patient might be very different from their European or American counterparts. Biccard and colleagues noted that the "weighting" or clinical importance of clinical variables associated with poor peri-operative outcomes in South African vascular surgery patients,[113,114] might be different from that observed for the same clinical variables in overseas non-cardiac surgical populations.[115]

Control of hypertension in the general South African population is poorer than that described for overseas populations,[106,116] and although blood pressure control has not been described in the South African non-cardiac surgery patient, it is likely that a large proportion of surgical patients would also present for surgery with poorly controlled blood pressure. Furthermore, the prevalence of hypertension in South African patients undergoing non-cardiac vascular surgery might be as high as 66%,[117] which is much higher than the overall prevalence described for overseas populations in the Howell

meta-analysis.[89] Therefore, it might be possible that a pre-operative history of hypertension is a risk factor for peri-operative morbidity and mortality in South African non-cardiac surgery patients. In order to improve peri-operative risk stratification in South African patients there is a need for further research which seeks to determine the impact of a pre-operative history of hypertension (including anti-hypertensive medication use) on peri-operative morbidity and mortality in this population.

In this research a patient was considered to have a pre-operative history of hypertension if the patient had a physician-based diagnosis of hypertension made prior to surgery, or if the patient was taking any anti-hypertensive medications prior to their surgery. In addition, the majority of this research has focused on patients undergoing non-cardiac vascular surgical procedures.

2.6 Aim of Research:

The aim of this research was to study the impact of a pre-operative history of hypertension on mortality and poor cardiac, renal, and neurological outcomes following non-cardiac surgical procedures in South African patients.

The primary research question was: 'Is a pre-operative history of hypertension associated with mortality following non-cardiac surgical procedures in South African patients?' The secondary research question was: 'Is a pre-operative history of hypertension associated with cardiac, renal, or neurological morbidity following non-cardiac surgical procedures in South African patients?'

2.7 Objectives of Research:

All the objectives of this research were achieved through a series of five research manuscripts, which have been published in peer-reviewed medical journals.

For objective 1, a large hospital administrative database was used to determine the impact of a pre-operative history of hypertension on in-hospital mortality following mixed non-cardiac surgery in South African patients (Manuscript 1). Manuscript 1 exemplified the inherent difficulties of using hospital administrative databases for medical research. However, the most severe peri-operative patient outcome, in-hospital mortality, can be easily identified from an administrative database. In keeping with the international literature, a descriptive analysis of trends associated with in-hospital mortality in this research showed vascular surgery to be one of the non-cardiac surgical specialties associated with a high risk of post-operative in-hospital mortality (Manuscript 1). It was therefore decided that the impact of a pre-operative history of hypertension on peri-operative outcomes would be investigated using prospectively collected data, to avoid the challenges experienced when using administrative data, in the high-risk vascular surgery population (Objectives 2-5).

For objective 2, prospectively collected data from adult South African patients attending a tertiary hospital was used to determine the impact of several established clinical risk factors, as well as hypertension, on the incidence of peri-operative cardiac morbidity and mortality following mixed vascular surgery (Manuscript 2). Hypertension was included in the analysis as it is highly prevalent in the South African vascular surgery

population[117] and it had been previously found to be associated with poor intermediate and long-term patient outcomes following vascular surgery.[113]

This research also sought to determine the impact of acute pre-operative β-blocker use on peri-operative major adverse cardiac events in South African mixed vascular surgery patients with a pre-operative history of hypertension (Objective 3, manuscript 3). Acute peri-operative β-blockade in the non-cardiac surgery patient is currently very controversial. A meta-analysis of randomised controlled trials of acute β-blockade to prevent peri-operative death in non-cardiac surgery by Bouri et al., found that when several of the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) studies were analysed separately from "secure studies", the pooled findings of the DECREASE studies contradicted the findings of an overall increase in peri-operative mortality of 27% after peri-operative β-blockade in "secure studies".[118] It is possible that the potential morbidity associated with peri-operative β-blockade may be aggravated in South African hypertensive patients, particularly as the blood pressure control is poorer in South African patients than reported in international trials. It was decided to restrict the analysis for manuscript 3 to hypertensive South African vascular surgery patients as these patients are likely to present for surgery with poorly controlled blood pressure,[106] which might aggravate the peri-operative haemodynamic instability induced by acute β-blockade,[119] resulting in a higher risk of peri-operative major adverse cardiac events.

For objective 4, prospectively collected data from adult patients who attended a tertiary South African hospital was once again used to determine the impact of several established clinical risk factors and medication use on the incidence of post-operative

acute kidney injury (AKI) in vascular surgery patients with a pre-operative history of hypertension (Manuscript 4). However, as AKI is well described in patients undergoing suprainguinal vascular surgery,[120] manuscript 4 describes the incidence and risk factors for AKI in hypertensive patients undergoing more common, less complex non-suprainguinal procedures, namely peripheral bypass artery surgery and lower limb amputation,[121] which is less well described in the literature.

For objective 5, retrospectively collected data from patient medical records was used to determine the impact of several comorbid conditions (including pre-operative haemodynamics) on the incidence of in-hospital cerebrovascular accident following carotid endarterectomy in South African patients with a pre-operative history of hypertension (Manuscript 5). The carotid endarterectomy population was selected for this aspect of the research as these patients are at a higher risk of developing poor peri-operative neurological outcomes than patients undergoing major non-carotid vascular surgery.[122]

2.8 Novelty of this research:

The relationship between a pre-operative history of hypertension and poor peri-operative outcomes is unclear, particularly in the South African surgical population. This research adds to the limited literature available on the topic of hypertension and peri-operative outcomes, such as mortality and adverse cardiovascular events, in South African patients. This research used a unique, large database to describe the epidemiology of non-cardiac surgery in a population of South African patients, as well

as determine the clinical importance of common comorbidities on in-hospital mortality following non-cardiac surgery.

The development of a new peri-operative risk stratification tool, which is specific to the South African vascular surgery population, is described in manuscript 2. In addition, this research was the first to describe the impact of acute pre-operative β-blockade on cardiac outcomes in South African non-cardiac vascular surgery patients with a pre-operative history of hypertension, a population which is expected to experience more peri-operative haemodynamic instability than their overseas counterparts, thereby potentially placing this population at higher risk of poor peri-operative cardiac outcomes (Manuscript 3). The first description of the impact of acutely administered anti-hypertensive drugs during the pre-operative period on the subsequent incidence of post-operative AKI in a cohort of South African vascular surgery patients with a pre-operative history of hypertension is also provided in this research (Manuscript 4). A unique preliminary description of the impact of pre-operative haemodynamics on peri-operative neurological outcomes in a cohort of South African patients undergoing carotid endarterectomy is also made (Manuscript 5).

CHAPTER 3:

Manuscript 1

Predictors of in-hospital mortality following noncardiac surgery: Findings from an analysis of a South African hospital administrative database (S Afr Med J 2015;105:126-129).

Predictors of in-hospital mortality following non-cardiac surgery: Findings from an analysis of a South African hospital administrative database

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Background. Predictors of in-hospital mortality (IHM) following non-cardiac surgery in South African (SA) patients are not well described.
Objective. To determine the association between patient comorbidity and IHM in a cohort of SA non-cardiac surgery patients.
Methods. Data related to comorbidity and IHM for 3 727 patients aged ≥45 years were obtained from a large administrative database at a tertiary SA hospital. Logistic regression analysis was used to determine independent predictors of IHM. In addition, population-attributable fractions (PAFs) were calculated for all clinical factors identified as independent predictors of IHM.
Results. Renal dysfunction, congestive heart failure, cerebrovascular disease, male gender and high-risk surgical specialties were independently associated with IHM (odds ratios (95% confidence intervals) 7.585 (5.480 - 10.50); 2.604 (1.119 - 6.060); 2.645 (1.414 - 4.950); 1.433 (1.107 - 1.853); and 1.646 (1.213 - 2.233), respectively). Ischaemic heart disease, diabetes and hypertension were not identified as independent predictors of IHM in SA non-cardiac surgery patients. Renal dysfunction had the largest contribution to IHM in this study (PAF 0.34), followed by high-risk surgical specialties (PAF 0.15), male gender (PAF 0.08), cerebrovascular disease (PAF 0.03) and congestive heart failure (PAF 0.03).
Conclusion. Renal dysfunction, congestive heart failure, cerebrovascular disease, male gender and high-risk surgical specialties were major contributors to increased IHM in SA non-cardiac surgery patients. Prospectively designed research is required to determine whether ischaemic heart disease, diabetes and hypertension contribute to IHM in these patients.

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Weiser *et al.*[1] estimated the global number of patients undergoing surgery in 2004 to be over 234 million, with 0.5% of these patients dying during or shortly after their surgical procedure. These alarming statistics emphasise the importance of surgical safety and the need to identify risk factors associated with in-hospital mortality (IHM) in patients before their surgery, so that these risk factors may be appropriately managed to reduce the risk of perioperative IHM. Studies of perioperative mortality have been confined primarily to European[2] and North American[3] surgical populations. Interestingly, the clinical importance of comorbidities in the pathology of adverse outcomes may differ between South African (SA) patients and patients from Europe and North America.[4] The current epidemiological transition towards a higher burden of non-communicable disease in SA patients appears to explain these observed differences.[4,5] For example, while hypertension has been associated with an almost four-fold increased risk of postoperative mortality in SA non-cardiac vascular surgery patients,[5] similar research by a vascular surgery research group in New England, USA, did not identify hypertension as a predictor of adverse perioperative events.[6] It is therefore imperative that SA non-cardiac patients be stratified for perioperative risk through a country-specific list of appropriate comorbid risk factors. We sought to determine the relationship between several common comorbid conditions and IHM in a cohort of SA non-cardiac surgery patients.

Methods

This study was conducted at Inkosi Albert Luthuli Central Hospital (IALCH), Durban, SA. The hospital provides a tertiary service to patients living in the province of KwaZulu-Natal. Ethical approval was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal before commencing the study. The hospital's administrative database was used to identify all patients aged ≥45 years who underwent elective non-cardiac surgery at the hospital between 2005 and 2012. *International Statistical Classification of Diseases and Related Health Problems* (10th edition) (ICD-10) codes were then used to extract data related to comorbidities from patient electronic medical records and create a database for statistical analysis. We used an age of ≥45 years as an inclusion criterion for this study, in keeping with other large studies of perioperative outcomes.[7] The effects of the following comorbidities on IHM were investigated: hypertension, diabetes, renal dysfunction, ischaemic heart disease, congestive heart failure and cerebrovascular disease/stroke. Hypertension was included because it is highly prevalent in the SA surgical population.[5] The other five comorbidities are established risk factors for poor perioperative outcomes and form part of Lee's Revised Cardiac Risk Index (RCRI),[8] which is commonly used as a perioperative risk stratification tool at IALCH. In-hospital death was determined by evaluating each patient's discharge record following their surgery. Vascular surgery, thoracic surgery and general surgery were classified as high-risk surgical specialties.[2] Duplicate records, patients aged <45 years, cardiac surgery patients and non-surgical patients were excluded from the final data set. Categorical data were analysed using the χ^2 test or Fisher's exact test, where appropriate. Binary logistic regression was used to identify independent associations between comorbidities and IHM. A result was considered statistically significant at a p-value of <0.05. Results for the logistic regression analysis are presented as odds ratios (ORs) with 95% confidence intervals (CIs). The

population-attributable fraction (PAF) for each factor independently associated with a higher incidence of IHM was also calculated.[9] Univariate and multivariate statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21 (SPSS Inc., USA).

Results

The final study cohort comprised 3 727 non-cardiac surgery patients. Reasons for excluding patients from the final data set are shown in Fig. 1. Overall, the cumulative incidence of IHM in this study was 7.5%. Table 1 shows the proportion of patients in the final study cohort by surgical specialty. Almost half of all patients underwent surgery that fell within a high-risk surgical specialty group. Renal surgery and vascular surgery were the surgical specialties associated with the highest levels of IHM (incidences of 24.3% and 7.0%, respectively).

The preoperative clinical characteristics of the study cohort are shown in Table 2. There was a high prevalence of diabetes and hypertension in the cohort (46.7% and 79.1%, respectively). Statistically significant univariate associations were observed between IHM and male gender ($p<0.001$), elderly age ($p<0.001$), diabetes ($p<0.001$), cerebrovascular disease ($p=0.007$) and renal dysfunction ($p<0.001$) (Table 2).

Three comorbid conditions (renal dysfunction, congestive heart failure and cerebrovascular disease) were independently associated with an increased risk of IHM following non-cardiac surgery (Table 3). In addition, male gender and high-risk surgical specialties were also independently associated with an increased risk of IHM in this study (Table 3).

The results of the PAF analysis for each predictor of IHM are shown in Table 4. Renal dysfunction had the largest contribution to IHM in this study (PAF 0.34), followed by

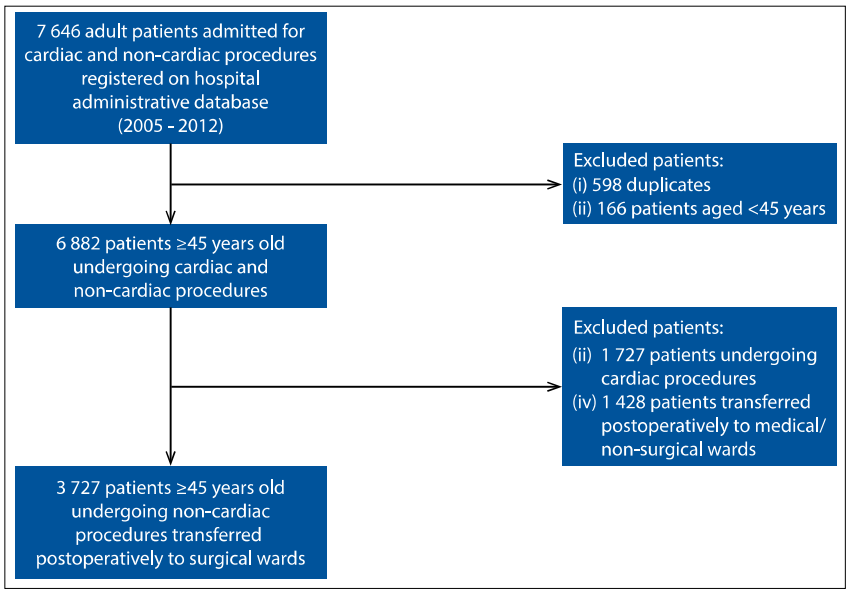

Fig. 1. Study profile.

Table 1. Proportion of patients in the final study cohort by surgical specialty

Surgical specialty	*n* (% of final study cohort)
Gynaecological surgery	130 (3.5)
General surgery	481 (12.9)
Vascular surgery	1 164 (31.2)
Plastic surgery	91 (2.4)
Orthopaedic surgery	321 (8.6)
Urological surgery	370 (9.9)
Ear, nose and throat surgery	96 (2.6)
Renal surgery	494 (13.3)
Thoracic surgery	162 (4.4)
Ophthalmological surgery	418 (11.2)
Total	3 727 (100.0)

Table 2. Baseline patient clinical characteristics expressed as a frequency (%)

Patient characteristic	Total cohort (*N*=3 727) *n* (%)	Patients with in-hospital mortality (*N*=278) *n* (%)	Patients without in-hospital mortality (*N*=3 449) *n* (%)	*p*-value*
Male gender	1 591 (42.7)	150 (54.0)	1 441 (41.8)	<0.001
Age >65 years	1 265 (33.9)	65 (23.4)	1 200 (34.8)	<0.001
Ischaemic heart disease	420 (11.3)	23 (8.3)	397 (11.5)	0.101
Diabetes	1 739 (46.7)	98 (35.3)	1 641 (47.6)	<0.001
Congestive heart failure	50 (1.3)	7 (2.5)	43 (1.2)	0.095
Renal dysfunction	487 (13.1)	119 (42.8)	368 (10.7)	<0.001
Cerebrovascular disease/stroke	87 (2.3)	13 (4.7)	74 (2.1)	0.007
Hypertension	2 948 (79.1)	209 (75.2)	2 739 (79.4)	0.095
High-risk surgical specialty	1 807 (48.5)	125 (45.0)	1 682 (48.8)	0.222

*$p<0.05$ was considered statistically significant.

Table 3. Results of multivariate analysis: clinical variables independently associated/not independently associated with IHM

Clinical variable	OR (95% CI)	*p*-value*
Male gender	1.433 (1.107 - 1.853)	0.006
Age >65 years	0.840 (0.616 - 1.147)	0.273
Ischaemic heart disease	0.815 (0.515 - 1.290)	0.383
Diabetes	0.832 (0.634 - 1.092)	0.185
Congestive heart failure	2.604 (1.119 - 6.060)	0.026
Renal dysfunction	7.585 (5.480 - 10.50)	<0.001
Cerebrovascular disease/stroke	2.645 (1.414 - 4.950)	0.002
Hypertension	1.119 (0.823 - 1.522)	0.474
High-risk surgical specialty	1.646 (1.213 - 2.233)	<0.001

*$p<0.05$ was considered statistically significant.

Table 4. PAFs for clinical variables associated with IHM in SA non-cardiac surgery patients

Comorbidity	PAF
Congestive heart failure	0.03
Renal dysfunction	0.34
Cerebrovascular disease/stroke	0.03
High-risk surgical specialty	0.15
Male gender	0.08

high-risk surgery (PAF 0.15), male gender (PAF 0.08), cerebrovascular disease (PAF 0.03) and congestive heart failure (PAF 0.03).

Discussion

The incidence of postoperative IHM in our study was much higher than that reported for most Nothern and Western European countries.[10] This may be explained in part by the fact that almost half our patient population underwent surgery in a high-risk specialty, placing them at increased risk of IHM after the procedures.

We found univariate associations between increased IHM and male gender, age >65 years, diabetes, renal dysfunction, cerebrovascular disease and high-risk surgery. Interestingly, while our observation that renal dysfunction and cerebrovascular disease were more common in patients who died in hospital was in agreement with the studies of Pearse *et al.*,[10] Charlson *et al.*[11] and Elixhauser *et al.*,[12] our observation that diabetes was significantly more common in patients who did not suffer IHM was in contrast to the findings of these studies.

Following multivariate statistical analysis, male gender, renal dysfunction, congestive heart failure, cerebrovascular disease and high-risk surgical specialties were identified as independent predictors of IHM in SA non-cardiac surgery patients. While the importance of renal dysfunction has been described in overseas surgical populations, its contribution to IHM in SA non-cardiac surgery patients is of concern, with just over one-third of the risk associated with IHM being attributed to renal dysfunction.

Waikar *et al.*[13] found that although IHM rates among patients with acute renal dysfunction had decreased between 1988 and 2002, mortality rates for patients not requiring dialysis and those requiring dialysis were >20% and >30%, respectively. In the perioperative setting, a serum creatinine level of >177 µmol/L has previously been shown to be an independent predictor of perioperative cardiovascular morbidity and mortality in non-cardiac surgery patients.[8] 'Renal disease' and 'renal failure' were also associated with IHM in the studies of Charlson *et al.*[11] and Elixhauser *et al.*,[12] respectively.

In addition to the risk stratification studies of Charlson *et al.*[11] and Elixhauser *et al.*,[12] congestive heart failure was also identified as an independent predictor of cardiovascular morbidity and mortality in patients undergoing non-cardiac surgery by Lee *et al.*,[8] as well as in the validation study of Lee's RCRI.[14] Hernandez *et al.*[15] observed substantial levels of morbidity and mortality in older patients with congestive heart failure who underwent non-cardiac surgery. Similarly, Hammill *et al.*[16] found that patients with heart failure were at higher risk of operative mortality than those without (adjusted OR 1.63; 95% CI 1.52 - 1.74).

It is estimated that up to 14% of patients with a first-time stroke may have stroke recurrence within a year.[17] Patients with recurrent stroke have a higher mortality rate than those with a first-time stroke,[18] with surgery and its associated physiological stresses likely to increase the risk of mortality. The findings of this study are once again in agreement with the studies by Lee *et al.*[8] and Charlson *et al.*,[11] who observed a higher risk of perioperative mortality in patients with a history of cerebrovascular disease.

High-risk surgical specialties were also found to be associated with an increased risk of IHM in our study, which is in agreement with a large database study of 3.7 million surgical procedures conducted in 102 Dutch hospitals by Noordzij *et al.*[2]

We did not find ischaemic heart disease, diabetes or hypertension to be independently associated with IHM in this study. It is likely that these comorbidities were under-diagnosed in our non-cardiac surgery population, in particular in the group of patients who suffered IHM. The problem of under-diagnosis of comorbidities has been established by a number of studies,[19-21] although the reasons for under-diagnosis, as in our study, remain unclear. In addition, we did not observe elderly age to be an independent predictor of IHM following non-cardiac surgery in SA patients, although this finding may be related to the fact that only a third of our cohort was >65 years old.

Study limitations

This study was not without limitations. The identification of comorbidities in this study was based on a physician's diagnosis at admission and the subsequent coding of this diagnosis on the hospital administrative database. As such, we were unable to measure the extent of undiagnosed comorbidity in our study, which is likely to be an important determinant of the findings for ischaemic heart disease, diabetes and hypertension. Also, the administrative database was limited by the accuracy with which perioperative medication was recorded; we were therefore unable to investigate the impact of medication use on IHM following non-cardiac surgery. A prospectively designed study that includes appropriate measures to diagnose patient comorbidity, as well as perioperative medication use, is required.

Conclusion

The incidence of IHM following non-cardiac surgery in our study was much higher than that reported for several developed-world European countries. This finding highlights the importance of identifying independent predictors of IHM in non-cardiac surgery patients, so that attempts can be made to optimise a patient's condition prior to their surgery and reduce their risk of postoperative IHM.

Adequate preoperative management of renal dysfunction, congestive heart failure and cerebrovascular disease may improve outcome after surgery. It is likely that ischaemic heart disease, diabetes and hypertension are under-diagnosed in SA non-cardiac surgery patients. Further prospectively designed research is required to confirm our findings.

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CHAPTER 4:

Manuscript 2

The South African Vascular Surgical Cardiac Risk Index: A prospective observational study (S Afr Med J 2013;103:746-750).

The South African Vascular Surgical Cardiac Risk Index (SAVS-CRI): A prospective observational study

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Background. Recent evidence suggests that application of the Revised Cardiac Risk Index (RCRI) for peri-operative cardiovascular risk stratification in vascular surgery patients may be inappropriate, necessitating the development of risk indices specific to vascular surgery patients.
Objectives. To identify risk factors for cardiovascular morbidity and mortality in South African patients undergoing major vascular surgery, and to develop an appropriate cardiovascular risk stratification index, the South African Vascular Surgical Cardiac Risk Index (SAVS-CRI), which could be used to predict the risk of peri-operative major adverse cardiovascular events (MACEs) in South African vascular surgery patients.
Methods. We prospectively collected data related to peri-operative MACE occurrence and established risk factors for peri-operative MACEs from adult patients who underwent elective vascular surgery at a tertiary hospital in Durban, South Africa, between February 2008 and March 2011. We determined independent predictors of peri-operative MACEs in our cohort by binary logistic regression and used the identified predictors to create a risk index that stratified patients into low-, intermediate- or high-risk groups.
Results. Six independent predictors of peri-operative MACEs were identified in the vascular surgery cohort: age >65 years, a history of ischaemic heart disease, a history of diabetes, chronic β-blockade, prior coronary revascularisation, and the vascular surgical procedure. The risk model derived from these risk factors appeared to discriminate between the three risk groups more accurately than the RCRI.
Conclusion. The RCRI is not appropriate for peri-operative cardiovascular risk stratification in vascular surgery patients. The SAVS-CRI may be preferable for risk stratification in South African vascular surgery patients, although independent validation is required.

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It is estimated that 234 million major non-cardiac surgical procedures are undertaken worldwide each year,[1] with rates of cardiac morbidity or mortality following these procedures ranging between 0.5% and 30%.[2] Pre-operative cardiac evaluation and prognostication using clinical risk scores may allow physicians to reduce cardiac risk following non-cardiac surgery. Risk stratification allows physicians to identify patients at risk for cardiac complications, optimise treatment of co-morbid conditions before surgery, or offer high-risk patients the option of conservative management rather than surgery.[3]

Lee's Revised Cardiac Risk Index (RCRI) has superseded several early risk stratification models.[4-6] The RCRI consists of six independent predictors of major adverse cardiac events (MACEs) following non-cardiac surgery: ischaemic heart disease, cerebrovascular accident, congestive heart failure, renal impairment, major surgery and diabetes. The peri-operative risk of MACEs depends on the number of risk factors present, ranging between approximately 0.5% (no risk factors present) and 11% (three or more risk factors present). Although it is widely utilised and has been validated in several surgical populations, the appropriateness of the RCRI for risk stratification in some populations remains debatable. A recent meta-analysis by Ford *et al.*[7] found that although the RCRI was able to discriminate well between low- and high-risk patients who underwent mixed non-cardiac surgery, it performed poorly in patients who underwent vascular surgery. The Vascular Study Group of New England (VSG) developed a risk scoring model, the VSG cardiac risk index (VSG-CRI), for vascular surgical patients from a retrospective cohort which appears to perform better than the RCRI at predicting peri-operative MACEs in vascular surgery patients.[8] This clinical scoring system identified nine clinical variables, namely age, smoking, prior surgical intervention for coronary artery disease, diabetes, ischaemic heart disease, heart failure, chronic β-blockade, chronic obstructive airway disease and renal impairment, to stratify vascular surgery patients into increasing levels of cardiac risk. However, the VSG-CRI requires prospective validation prior to its use in clinical practice.

While the RCRI has been validated in European and American surgical populations, data from developing countries remain scant. In addition, shifts in disease patterns are becoming more common in developing countries. This epidemiological transition may impact on the importance and weighting of several risk factors associated with MACEs following non-cardiac surgery between developing and developed countries.[9] A retrospective study by Biccard and Bandu[9] found that of all the RCRI risk factors, only elevated serum creatinine was a predictor of cardiac mortality in South African (SA) vascular surgery patients. A history of smoking, which is not an RCRI risk factor, was also found to be a predictor of cardiac mortality in the same study. These conflicting findings necessitate further research regarding risk factors for peri-operative MACEs in SA vascular surgical patients.

Objectives

- **Primary:** To determine clinical risk predictors of MACEs following vascular surgery in a SA cohort through an adequately powered, prospective, observational study design.
- **Secondary:** To develop an appropriate cardiovascular risk stratification index that could be used to predict the risk of peri-operative MACEs in SA vascular surgery patients.

Methods

Setting, patients and outcomes

Ethical approval for this study was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal, Durban, SA. The study was conducted at the Inkosi Albert Luthuli Central Hospital (IALCH), Durban. The hospital provides a tertiary/quaternary service to patients living in the province of KwaZulu-Natal. A registry of consenting adult patients who underwent elective vascular surgery at IALCH between February 2008 and March 2011 was created to prospectively collect data related to demographic variables, established cardiac risk factors for peri-operative MACEs,[4,8] and other possible clinical risk factors such as hypertension.[3] Definitions of established cardiac risk factors for peri-operative MACEs were adopted from the study of Lee *et al.*[4]

Patients' troponin-I levels were measured on the first 3 postoperative days, with a level of ≥0.1 ng/ml considered a positive result.[10] The primary outcome was a MACE, defined as a composite of death within 30 days of surgery or peri-operative troponin-I leak. We have used this definition of MACE in a previous publication that used this dataset.[10]

Statistical analysis

Independent Student's *t*-tests and analysis of variance (ANOVA) were used to analyse continuous data, expressed as means (± standard deviation (SD)) or medians (interquartile range (IQR)). Categorical data were analysed using descriptive statistics and χ^2 or Fisher's exact tests, where appropriate. Friedman's two-way ANOVA was used to describe the postoperative troponin-I leaks. Clinical risk factors for peri-operative MACEs were determined by binary logistic regression, which included all the potential clinical risk predictors identified in the RCRI[4] and the VSG-CRI[8] models (with the exception of data related to chronic obstructive pulmonary disease, which were not collected), and previous SA retrospective studies.[3,9] There were >10 outcome events per variable, which enabled us to enter all potential clinical predictors into the regression equation,[11] along with a surgical 'procedural severity' risk factor. Surgical procedures were classified as carotid interventions (reference surgery group), extraperitoneal vascular procedures (intermediate-risk surgery group) and intraperitoneal vascular surgery (high-risk surgery group). Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs).

A clinical score based on the final logistic regression model was developed using the method described by Sullivan *et al.*[12] Age was converted into a dichotomous variable for the clinical risk model, using the optimal discriminatory point identified on a receiver operating characteristic (ROC) curve. The weighted point score for each clinical variable was calculated by dividing each β-coefficient by the smallest β-coefficient in the analysis. The predictive accuracy of our model was evaluated by ROC curve analysis.[13] The diagnostic and general optimal test cut-offs were used to determine three risk categories (low, intermediate and high risk). The general optimal test cut-off value is the point where the rate of true positives is optimised while minimising the rate of false positives, thereby reflecting the point with the highest accuracy for prediction of the study's primary outcome. This was defined by ROC statistics using a 1:1 weighting of sensitivity and specificity and the point

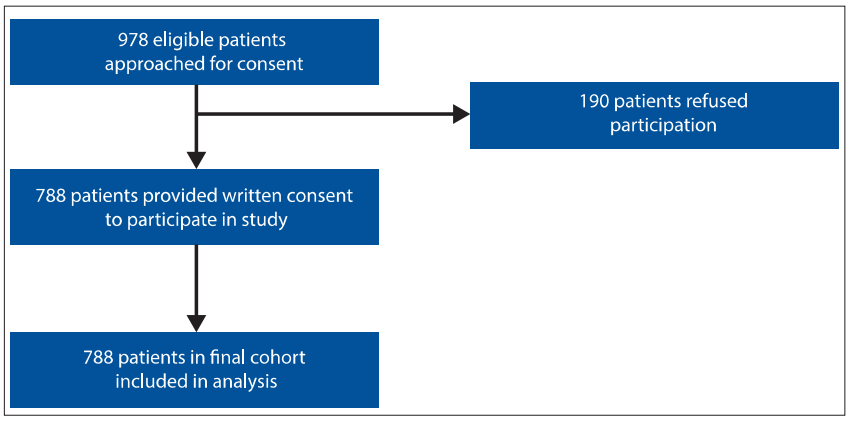

Fig. 1. Flow diagram of recruited patients.

Table 1. Baseline patient clinical characteristics

Patient characteristic	Total cohort (*N*=788)	Patients with/without peri-operative MACE		
		With (*N*=136)	Without (*N*=652)	*p*-value
Males, *n* (%)	512 (65)	80 (58.8)	432 (66.3)	0.114
Age (years), mean (±SD)	58.3 (±14.2)	62.4 (±13.4)	57.4 (±14.3)	0.001
History of ischaemic heart disease, *n* (%)	275 (34.9)	74 (54.4)	201 (30.8)	<0.001
Diabetes, *n* (%)	338 (42.9)	78 (57.4)	260 (39.9)	<0.001
History of congestive heart failure, *n* (%)	37 (4.7)	11 (8.1)	26 (4)	0.046
History of CVA, *n* (%)	159 (20.2)	23 (16.9)	136 (20.9)	0.348
Renal impairment (*N*=730), *n* (%)	18 (2.5)	4 (3.1)	14 (2.3)	0.543
Hypertension, *n* (%)	540 (68.5)	107 (78.7)	433 (66.4)	0.005
History of smoking, *n* (%)	546 (69.3)	86 (63.2)	460 (70.6)	0.102
Chronic β-blockade, *n* (%)	267 (33.9)	82 (60.3)	185 (28.4)	<0.001
History of prior coronary revascularisation, *n* (%)*	47 (6)	9 (6.6)	38 (5.8)	0.692

SD = standard deviation; CVA = cerebrovascular accident; MACE = major adverse cardiovascular event.
*Previous coronary artery bypass grafting in 89% of the MACE cohort and 84% of the non-MACE group.

determined by the value with the minimum distance when using the formula: Distance = (1 - sensitivity)^2 + (1 - specificity)^2.[14] The diagnostic cut-off point was chosen at a specificity of 95% while optimising sensitivity.[14]

All statistical analyses were performed using SPSS version 19.

Results

Of the 978 patients eligible for the study, 788 consented and were included in the final risk model cohort (Fig. 1). There was a peri-operative MACE rate of 17.3% (136/788 patients). Of the 136 patients with peri-operative MACEs, 43 (31.6%) died within 30 days of their surgery.

The medical characteristics of the patients are shown in Table 1. More than two-thirds were male. Increasing age, and a history of ischaemic heart disease, diabetes, hypertension, congestive heart failure and β-blocker prescription, had univariate associations with peri-operative MACEs.

The characteristics of the troponin-I leak in 136 patients with peri-operative MACEs are shown in Table 2. There were no significant differences in postoperative troponin-I measurements between days (p=0.64).

Six independent risk factors for peri-operative MACEs were identified: age, a history of ischaemic heart disease, chronic β-blockade, a history of diabetes, a prior history of coronary revascularisation, and the vascular surgical procedure (Table 3). The SAVS-CRI points scoring system is also shown in Table 3.

Table 2. Postoperative troponin-I measurements at days 1, 2 and 3

	Troponin-I (ng/ml)	
Postoperative day	Median	Interquartile range
Day 1	0.33	0.04 - 2.15
Day 2	0.82	0.17 - 4.30
Day 3	0.84	0.17 - 3.42

The proportion of peri-operative MACEs associated with the low-, intermediate- and high-risk RCRI categories as proposed by the American College of Cardiology/American Heart Association (ACC/AHA) and the SAVS-CRI categories are shown in Tables 4 and 5, respectively. There were significant differences in the proportions of peri-operative MACEs between categories in each index (p<0.001 for the RCRI categories and p<0.001 for the SAVS-CRI categories). The area under the curve (AUC) for the RCRI categories was 0.59 (95% CI 0.54 - 0.64; p=0.001) and that for the SAVS-CRI was 0.736 (95% CI 0.69 - 0.78; p<0.001).

The results of the multivariate analysis for the SAVS-CRI model and the RCRI[4] categories are shown in Table 6. Our index was able to predict peri-operative MACEs more accurately in all three risk categories than Lee's RCRI.[4]

Discussion

The main finding of this study was that the SAVS-CRI appears to perform better than the RCRI in risk-stratifying SA vascular surgical patients. The AUC of the SAVS-CRI does not overlap with that of the RCRI, and the CIs of the SAVS-CRI are discrete in comparison with the RCRI risk categories in this cohort.

The clinical risk factors for peri-operative MACEs in SA vascular surgery patients differ in their importance from the clinical risk factors described in the international literature. Our data suggest that of the RCRI[4] risk factors, only a history of diabetes and ischaemic heart disease are independently associated with peri-operative MACEs. Other risk factors, such as smoking, are unlikely to be robust risk predictors because they do not characterise the end-organ damage associated with cardiovascular disease in the same way that established risk factors (such as a history of ischaemic heart disease) do.[15] Adoption of the VSG-CRI for SA patients is also inappropriate, as only 5 of the 9 clinical variables identified in the VSG-CRI study[8] were independently associated with peri-operative MACEs in our study.

Our data also suggest that the weighting of the risk factors associated with cardiac morbidity differs in SAs when compared with the VSG-CRI,[8] which is consistent with previous suggestions that the

Table 3. Independent risk factors for peri-operative MACEs following vascular surgery

Patient characteristic	OR (95% CI)	p-value	SAVS-CRI point score*
Clinical risk factors in the model			
Age (>65 years)	2.014 (1.3 - 3.121)	0.002	2
History of ischaemic heart disease	1.875 (1.178 - 2.986)	0.008	2
Chronic β-blockade	3.237 (2.056 - 5.095)	<0.001	4
Diabetes	1.830 (1.125 - 2.979)	0.015	2
Prior surgical intervention for coronary artery disease	0.406 (0.165 - 1)	0.050	-3
Intermediate-risk surgery	2.556 (1.131 - 5.775)	0.024	3
Open supra-inguinal vascular surgery	8.354 (3.105 - 22.475)	<0.001	7
Clinical risk factors not in the model			
Male gender	0.889 (0.529 - 1.495)	0.657	-
Smoker	0.857 (0.499 - 1.471)	0.576	-
Congestive cardiac failure	1.358 (0.593 - 3.112)	0.470	-
Cerebrovascular accident	1.037 (0.541 - 1.990)	0.912	-
Hypertension	0.740 (0.416 - 1.315)	0.305	-
Creatinine >177 μmol/l	1.438 (0.396 - 5.222)	0.581	-

OR = odds ratio; CI = confidence interval; SAVS-CRI = South African Vascular Surgical Cardiac Risk Index; MACE = major adverse cardiovascular event.
*Minimum cumulative SAVS-CRI score = -1; maximum cumulative SAVS-CRI score = 17.

Table 4. RCRI risk categories and associated proportions of MACEs following vascular surgery

Risk group	Score range	Proportion of MACEs within risk group (95% CI)
Low	0	0.11 (0.07 - 0.15)
Intermediate	1 - 2	0.20 (0.16 - 0.24)
High	>2	0.28 (0.17 - 0.39)

RCRI = Revised Cardiac Risk Index; MACE = major adverse cardiovascular event; CI = confidence interval.

Table 5. SAVS-CRI risk categories and associated proportions of MACEs following vascular surgery

Risk group	Score range	Proportion of MACEs within risk group (95% CI)
Low	<7	0.07 (0.04 - 0.09)
Intermediate	7 - 11	0.21 (0.16 - 0.26)
High	>11	0.47 (0.38 - 0.56)

SAVS-CRI = South African Vascular Surgical Cardiac Risk Index; MACE = major adverse cardiovascular event; CI = confidence interval.

Table 6. Comparison of models (RCRI v. SAVS-CRI)

Model	Risk group	OR (95% CI)	*p*-value
RCRI	Low	1 (reference)	0.002
	Intermediate	1.999 (1.268 - 3.152)	0.003
	High	2.998 (1.539 - 5.839)	0.001
SAVS-CRI	Low	1 (reference)	<0.001
	Intermediate	3.541 (2.179 - 5.753)	<0.001
	High	11.771 (6.980 - 19.850)	<0.001

RCRI = Revised Cardiac Risk Index; SAVS-CRI = South African Vascular Surgical Cardiac Risk Index; OR = odds ratio; CI = confidence interval.

SA risk profile may differ from that of North American and European populations.[3] This suggests that clinical indices of peri-operative cardiovascular risk that are not derived in SA may have inferior performance when applied to SAs.[3]

When compared with the cohorts of Lee *et al.*[4] and Boersma *et al.*,[16] the prevalence of cardiac risk predictors in our surgical cohort was similar or higher, with the exception of congestive heart failure. Since the study of Lee *et al.*,[4] congestive heart failure has been considered a significant risk factor for peri-operative cardiovascular events in patients undergoing non-cardiac surgery. It is possible that congestive cardiac failure may be an important risk factor; however, we could not demonstrate this in our study. This may be due to the small sample size, a potential bias to manage some of these patients conservatively, and the notoriously difficult clinical diagnostic criteria.[15]

Multivariable analysis of our study data suggests that age, a history of ischaemic heart disease, diabetes, chronic β-blockade, prior coronary revascularisation and the vascular surgical procedure are important independent clinical risk predictors of cardiac morbidity/mortality in SA vascular surgery patients. Belmont *et al.*[17] also found age to be associated with 30-day mortality and complications following lower limb amputation (OR 1.03, 95% CI 1.02 - 1.05; $p<0.0001$). McFalls *et al.*[18] showed that age >70 years was an independent predictor of troponin leak during the peri-operative period in a vascular surgery cohort with documented coronary artery disease (OR 1.84, 95% CI 1.14 - 2.98; $p=0.01$). Increasing age is associated with an increased prevalence of co-morbidities such as hypertension, heart disease and stroke. When Lee's RCRI was adapted to include age, the adapted index showed improved cardiovascular mortality prediction.[19] In addition to the abovementioned studies, our study confirms the significance of an increased duration of exposure to cardiovascular risk factors as a function of age on peri-operative cardiovascular morbidity/mortality in vascular surgery patients.[15]

Ischaemic heart disease and diabetes have long been identified as independent predictors of peri-operative MACEs in several previous studies of vascular surgery cohorts.[4,18,19] Coronary artery stenosis may aggravate myocardial ischaemia in the peri-operative period. Furthermore, in patients with coronary artery disease there may be peri-operative atherosclerotic plaque rupture and resulting thromboembolism-associated myocardial infarction.[20]

Although β-blockade has been shown to be beneficial in reducing peri-operative myocardial ischaemia and arrhythmias,[21,22] there is some evidence to suggest that chronic β-blocker use may have detrimental effects after major surgery. A meta-analysis by Giles *et al.*[23] found a significant association between chronic β-blockade and peri-operative myocardial infarction (OR 2.14, 95% CI 1.29 - 3.56). In agreement with this meta-analysis, the VSG-CRI study,[8] studies by Biccard and Pooran[24] and Hoeks *et al.*,[25] and our study have also found chronic β-blockade to be associated with peri-operative MACEs. There may be several explanations for our observations. Chronic β-blockade is associated with an up-regulation of β-adrenoreceptors.[26] As such, patients receiving a chronic β-blocker may be more likely to develop a peri-operative tachycardia than their acutely β-blocked peers. Peri-operative tachycardia may result in peri-operative myocardial ischaemia at lower than expected heart rates.[23] In addition, patients may not be able to take their chronic oral medications, such as β-blockers, after their operations.[27] This would equate to withdrawal of chronic β-blockade, which in the peri-operative period is associated with an increased likelihood of short-term MACEs and mortality,[28] as well as increased mortality at 1 year post-surgery.[25] Our observed association of chronic β-blockade with peri-operative MACEs may therefore be due to the impact of β-blocker withdrawal in the peri-operative period. When compared with the VSG-CRI study,[8] chronic β-blockade appears to be associated with more risk in our patients, perhaps reflecting more frequent withdrawal of chronic β-blockade.

The benefit of prophylactic pre-operative coronary revascularisation prior to surgery remains debatable. Two prospective studies (the Coronary Artery Revascularization Prophylaxis and Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo-V studies)[29,30] have shown that prophylactic coronary revascularisation before major vascular surgery does not reduce the risk of peri-operative myocardial infarction. However, in vascular patients with an incidental history of prior coronary revascularisation, the VSG-CRI study group found it to be associated with a protective effect against peri-operative MACEs.[8] Our findings are in agreement with the VSG-CRI study and suggest that coronary revascularisation, if indicated prior to major vascular surgery, may reduce peri-operative cardiovascular risk. As coronary artery disease contributes proportionally more to risk in our patients, it is not surprising that prior coronary revascularisation appears to provide greater protection in our patients than was seen in the VSG-CRI study.[8]

The SAVS-CRI appears to have superior clinical performance compared with the RCRI in SA vascular surgical patients, as evidenced by the significantly higher AUC in the ROC curve analysis and a significantly different incidence of MACEs between risk categories.

The observed peri-operative MACE rates may be considered high across all three risk categories. This may partly be due to our definition of MACE, which only required a troponin leak

above the upper reference limit. Troponin-I is a highly sensitive biomarker of myocardial damage, and concerns have been raised regarding overestimation of the extent of perceived myocardial damage following an abnormal but low troponin-I measurement. However, even a perceived minor troponin leak of this nature has prognostic importance, as recently confirmed in the Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Study.[31] Previously, Le Manach *et al.* observed that patients with abnormal but low postoperative troponin-I levels are at increased risk of a 'delayed' peri-operative myocardial infarction and mortality.[32] Duration of hospital stay and mortality were also significantly increased in the group with a diagnosis of myocardial damage (a troponin leak that did not fulfil the study criteria for myocardial infarction) compared with patients without a troponin leak.[31] The results of the VISION study showed that even peak troponin values far lower than the commonly used threshold for a 'medical' myocardial infarction following non-cardiac surgery are a strong independent predictor of 30-day mortality, with over 40% of deaths being attributable to elevated postoperative troponins.[31]

Furthermore, approximately half of the patients who died following a troponin leak during the VISION study died of non-vascular causes. Myocardial injury may decrease the likelihood of surviving subsequent non-vascular peri-operative complications, such as pneumonia, and could explain the association observed between postoperative troponin leak and all-cause mortality in the VISION study.[31] This is supported by the observation that the complications resulting in the majority of non-cardiovascular deaths have often developed later in the clinical course, following an earlier troponin leak.[31] For these reasons, we believe the definition of MACE used in this study to be clinically relevant.

The results of this study require prospective validation in an independent cohort.

Study strengths

We prospectively collected data on potential cardiac risk factors over a 3-year period in SA vascular surgical patients. The dataset was complete for all patients who consented to participate in the study.

Study limitations

Data on chronic obstructive pulmonary disease, which was an independent predictor of adverse outcomes in the VSG-CRI model, were not collected. We were also unable to assess postoperative compliance with chronic medication and hence can only speculate on the withdrawal of β-blockers and any association with peri-operative MACEs. The impact of HIV-associated vasculopathy on peri-operative MACEs could not be investigated owing to the small sample (n=73) of known HIV-positive patients. Another limitation is that our study was an analysis of data from a single clinical trial site; larger studies, comprising multiple clinical trial sites in different geographical areas in SA, are required to validate the general application of the SAVS-CRI.

Conclusion

The SAVS-CRI identified six independent predictors of MACEs. Importantly, in agreement with the VSG-CRI model, only two of these risk factors were identified in the RCRI, while the other three risk factors were also identified in the VSG-CRI. This study confirms that it is probably inappropriate to risk-stratify SA vascular surgical patients using the RCRI. Development and validation of a suitable cardiac risk index for use in SA patients undergoing vascular surgery is therefore necessary.

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CHAPTER 5:

Manuscript 3

The impact of acute pre-operative β-blockade on peri-operative cardiac morbidity and all-cause mortality in hypertensive South African vascular surgery patients (S Afr Med J 2015;105:476-479)

The impact of acute preoperative beta-blockade on perioperative cardiac morbidity and all-cause mortality in hypertensive South African vascular surgery patients

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Background. Acute β-blockade has been associated with poor perioperative outcomes in non-cardiac surgery patients, probably as a result of β-blocker-induced haemodynamic instability during the perioperative period, which has been shown to be more severe in hypertensive patients.
Objective. To determine the impact of acute preoperative β-blockade on the incidence of perioperative cardiovascular morbidity and all-cause mortality in hypertensive South African (SA) patients who underwent vascular surgery at a tertiary hospital.
Methods. We conducted two separate case-control analyses to determine the impact of acute preoperative β-blockade on the incidence of major adverse cardiovascular events (MACEs, a composite outcome of a perioperative troponin-I leak or all-cause mortality) and perioperative troponin-I leak alone. Case and control groups were compared using χ^2, Fisher's exact, McNemar's or Student's *t*-tests, where applicable. Binary logistic regression was used to determine whether acute preoperative β-blocker use was an independent predictor of perioperative MACEs/troponin-I leak in hypertensive SA vascular surgery patients.
Results. We found acute preoperative β-blockade to be an independent predictor of perioperative MACEs (odds ratio (OR) 3.496; 95% confidence interval (CI) 1.948 - 6.273; $p<0.001$) and troponin-I leak (OR 5.962; 95% CI 3.085 - 11.52; $p<0.001$) in hypertensive SA vascular surgery patients.
Conclusions. Our findings suggest that acute preoperative β-blockade is associated with an increased risk of perioperative cardiac morbidity and all-cause mortality in hypertensive SA vascular surgery patients.

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Beta-blockers are prescribed as fourth-line treatment options for hypertension in South African (SA) patients.[1,2] Withdrawal of chronic β-blockade during the perioperative period is associated with poor outcomes in non-cardiac surgery patients.[3] However, acute initiation of β-blockade during the perioperative period has also been shown to be associated with a higher risk of adverse outcomes following non-cardiac surgery,[4,5] probably as a consequence of perioperative haemodynamic instability modulated by acute β-blockade.[6] A large percentage of SA vascular patients have mean blood pressures above the therapeutic target.[7] Acknowledging that poorly controlled hypertension is highly prevalent in the SA vascular patient population, it is possible that uncontrolled hypertension could further aggravate haemodynamic instability caused by acute β-blockade, resulting in high levels of perioperative cardiac morbidity and mortality.

Objective

To determine the impact of acute preoperative β-blockade on the incidence of perioperative cardiovascular morbidity and all-cause mortality in hypertensive SA patients who underwent vascular surgery at a tertiary hospital.

Methods

Study design, setting, and patients

This study consisted of two separate case-control analyses, and was a sub-study of the South African Vascular Surgical-Cardiac Risk Index (SAVS-CRI) study.[8] Briefly, the SAVS-CRI study was a prospective cohort study conducted at Inkosi Albert Luthuli Central Hospital in Durban, SA, which sought to determine risk factors for perioperative major adverse cardiovascular events (MACEs) in vascular surgery patients. The study was approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee (Protocol BF068/07, BCA117/010). A registry of consenting adult patients who underwent elective vascular surgery at the hospital between February 2008 and March 2011 was created to prospectively collect data related to demographic variables, medication use, and established risk factors for the primary outcome of this study, perioperative MACEs in vascular surgery patients receiving acute preoperative β-blockade. We did not exclude patients with respiratory, endocrine or neurological disorders from the registry, except when they were unable to provide appropriate written informed consent for inclusion in the registry. A MACE was defined as a composite of all-cause mortality within 30 days of surgery or a perioperative troponin-I leak of ≥0.1 ng/ml that occurred within 3 days after a patient's surgery. We defined patients receiving acute preoperative β-blockade as those who had a β-blocker prescribed or administered during the same hospital admission for surgery. The definitions of established risk factors for adverse perioperative outcomes used in the SAVS-CRI study[8] and in this study were adopted from the study of Lee *et al.*[9] We filtered the SAVS-CRI cohort for vascular surgery patients with a history of hypertension (patients diagnosed with hypertension by a doctor, or patients taking antihypertensive medications).

Matching of cases and controls

Propensity scores for all hypertensive patients were calculated following matching according to demographic factors (age, gender), clinical

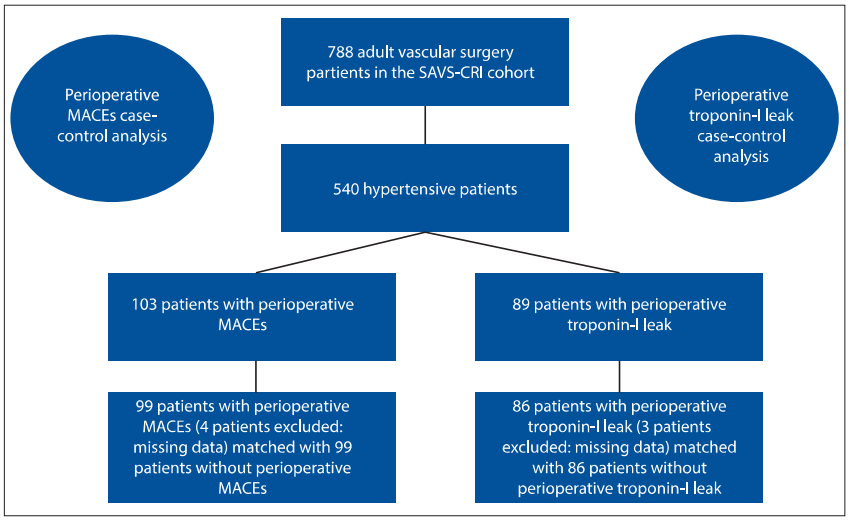

Fig. 1. Study profiles of the perioperative MACEs and perioperative troponin-I leak case-control analyses.

factors (ischaemic heart disease, diabetes, cerebrovascular disease, renal impairment and congestive heart failure), and antihypertensive medication use (angiotensin-converting enzyme inhibitors and calcium channel blockers, but not β-blockers). For the perioperative MACEs case-control analysis, cases were defined as patients who suffered perioperative MACEs, while controls were defined as patients who did not suffer perioperative MACEs. Patients were matched in a 1:1 case-to-control ratio based on similar propensity scores, resulting in a total of 99 matched pairs that were included in the analysis for the MACEs case-control analysis.

We also conducted a case-control analysis to determine the impact of acute preoperative β-blockade on the incidence of perioperative troponin-I leak alone in hypertensive SA vascular surgery patients. Patients were matched using a methodology similar to that described for the MACEs case-control analysis, resulting in a total of 86 matched pairs that were included in the analysis for the perioperative troponin-I leak case-control analysis.

Statistical analysis

Categorical data were analysed using χ^2, Fisher's exact or McNemar's tests, where appropriate. Student's *t*-tests were used to analyse continuous data. A binary logistic regression model was used to determine whether acute preoperative β-blockade was a predictor of perioperative MACEs or perioperative troponin-I leak. Results for the categorical data analysis are presented as frequencies and percentages, while results for the binary logistic regression analyses are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Any *p*-value <0.05 was considered to be statistically significant. All statistical analyses, including the derivation of the propensity scores for each patient, were performed using the Statistical Package for the Social Sciences (SPSS), version 21 (SPSS Inc., USA).

Results

The study profiles for both the perioperative MACEs and the perioperative troponin-I leak case-control analyses are illustrated in Fig. 1. A total of 540/788 patients from the SAVS-CRI cohort (68.5%) were hypertensive and were screened for inclusion in the matching process. There were 103 perioperative MACEs and 89 perioperative troponin-I leaks in these 540 patients. Four patients with perioperative MACEs and 3 with perioperative troponin-I leak were excluded owing to missing comorbidity data, namely preoperative serum creatinine measurements, which were required to match cases and controls based on the criterion for renal impairment of serum creatinine >177 μmol/l as defined by Lee *et al.*[9] The final study population for the perioperative MACEs case-control analysis therefore consisted of 99 matched pairs of cases and controls (*n*=198). A total of 31/99 patients (31.4%) had died within 30 days of surgery,

Table 1. Clinical characteristics of cases and controls in the perioperative MACEs case-control analysis

Clinical characteristic	All patients (*N*=198)	Patients with perioperative MACEs (cases, *N*=99)	Patients without perioperative MACEs (controls, *N*=99)	*p*-value*
Male gender, *n* (%)	103 (52.0)	53 (53.5)	50 (50.5)	0.670
Age (years), mean (SD)	64.4 (11.4)	64.6 (12.3)	64.2 (10.3)	0.793
Ischaemic heart disease, *n* (%)	119 (60.1)	57 (57.6)	62 (62.6)	0.468
Diabetes, *n* (%)	134 (67.7)	64 (64.6)	70 (70.7)	0.362
Congestive heart failure, *n* (%)	21 (10.6)	10 (10.1)	11 (11.1)	0.817
Renal impairment, *n* (%)	8 (4.0)	4 (4.0)	4 (4.0)	1.000
History of cerebrovascular accident, *n* (%)	42 (21.2)	21 (21.2)	21 (21.2)	1.000
High-risk surgical procedures, *n* (%)	28 (14.1)	15 (15.2)	13 (13.1)	0.683
Acute preoperative aspirin use, *n* (%)	190 (96.0)	94 (94.9)	96 (97.0)	0.721
Acute preoperative calcium channel blocker use, *n* (%)	69 (34.8)	37 (37.4)	32 (32.3)	0.456
Acute preoperative angiotensin-converting enzyme inhibitor use, *n* (%)	139 (70.2)	70 (70.7)	69 (69.7)	0.877
Acute preoperative β-blocker use, *n* (%)	100 (50.5)	65 (65.7)	35 (35.4)	<0.001

SD = standard deviation.
*$p<0.05$ was considered a statistically significant result.

with perioperative troponin leaks noted in 15 of these cases (48.4%). The final study population for the perioperative troponin-I leak case-control analysis consisted of 86 matched pairs of cases and controls (n=172).

The clinical characteristics of the case and control groups in the perioperative MACEs case-control analysis are shown in Table 1. With the exception of acute preoperative β-blocker use (p<0.001), no statistically significant results were noted on χ^2 testing between any other clinical characteristics in the case and control groups, indicating appropriate matching of the individual cases and corresponding controls. The results of McNemar's test also showed that the association between acute preoperative β-blocker use and perioperative MACEs was statistically significant in this study (p<0.001). When entered into a logistic regression equation, acute preoperative β-blocker use was associated with an almost 3.5-fold increased risk of developing perioperative MACEs following vascular surgery in hypertensive SA patients (OR 3.496; 95% CI 1.948 - 6.273; p<0.001).

Table 2 shows the clinical characteristics of cases and controls in the perioperative troponin-I leak case-control analysis. As with the perioperative MACEs case-control analysis, cases and controls in the perioperative troponin-I leak case-control analysis appeared to be efficiently matched with regard to clinical comorbidities, procedural risk, and calcium channel blocker and angiotensin-converting enzyme inhibitor use. A statistically significant association between preoperative acute β-blockade and perioperative troponin-I leak was observed following χ^2 testing (p<0.001). When case-control pairs were analysed via McNemar's test, an association between acute preoperative β-blockade and perioperative troponin-I leak was observed (p<0.001). When entered into a logistic regression equation, acute preoperative β-blocker use was associated with an increased risk of developing perioperative troponin-I leak following vascular surgery in hypertensive SA patients (OR 5.962; 95% CI 3.085 - 11.52; p<0.001). A description of acute preoperative β-blocker use for both case-control analyses is presented in Table 3.

Table 2. Clinical characteristics of cases and controls in the perioperative troponin-I leak case-control analysis

Clinical characteristic	All patients (N=172)	Patients with perioperative troponin-I leak (cases, N=86)	Patients without perioperative troponin-I leak (controls, N=86)	p-value*
Male gender, *n* (%)	87 (50.6)	45 (52.3)	42 (48.8)	0.647
Age (years), mean (SD)	63.8 (11.1)	64.2 (12.2)	63.4 (9.9)	0.657
Ischaemic heart disease, *n* (%)	109 (63.4)	53 (61.6)	56 (65.1)	0.635
Diabetes, *n* (%)	121 (70.3)	58 (67.4)	63 (73.3)	0.404
Congestive heart failure, *n* (%)	18 (10.5)	9 (10.5)	9 (10.5)	1.000
Renal impairment, *n* (%)	6 (3.5)	3 (3.5)	3 (3.5)	1.000
History of cerebrovascular accident, *n* (%)	39 (22.7)	20 (23.3)	19 (22.1)	0.856
High-risk surgical procedures, *n* (%)	27 (15.7)	14 (16.3)	13 (15.1)	0.834
Acute preoperative aspirin use, *n* (%)	165 (95.9)	81 (94.2)	84 (97.7)	0.443
Acute preoperative calcium channel blocker use, *n* (%)	58 (33.7)	32 (37.2)	26 (30.2)	0.333
Acute preoperative angiotensin-converting enzyme inhibitor use, *n* (%)	114 (66.3)	59 (68.6)	55 (64.0)	0.519
Acute preoperative β-blocker use, *n* (%)	88 (51.2)	62 (72.1)	26 (30.2)	<0.001

SD = standard deviation.
*p<0.05 was considered a statistically significant result.

Table 3. Description of acute preoperative β-blocker use in both case-control analyses

	Perioperative MACEs case-control analysis			Perioperative troponin-I leak case-control analysis		
Beta-blockers used	All patients	Patients with perioperative MACEs	Patients without perioperative MACEs	All patients	Patients with perioperative troponin-I leak	Patients without perioperative troponin-I leak
Atenolol only, *n* (%)	80 (80.0)	53 (81.5)	27 (77.1)	71 (80.7)	49 (79.0)	22 (84.6)
Atenolol + carvedilol, *n* (%)	5 (5.0)	3 (4.6)	2 (5.7)	5 (5.7)	3 (4.8)	2 (7.7)
Atenolol + labetalol, *n* (%)	2 (2.0)	1 (1.5)	1 (2.9)	1 (1.1)	1 (1.6)	0 (0.0)
Carvedilol only, *n* (%)	12 (12.0)	7 (10.9)	5 (14.3)	10 (11.4)	8 (13.0)	2 (7.7)
Labetalol only, *n* (%)	1 (1.0)	1 (1.5)	0 (0.0)	1 (1.1)	1 (1.6)	0 (0.0)
Total, *n* (%)	100 (100.0)	65 (100.0)	35 (100.0)	88 (100.0)	62 (100.0)	26 (100.0)

Discussion

We found acute preoperative β-blockade to be an independent predictor of perioperative cardiac morbidity (as evidenced by perioperative troponin-I measurements) and all-cause mortality in hypertensive SA vascular surgery patients.

We suspect that these results are related to perioperative haemodynamic instability. Hypotension is a common perioperative complication in vascular surgery patients with a history of poorly controlled hypertension, with a study by Charlson *et al.*[10] reporting a higher incidence of perioperative hypotension in patients who had preoperative mean arterial blood pressures ≥110 mmHg than in those with preoperative mean arterial blood pressures of <100 mmHg. In another study by Charlson *et al.*,[11] a decrease in mean arterial blood pressure of ≥20 mmHg for ≥5 minutes was associated with an increased incidence of perioperative cardiac complications in non-cardiac surgery patients. Perioperative hypotension is therefore an important determinant of perioperative cardiac outcomes in non-cardiac surgery patients, in particular those with poorly controlled hypertension.

Acute preoperative β-blockade may further aggravate the haemodynamic instability associated with a history of poorly controlled hypertension. The POISE-I study was a randomised controlled trial comparing the effect of acutely administered, extended-release β-blocker (metoprolol succinate) with that of placebo on the 30-day risk of major cardiovascular events in patients with, or at risk of, atherosclerotic disease who were undergoing non-cardiac surgery.[12] In this study, patients randomised to acute preoperative β-blockade had significantly more hypotension. Furthermore, hypotension was associated with perioperative mortality (hazard ratio (HR) 1.33; 95% CI 1.03 - 1.74; p=0.0317). An analysis of the causation of perioperative deaths in the POISE-I study suggested that hypotension was partly associated with some of the mortality.[12]

Although the POISE-I study[12] did not find perioperative hypotension to be associated with perioperative myocardial infarction in non-cardiac surgery patients, the POISE-II study,[13] which was a randomised controlled study of clonidine v. placebo, found clinically important hypotension to be independently associated with perioperative myocardial infarction (HR 1.37; 95% CI 1.16 - 1.62; p<0.001).[13]

It is therefore likely that our study population of hypertensive vascular surgery patients with previously documented poorly controlled hypertension may have been predisposed towards perioperative hypotension, which could have been further exacerbated by acute preoperative β-blockade, resulting in the observed increased incidence of perioperative cardiac morbidity and all-cause mortality. These findings have important implications for primary and secondary prevention of myocardial ischaemia in the perioperative period in hypertensive vascular surgery patients.

Study limitations

Our study had several limitations. We only collected data related to perioperative cardiac outcomes and all-cause mortality during this study, and we were unable to evaluate the impact of acute preoperative β-blockade on other perioperative complications that might have occurred, such as stroke and clinically important hypotension. Based on results from POISE-I,[12] it is likely that acute preoperative β-blockade may also further increase perioperative stroke risk in SA hypertensive vascular surgical patients. We did not collect data related to chronic obstructive airway disease and were therefore unable to control for this factor in either of the case-control analyses. We also did not collect data related to neurological disorders other than cerebrovascular disease. While we did not collect data related to diabetes treatment, it is likely that diabetic patients were placed on an insulin sliding scale preoperatively, in line with current local practice. Although we did not collect information related to the actual dosage of the drugs administered to vascular patients in our institution, atenolol is commonly prescribed at a dose of 50 mg orally per day, labetalol is titrated to effect with heart rate control when patients cannot take medications orally, and carvedilol is prescribed for heart failure and is up-titrated to the desired effect over a period of time.

In addition, we were unable to access information related to patients' cause of death once they had been discharged from hospital. Another limitation is that our patient population was drawn from a single tertiary hospital and represented a population with substantial medical comorbidity at high-risk for perioperative cardiac complications or death, requiring specialist vascular surgery. It is therefore possible that the epidemiology of acute preoperative β-blocker administration and patient comorbidities in our study population may be different from that in patients attending lower-level facilities, or even facilities in different geographical locales within SA.

Conclusions

Acute preoperative β-blocker administration was associated with an increased risk of perioperative cardiac morbidity and all-cause mortality in hypertensive SA vascular surgery patients. A cautious approach should be taken when considering initiating acute preoperative β-blockade in hypertensive surgical patients.

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CHAPTER 6:

Manuscript 4

Post-operative acute kidney injury in non-suprainguinal vascular surgery patients with a pre-operative history of hypertension (EXCLI J 2015;14:379-384).

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Original article:

POST-OPERATIVE ACUTE KIDNEY INJURY IN NON-SUPRAINGUINAL VASCULAR SURGERY PATIENTS WITH A PRE-OPERATIVE HISTORY OF HYPERTENSION

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ABSTRACT

Hypertension is an independent predictor of acute kidney injury (AKI) in non-cardiac surgery patients. There are a few published studies which report AKI following non-suprainguinal vascular procedures, but these studies have not investigated predictors of AKI, including anti-hypertensive medications and other comorbidities, in the hypertensive population alone. We sought to identify independent predictors of post-operative AKI in non-suprainguinal vascular surgery patients with a pre-operative history of hypertension. We performed univariate (chi-squared, or Fisher's exact testing) and multivariate (binary logistic regression) statistical analysis of prospectively collected data from 243 adult hypertensive patients who underwent non-suprainguinal vascular surgery (lower limb amputation or peripheral artery bypass surgery) at a tertiary hospital between 2008 and 2011 in an attempt to identify possible associations between comorbidity, acute pre-operative antihypertensive medication administration, and post-operative AKI (a post-operative increase in serum creatinine of ≥ 25 % above the pre-operative measurement) in these patients. The incidence of post-operative AKI in this study was 5.3 % (95 % Confidence Interval: 3.2-8.9 %). Acute pre-operative β-blocker administration was independently associated with post-operative AKI in non-suprainguinal vascular surgery patients with a pre-operative history of hypertension (Odds Ratio: 3.24; 95 % Confidence Interval: 1.03-10.25). The acute pre-operative administration of β-blockers should be carefully considered in non-suprainguinal vascular surgery patients with a pre-operative history of hypertension, in lieu of an increased risk of potentially poor post-operative renal outcomes.

Keywords: Acute kidney injury, vascular surgery, hypertensive

INTRODUCTION

Acute kidney injury (AKI) is a significant cause of in-hospital morbidity and mortality in hospitalized patients (Borthwick and Ferguson, 2010; Chertow et al., 2005). The prevalence of AKI following major non-cardiac surgery varies between 1 % (Kheterpal et al., 2009) and 57 % (Macedo et al., 2008). Hypertension has been identified as an independent predictor of AKI in non-cardiac surgery patients (Kheterpal et al., 2009). Amongst vascular surgery patients, most studies describe peri-operative renal outcomes following suprainguinal procedures, namely abdominal aortic aneurysm repair (Thakar, 2013), where an excessively high burden of post-operative renal injury is often reported. Whilst there are studies

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which report post-operative AKI following non-suprainguinal procedures, such as lower limb amputation and peripheral artery bypass surgery (Adalbert et al., 2013; Arora et al., 2013), these studies have failed to investigate predictors of poor post-operative renal outcomes, including anti-hypertensive medications and other comorbidities, in the hypertensive population alone. We sought to identify independent predictors of post-operative AKI in non-suprainguinal vascular surgery patients with a pre-operative history of hypertension.

MATERIALS AND METHODS

This study was a sub-analysis of data from an ethically approved (University of Kwazulu-Natal Biomedical Research Ethics Committee approval reference: BF068/07, BCA117/010) prospective database of adult patients who underwent elective vascular surgery at a tertiary hospital located in Durban, South Africa between 2008 and 2011 (Moodley et al., 2013). We considered a patient to be hypertensive if the patient was diagnosed as having hypertension by a physician, or if the patient was taking any anti-hypertensive medications (Angiotensin converting enzyme inhibitors - ACEI, β-blockers - βB, or calcium channel blockers - CCB). A total of 243 patients were included in our final analysis, following the exclusion of i) patients who did not undergo non-suprainguinal vascular surgery (lower limb amputation or peripheral artery bypass surgery), ii) patients with missing peri-operative serum creatinine measurements, iii) patients with pre-operative renal dysfunction, as defined in the study by Abelha and colleagues (Abelha et al., 2009) as a pre-operative serum creatinine measurement of ≥ 141 μmol/L in men or ≥ 124 μmol/L in women, and iv) patients without a history of hypertension (Figure 1). Data elements collected from patient medical records included demographic information (age and gender), comorbid conditions (history of diabetes, ischaemic heart disease, congestive heart failure, stroke), acute pre-operative anti-hypertensive medication use (ACEI, βB, CCB), and peri-operative laboratory test results (pre- and post-operative serum creatinine measurements). The definitions of comorbid conditions used in this study were adopted from the study of Lee and colleagues (Lee et al., 1999). In this study we defined post-operative AKI as an increase in post-operative serum creatinine ≥ 25 % above the pre-operative measurement. We had chosen this threshold rather than the current Kidney Disease Improving Global Outcomes group defined serum creatinine increase threshold (Kellum and Lameire, 2013) as a large hospital administrative database study found a 25 % increase in serum creatinine from the baseline measurement was associated with a 2-fold increased risk of mortality in hospitalized patients (Chertow et al., 2005). Furthermore, a published meta-analysis found a 3- to 7-fold increase in risk for mortality in hospitalized (surgical and non-surgical) patients with serum creatinine increases of > 25 % from baseline (Coca et al., 2007). Lastly, our definition of AKI is in keeping with the definition used in a meta-analysis of renal outcomes in patients undergoing major surgery (Ho and Morgan, 2009). Use of the less liberal Kidney Disease Improving Global Outcomes group definition (serum creatinine increase of ≥ 26.5 μmol/l from the baseline/pre-operative measurement, or an increase in post-operative serum creatinine to ≥ 1.5 times the baseline/pre-operative measurement) would have therefore excluded patients from the analysis with a prognostically important serum creatinine measurement in the post-operative period.

Univariate statistical methods used to analyse data included chi-squared and Fisher's Exact testing, where appropriate. For the multivariate statistical analysis, a binary logistic regression model was used to identify independent predictors of post-operative AKI in non-suprainguinal vascular surgery patients with a pre-operative history of hypertension. The clinical variables entered into the logistic regression equation were purposefully selected, with variables attain-

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ing a significance level of p <0.1 at the univariate analysis level being included in the regression analysis. Results for the univariate data analysis are presented as frequencies and percentages, whilst results for the binary logistic regression analyses are presented as odds ratios (OR) with 95 % confidence intervals (95 % CI). Any p-value < 0.05 was considered to be a statistically significant result. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21 (SPSS Inc., Chicago, IL, USA).

RESULTS

The process by which patients were selected for inclusion in this study is shown in Figure 1. Thirteen of the 243 (5.3 %; 95 % CI: 3.2-8.9 %) patients included in our study developed post-operative AKI. The baseline characteristics of patients included in our final analysis are shown in Table 1. A large proportion of patients who underwent surgery in the entire cohort were elderly. In addition, almost two-thirds of the entire cohort was male. Diabetes and ischaemic heart disease were the most prevalent comorbid conditions in the entire cohort. With regard to anti-hypertensive medication use, it was common for ACEI or βB, and to a lesser extent CCBs, to have been acutely administered prior to a patient's surgery.

When stratified by post-operative AKI status, no statistically significant univariate associations were observed between patient demographic factors, comorbidities and post-operative AKI (Table 1). The point estimates for acute pre-operative ACEI and CCB administration showed a trend toward post-operative renal protection in the presence of these anti-hypertensive medications. A statistical trend was also observed for the association between acute pre-operative βB administration and post-operative AKI (p=0.067, Table 1). This statistical trend satisfied the inclusion criterion for the entry of a clinical variable into the logistic regression analysis in our study (p<0.1 at the univariate

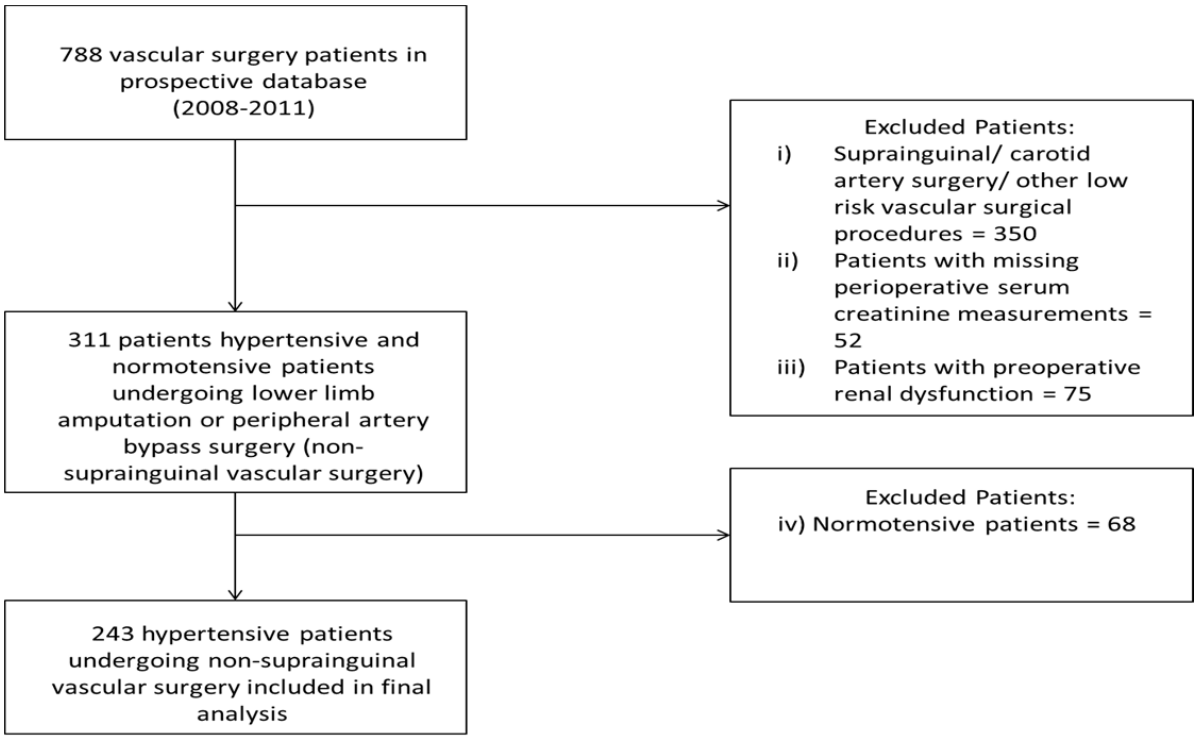

Figure 1: Derivation of the final study cohort

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analysis level). When entered into a logistic regression equation, acute pre-operative βB administration was found to be independently associated with post-operative AKI in non-suprainguinal vascular surgery patients who had a pre-operative history of hypertension (OR: 3.24; 95 % CI: 1.03-10.25).

DISCUSSION

Five of every 100 hypertensive patients undergoing non-suprainguinal vascular surgery in this study suffered post-operative AKI. The incidence of post-operative AKI in our study was lower than that reported for two other studies of non-suprainguinal vascular surgery, which reported the incidence of post-operative AKI to be 12 % and 12.7 % (Adalbert et al., 2013; Arora et al., 2013). Pre-operative renal dysfunction is an important determinant of post-operative renal outcomes. Although a lower incidence of post-operative AKI in the combined hypertensive-normotensive populations described in the aforementioned studies would be expected, our study population was different in that we had investigated renal outcomes in patients with normal pre-operative renal function, and excluded patients with pre-operative renal dysfunction from our final analysis. However, patients with pre-operative renal dysfunction were included in the two other studies of AKI in non-suprainguinal vascular surgery patients (Adalbert et al., 2013; Arora et al., 2013), thereby explaining the higher incidence of post-operative AKI reported in these studies.

In contrast to other studies of non-cardiac and vascular surgery patients (Adalbert et al., 2013; Arora et al., 2013; Kheterpal et al., 2009), we did not observe associations between any of the patient demographic characteristics or comorbidities and post-operative AKI in our study. It is likely that our study was not adequately powered to determine the impact of these variables on post-operative AKI. Similarly, it appears our study was not adequately powered to investigate the effects of acute pre-operative ACEI and CCB administration on post-operative renal outcomes. It is important to note however, that ACEI and CCB were associated with a trend toward renal protection in the post-operative period, as opposed to acute pre-operative βB use, which was associated with post-operative renal injury.

Table 1: Clinical characteristics of patients with and without post-operative AKI expressed as a frequency (percentage)

Clinical characteristic	All patients (n=243)	Patients with post-operative AKI (n=13)	Patients without post-operative AKI (n=230)	p-value
Male gender	160 (65.8)	8 (61.5)	152 (66.1)	0.768
Age > 65 years old	107 (44.0)	8 (61.5)	99 (43.0)	0.191
Ischaemic heart disease	110 (45.3)	7 (53.8)	103 (44.8)	0.523
Diabetes	166 (68.3)	7 (53.8)	159 (69.1)	0.357
Congestive heart failure	15 (6.2)	2 (15.4)	13 (5.7)	0.187
Stroke	34 (14.0)	2 (15.4)	32 (13.9)	1.000
Acute pre-operative CCB administration	47 (19.3)	2 (15.4)	45 (19.6)	1.000
Acute pre-operative ACEI administration	143 (58.8)	6 (42.2)	137 (59.6)	0.339
Acute pre-operative βB administration	84 (34.6)	8 (61.5)	76 (33.0)	0.067

AKI: Acute kidney injury, CCB: Calcium channel blockers, ACEI: Angiotensin converting enzyme inhibitors, βB: β-blockers; $p < 0.05$ was considered a statistically significant result.

We found acute pre-operative βB administration to be associated with a 3-fold increased risk of developing post-operative AKI in this study. In another study, we had reported that acute pre-operative βB administration was associated with a higher risk of peri-operative troponin leak and peri-operative major adverse cardiovascular events in vascular surgery patients with a pre-operative history of hypertension (Moodley and Biccard, 2015). In that study we postulated that vascular surgery patients with a pre-operative history of poorly controlled hypertension might be pre-disposed towards peri-operative hypotension. The peri-operative hypotension might have been further exacerbated by acute pre-operative βB administration, resulting in a higher incidence of peri-operative cardiac morbidity and mortality in patients who received acute pre-operative βB versus patients who did not receive acute pre-operative βB in that study (Moodley and Biccard, 2015). Similarly, it is therefore possible that acute pre-operative βB administration exacerbates global peri-operative hypotension in patients with poorly controlled pre-operative hypertension, resulting in ischaemic injury of the kidney. The potentially aggravating effects of acute pre-operative βB administration on global peri-operative hypotension observed in this study are further supported by the findings of the POISE study (Devereaux et al., 2008), wherein acutely administered pre-operative metoprolol was found to be independently associated with a higher incidence of peri-operative hypotension and peri-operative stroke following non-cardiac surgery. The findings of our research have potential implications for peri-operative medication management in vascular surgery patients, particularly those with a pre-operative history of hypertension. Our study was not without limitations. It is likely that our study was underpowered to investigate the impact of patient demographic variables, other comorbidities, and the acute pre-operative use of ACEI and CCB on the incidence of post-operative AKI. A larger patient cohort would be required to adequately investigate this.

In conclusion, acute pre-operative β-blockade was associated with a higher risk of post-operative AKI in non-suprainguinal vascular surgery patients with a pre-operative history of hypertension. Although this research requires validation in a larger cohort, our findings suggest that the acute pre-operative administration of βB should be carefully considered in non-suprainguinal vascular surgery patients who have a pre-operative history of hypertension.

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Conflict of interest

The authors declare that they have no conflict of interest.

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CHAPTER 7:

Manuscript 5

The association between pre-operative clinical risk factors and in-hospital stroke and death following carotid endarterectomy in South African patients (South Afr J Anaesth Analg 2014;20:152-154).

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RESEARCH

The association between preoperative clinical risk factors and in-hospital strokes and death following carotid endarterectomy in South African patients

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Background: Current surgical management of carotid artery disease includes carotid endarterectomy (CEA). In-hospital strokes and death following CEA might be associated with preinduction blood pressure (BP) measurements and other clinical risk factors.
Method: The aim of our study was to determine whether or not there is an association between preinduction BP, other clinical risk factors, and in-hospital strokes or death following CEA in a cohort of South African patients. We collected data from medical records relating to clinical risk factors in patients, preinduction BP measurements, and in-hospital strokes and death, following CEA. The association between preinduction BP and clinical risk factors, and postoperative neurological morbidity and mortality, was analysed using univariate statistical methods.
Results: Our cohort consisted of 76 patients who underwent CEA. Eight of these patients had in-hospital strokes or death following their surgery. An association between a history of hypertension or other clinical risk factors and an in-hospital stroke and death was not identified in these 76 CEA patients following univariate analysis. However, patients with preinduction BP within the lowest or highest quartile for preinduction BP were at a significantly increased risk of an in-hospital stroke and death following their surgery (p-value = 0.003). A subanalysis of patients who were hypertensive also showed this univariate association (p-value = 0.003).
Conclusion: It is possible that extremes of preinduction BP might be associated with in-hospital strokes and death in CEA patients following their surgery, although further research is required to confirm this.

Keywords: carotid endarterectomy, carotid stenosis, mortality, strokes, surgery

Introduction

Carotid artery disease is associated with neurological morbidity and mortality. Stroke is among the leading causes of death worldwide. Carotid artery stenosis accounts for approximately 20% of strokes in adult populations.[1] Atheromatous plaques reduce the luminal diameter of carotid arteries, decreasing blood flow and promoting thrombus formation. Thromboembolism and neurological injury may result from plaque rupture.[1] Carotid endarterectomy (CEA) is commonly recommended in the treatment of carotid artery disease.[2,3]

However, even within the group of patients with accepted indications for CEA, a subgroup of patients remains who are at increased risk of an early postoperative stroke or death. A number of models have been developed to identify patients at increased risk of early postoperative neurological complications or death.[4,5] Several preoperative clinical risk factors, including hypertension, have been associated with major morbidity within 30 days of CEA. However, these risk factors have not been evaluated in South African vascular surgery patients, who are characterised by a higher burden of cardiovascular co-morbidities and significantly less adoption of established medical therapies than similar patients from developed-world studies.[6] This may be partly because of the epidemiological transition of cardiovascular disease in South Africa,[7] and inadequate access to effective primary health care. Therefore, it is important to determine what risk factors are associated with an increased risk of postoperative stroke and death in South African vascular surgery patients, e.g. patients undergoing CEA.

The aim of this study was to determine if an association exists between preinduction blood pressure (BP), other clinical risk factors and in-hospital strokes or death following CEA in a cohort of South African patients.

Method

Ethical approval for this study was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal. This study was conducted at the Inkosi Albert Luthuli Central Hospital, located in Durban. The hospital provides tertiary and quaternary service to patients residing in the province of KwaZulu-Natal. We defined a stroke as rapidly developing signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours, or leading to death with no apparent cause other than that of vascular origin.[8] Our observational cohort study consisted of 76 vascular surgery patients ≥ 45 years old, who had CEA at Inkosi Albert Luthuli Central Hospital between 2008 and 2012. The selection of patients for CEA, as opposed to carotid stenting, was made at the sole discretion of the attending vascular surgeon. The decision to proceed to CEA is made on an individualised basis within our surgical unit. In addition, there are no standard exclusion criteria for CEA in our unit. Surgeries were carried out by five experienced vascular surgeons over the four-year study period. We obtained information on preinduction BP measurements from pre-existing patient anaesthetic records. The preoperative co-morbidities (a history of ischaemic heart disease, diabetes mellitus requiring insulin therapy, a history of cerebrovascular accident, a history of congestive heart failure and a serum creatinine > 177 μmol/l) of the 76 CEA patients were prospectively collected using the definitions specified by Lee et al in their derivation of the Revised Cardiac Risk Index, a widely utilised perioperative cardiovascular risk stratification index.[9] We classified patients as having a history

of hypertension if they were diagnosed with hypertension by a physician prior to their surgery, or if they were taking antihypertensive medication. We identified in-hospital strokes and death following CEA from procedure notes, progress notes, and patient hospital discharge summaries. We were blinded to the clinical risk factors and preinduction BP when we evaluated the perioperative neurological outcomes. We also ensured that perioperative neuropraxia associated with the regional anaesthetic techniques was not incorrectly classified as a postoperative, in-hospital stroke.

We conducted univariate statistical analyses of our data, using the chi-square or Fisher's exact test for categorical data, and independent-sample Student's *t*-test for normally distributed continuous data. We were unable to analyse our data using multivariate statistical methods owing to the low number of outcomes per variable in our cohort.[10] Statistical analyses were performed using the Statistical Package for the Social Sciences® version 21.

Results

Over the four-year study period, 76 patients underwent CEA. Eight patients (10.5%) suffered in-hospital strokes or death following their surgery. The characteristics of our study cohort are shown in Table 1.

A large proportion of our patients presented with a history of hypertension (67/76 patients, 88%). More than 86% of patients presenting for surgery had symptomatic carotid artery disease, with a prior history of stroke.

Patients who presented with preinduction systolic BP within the lowest or highest quartile (extremes of BP) were associated with in-hospital stroke or death following CEA (*p*-value = .003, Table 1). Owing to poor BP control in our patients, the lowest quartile had a preinduction systolic BP (SBP) of < 145 mmHg, and the highest quartile had an SBP of >187 mmHg. A subanalysis of the 67 CEA patients with a preoperative history of hypertension identified an association between the quartile extremes of preinduction SBP (< 145 mmHg or > 195 mmHg) and poor clinical outcomes in these patients following CEA (*p*-value = 0.003, Table 2). We did not find a statistically significant association between any of the other clinical variables and in-hospital strokes or death following CEA in patients with a preoperative history of hypertension.

Discussion

Perioperative stroke is an important cause of morbidity and mortality, following intervention for carotid artery disease. Although the incidence of postoperative, in-hospital strokes and death in our cohort was concerning (10.5%), our results are in agreement with projected results based on the predictive model of Tu and colleagues.[4] Based on three of the five risk factors from the Tu model which we evaluated, our cohort had a projected risk of between 6.1% and 9.5% for a stroke or death following CEA. As we could not evaluate two of the five risk factors, this was obviously a very conservative risk estimate. In contrast to the findings of Tu and colleagues,[4] we did not find a statistically significant association between a prior history of a stroke, congestive heart failure or diabetes, and an in-hospital stroke or death, following CEA, in our study. It is likely that our findings of no statistically significant association between these clinical variables and poor postoperative clinical outcomes could be attributed to our modest sample size. However, the clinical significance of these variables (congestive heart failure, diabetes or a prior history of a stroke), should not be disregarded in patients undergoing CEA.

Hypertension is a common co-morbidity in patients with carotid artery disease. Some researchers have estimated a prevalence of approximately 66% in this group,[11] although 88% of our patients presented with a history of hypertension. Severe hypertension is associated with labile intraoperative arterial BP.[12] This haemodynamic instability may result in periods of intraoperative cerebral hypo- and hyperperfusion. A meta-analysis by Rothwell et al summarised the results of four studies on hypertension and CEA.[13] In a pooled sample of 4 814 patients (cases and controls) there was a statistically significant relationship between hypertension and stroke incidence post CEA (*p*-value < 0.0001). Wong, Findlay and Suarez-Almazor found a similar relationship between postoperative hypertension and stroke in a cohort of 291 consecutive patients undergoing CEA.[14] The rate was 5.2% for perioperative stroke or death. Postoperative hypertension was a significant risk factor (*p*-value = 0.04). Furthermore, the authors also found preoperative hypertension to be an independent predictor of postoperative hypertension. In a study by Asiddao et al on 166 patients undergoing CEA, the incidence of postoperative neurological deficit was three times higher in the presence of postoperative hypertension versus normotension.[11]

Overall, our study did not find any statistically significant association between a history of hypertension and in-hospital strokes or death following CEA. However, our subanalysis of hypertensive CEA patients demonstrated an association between extremes of preinduction systolic BP and poor postoperative clinical outcomes in these hypertensive patients. The prevalence of poor preoperative systolic BP control is a

Table 1: Baseline clinical characteristics of carotid endarterectomy patients, expressed as a frequency (percentage) or mean (standard deviation)

Patient characteristics	Total cohort *n* = 76	Patients with in-hospital strokes or death, *n* = 8	Patients without in-hospital strokes or death, *n* = 68	*p*-value
Female	29 (38.2)	3 (37.5)	26 (38.2)	1.000
Age	64.1 (7.8)	66 (6.6)	63.9 (8)	0.475
History of hypertension	67 (88.2)	7 (87.5)	60 (88.2)	1.000
History of ischaemic heart disease	39 (51.3)	6 (75)	33 (48.5)	0.263
Diabetes	41 (53.9)	6 (75)	35 (51.5)	0.275
History of congestive heart failure	4 (5.3)	1 (12.5)	3 (4.4)	0.365
Prior history of a stroke	66 (86.8)	6 (75)	60 (88.2)	0.282
Creatinine > 177 µmol/l (*n* = 72)	3 (3.9)	1 (12.5)	2 (2.9)	0.301
General anaesthesia	32 (42.1)	3 (37.5)	29 (42.6)	1.000
Preinduction mean (SBP, mmHg)	166.8 (30.4)	172.4 (41.8)	166.1 (29.1)	0.584
Preinduction mean (DBP, mmHg)	78.3 (12.6)	74.8 (15.7)	78.8 (12.2)	0.397
Preinduction SBP within the lowest or highest quartile for SBP	38 (50)	8 (100)	30 (44.1)	0.003

DBP: diastolic blood pressure, SBP: systolic blood pressure

Table 2: Baseline clinical characteristics of hypertensive carotid endarterectomy patients, expressed as a frequency (percentage) or mean (standard deviation)

Patient characteristics	Total cohort *n* = 67	Patients with in-hospital strokes or death, *n* = 7	Patients without in-hospital strokes or death, *n* = 60	*p*-value
Female	28 (41.8)	3 (42.9)	25 (41.7)	1.000
Age	64.9 (7.3)	66.1 (7.1)	64.8 (7.4)	0.650
History of ischaemic heart disease	35 (52.2)	5 (71.4)	30 (50)	0.431
Diabetes	38 (56.7)	6 (85.7)	32 (53.3)	0.129
History of congestive heart failure	4 (6)	1 (14.3)	3 (5)	0.364
Prior history of a stroke	58 (86.6)	5 (71.4)	53 (88.3)	0.235
Creatinine > 177 µmol/l (*n* = 63)	3 (4.8)	1 (14.3)	2 (3.6)	0.302
General anaesthesia	29 (43.3)	3 (42.9)	26 (43.3)	1.000
Preinduction mean (SBP, mmHg)	167.4 (30.7)	167.3 (42.4)	167.5 (29.4)	0.989
Preinduction mean (DBP, mmHg)	78.2 (13.3)	73.4 (16.5)	78.8 (13)	0.319
Preinduction SBP < 145 mmHg or > 195 mmHg	31 (46.3)	7 (10.4)	24 (35.8)	0.003

DBP: diastolic blood pressure, SBP: systolic blood pressure

concern. In our cohort, 54% of patients had a preoperative SBP > 160 mmHg, while in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) surgical cohort, the prevalence of preoperative patient SBP > 160 mmHg was 20%.[3] Certainly, based on the work of Rothwell et al,[13] this may have accounted for some of the morbidity observed in our patients.

In the NASCET study,[3] and the study by Tu and colleagues,[4] the prevalence of hypertension was approximately 60%, while it was nearly 90% in our patients. Therefore, it is possible that the degree of hypertension control in South African patients is a more important determinant of major morbidity and mortality following CEA than a history of hypertension itself. However, this hypothesis requires further research.

Limitations

A major limitation to our study was our small sample size. As a result, we could not conduct multivariate statistical analysis, and therefore we limited our results to univariate data analyses only. Furthermore, preinduction BP was taken as a single measurement. A single preinduction BP measurement may have been confounded by other factors, such as missed antihypertensive medication on the day of surgery or patient stress. We were also unable to present data stratified according to the severity of hypertension in hypertensive patients as these data were not routinely collected during the study period.

However, globally, the question of which preoperative clinical risk factors are associated with in-hospital strokes and death following CEA will no doubt be answered by the subanalysis of data from the Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) study, a multicentre observational study on 40 000 noncardiac surgery patients, in which patient recruitment was completed in late 2013. Our study highlights the possible importance of including preoperative BP control in these analyses.

Conclusion

The rate of in-hospital stroke and death following CEA in South African patients is high, and it is possible that the preoperative control of SBP could be an important determinant of adverse outcomes. Further research involving larger surgical cohorts is required to confirm our observations. We suggest that a South African collaborative research group attempt to verify the findings of this paper.

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CHAPTER 8:

Conclusions

8. CONCLUSIONS

8.1 Hypertension in South African non-cardiac surgery patients

Hypertension is highly prevalent in the adult South African non-cardiac surgery population. The findings of manuscript 1 suggest that hypertension is more prevalent in the South African non-cardiac surgical population than the corresponding burden of disease in the general South African population.[106,112] However, this observation might be due to the emphasis placed on the diagnosis and treatment of comorbid disease during the pre-surgical patient evaluation, as well as poor health-seeking practices in the general South African population.[108] It is possible that our findings for the burden of hypertensive disease in the adult South African non-cardiac surgery population might be underestimated. Possible under-diagnosis of hypertension has also been reported in the South African Demographic and Health Survey (SADHS) and South African General Household Survey (GHS).[106,112]

Another important factor which might account for a reported burden of hypertensive disease which is lower than the true burden is patients' awareness and knowledge of their diagnosis at lower level healthcare facilities. It is important that the patient adequately self-reports their hypertensive status during the pre-surgical evaluation when prompted to do so. However, awareness levels related to hypertension in the South African population remains low,[106,123] and there might be many hypertensive patients who do not report a prior physicians' diagnosis of hypertension during their pre-surgical evaluation. Further initiatives at the primary healthcare level are required to improve this. Although there might have been under-diagnosis of hypertension in this research,

the burden of disease was still unacceptably high. When compared with overseas non-cardiac surgical populations, the prevalence of hypertension in South African non-cardiac surgery patients is much higher.[89]

8.2 A pre-operative history of hypertension and in-hospital mortality following non-cardiac surgery in South African patients

An analysis of retrospective data in this research did not identify a pre-operative history of hypertension as an independent predictor of post-operative in-hospital mortality following non-cardiac surgical procedures in South African patients (Manuscript 1). This finding is consistent with the findings of other large, international observational studies in non-cardiac surgery patients. For instance, the Vascular events In non-cardiac Surgery patIents cOhort evaluatioN (VISION) study found that although the incidence of peri-operative mortality was higher in non-cardiac surgery patients with a pre-operative history of hypertension versus normotensive patients (2.3% versus 1.4%, respectively), this did not translate to an independent relationship when hypertension was included in a pre-operative risk stratification model (adjusted hazard ratio: 1.05; 95% Confidence Interval: 0.80-1.38; p-value=0.71).[88] Further prospective research in South African non-cardiac surgery patients is required to elucidate the impact of a pre-operative history of hypertension on the incidence of post-operative in-hospital mortality in these patients.

8.3 A pre-operative history of hypertension and morbidity following vascular surgery in South African patients

Four studies comprising this thesis focussed on peri-operative morbidity in vascular surgery patients, as these patients are considered as being at high risk for poor peri-operative outcomes. Three of the studies were conducted using prospectively collected data (Manuscripts 2, 3 and 4), whilst one study (Manuscript 5) was conducted using retrospectively collected data.

8.3.1 A pre-operative history of hypertension and major adverse cardiovascular events following vascular surgery in South African patients

Hypertension (which was present in almost 69% of the vascular surgery cohort) was found not to be an independent predictor of major adverse cardiovascular events (MACEs) in South African vascular surgery patients (Manuscript 2). However, ischaemic heart disease, for which hypertension is an established risk factor, was found to be associated with an almost two-fold increase in risk for MACEs following vascular surgery. Therefore, it is likely that a history of hypertension does contribute, indirectly somewhat, to a higher incidence of peri-operative MACEs following vascular surgery in South African patients. This contribution appears more apparent when one considers that a sub-analysis of data from a large, multinational cohort study, the VISION study, which found a history of hypertension to be independently associated with peri-operative myocardial injury in a mixed non-cardiac surgery population.[90] Manuscript 2 of this thesis reported that chronic β-blockade use was associated with a more than three-fold increase in the risk of peri-operative MACEs following vascular surgery. It

is likely that the peri-operative withdrawal of chronic β-blockers rather than the continuation of chronic β-blockade is responsible for these findings,[124] although it was not possible to distinguish which patients had their β-blockers discontinued peri-operatively in this research. β-blockers are often prescribed as higher level drug therapies for patients with poorly controlled hypertension,[125] and these findings emphasize the important role of prescribed medications during the peri-operative period. Hence, a history of hypertension in itself might be too non-specific as a clinical variable to effectively determine its impact on peri-operative cardiac outcomes in vascular surgery patients. For future research it might be worth stratifying hypertensive disease according to severity and monitoring peri-operative medication use, as an all-inclusive definition of hypertension (based on physicians diagnosis from blood pressure measurements or if a patient is taking anti-hypertensive treatment) may not be appropriate for stratifying peri-operative risk in vascular surgery patients.

8.3.2 Acute pre-operative β-blockade and peri-operative major adverse cardiovascular events in South African vascular surgery patients with a pre-operative history of hypertension

As manuscript 2 suggested that the use/non-use of anti-hypertensive drugs, namely β-blockers, appears more likely to determine peri-operative outcome in vascular surgery patients rather than a broadly defined pre-operative history of hypertension, it was decided investigate the impact of acute pre-operative β-blockade on peri-operative cardiac outcomes in South African vascular surgery patients with a pre-operative history of hypertension. This was especially important as acute pre-operative β-blockade is currently controversial in the setting of non-cardiac surgery. Using a case-control study

design, acute pre-opertive β-blockade was found to be independently associated with a two-fold increased risk of developing peri-operative MACEs and a six-fold increased risk of developing perioperative myocardial ischaemia in these patients (Manuscript 3). The findings reported in manuscript 3 are contrary to the findings of a recently published meta-analysis of non-South African studies involving acute peri-operative β-blockade which suggests that acute pre-operative β-blockade is cardio-protective.[118] It is possible that in patients receiving acute pre-operative β-blockade, the adverse cardiac events might be driven by peri-operative hypotension associated with acute pre-operative β-blockade.[119] This may be exacerbated in the presence of poorly controlled blood pressure, which in itself is common in the South African hypertensive population.[106,123] The blood pressure control of South African hypertensive surgical patients may therefore compromise the cardio-protective efficacy of acute pre-operative β-blockade, which may explain the divergent peri-operative outcomes observed when the findings of Manuscript 3 are compared with the meta-analysis of non-South African studies. It is therefore important that South African hypertensive vascular surgery cases be carefully evaluated prior to receiving pre-operative acute β-blockade.

8.3.3 Post-operative acute kidney injury in South African non-suprainguinal vascular surgery patients with a pre-operative history of hypertension

Hypertension has been established as a risk factor for the development of peri-operative acute kidney injury in non-cardiac surgery patients.[91] Risk factors for poor peri-operative renal outcomes in the hypertensive patient population are poorly described. In addition, when one considers the vascular surgery population, most research describes renal outcomes following suprainguinal procedures,[120] while a few studies report

findings from non-suprainguinal procedures.[126,127] This motivated the research which described aetiology of post-operative acute kidney injury in hypertensive patients undergoing common non-suprainguinal vascular surgery procedures, namely peripheral artery bypass surgery and lower limb amputation in hypertensive vascular surgery patients (Manuscript 4). The presence of other comorbid conditions identified as predictors of poor peri-operative renal outcomes elsewhere[91] did not appear to be associated with poor renal outcomes in this research, though it is likely that the modest sample size may have compromised our ability to identify these associations. Acute pre-operative β-blocker use was identified as an independent predictor of post-operative acute kidney injury in patients with a pre-operative history of hypertension undergoing non-suprainguinal vascular surgery. It is possible that ischaemic injury of the kidney might have been induced in these patients following a similar mechanism as described for poor cardiac outcomes in manuscript 3. The findings of this research are important as it supports a cautious approach to the administration of acute pre-operative β-blockers in vascular surgery patients, in lieu of potential global haemodynamic instability which may modulate ischaemic injury.

8.3.4 Hypertension and poor neurological outcomes following carotid endarterectomy in South African patients

Determining the impact of hypertension on poor peri-operative neurological outcomes in this research was difficult. In a high-risk carotid endarterectomy population, blood pressure control appears to be very poor in hypertensive South African vascular surgery patients. This is evidenced not only by the threshold for the upper quartile of systolic blood pressure measurements in the hypertensive cohort described in manuscript 5

(>195 mmHg), but also by the threshold for the lower quartile of systolic blood pressure measurements in this patient group, which lies above 140 mmHg. Furthermore, mean pre-operative systolic blood pressure measurements were still above the 140 mmHg threshold used to define hypertension in this research. Although this research was not sufficiently powered to determine independent associations between various clinical variables and poor peri-operative neurological outcome, it is hypothesis generating. It is possible that extremes of pre-induction systolic blood pressure are associated with poor peri-operative neurological outcomes following carotid endarterectomy in a cohort of South African patients. It is likely that the large, adequately-powered study of peri-operative outcomes in non-cardiac surgery patients, such as the VISION study,[88] will in the near future provide clarification on the peri-operative impact of pre-operative haemodynamics in carotid endarterectomy patients.

8.4 Final summary

In summary, this research shows that hypertension is highly prevalent in the South African non-cardiac surgical population. Furthermore, the burden of hypertension in this population might be underestimated. Vascular surgery was one of the non-cardiac surgical specialties associated with high levels of post-operative in-hospital mortality. Hypertension appears to be poorly controlled in most South African vascular surgery patients, as evidenced by fairly robust pre-induction blood pressure measurements observed in this research.

Acute pre-operative β-blocker use was found to be independently associated with poor peri-operative cardiac and renal outcomes in South African vascular surgery patients

with a pre-operative history of hypertension. Therefore, it appears that the class of anti-hypertensive drug used, as well as whether the drug is acutely administered might be important drivers of poor peri-operative cardiac and renal outcomes in South African vascular surgery patients who have a pre-operative history of hypertension. Overall, a history of hypertension on its own might not be an appropriate clinical variable to use to stratify peri-operative risk in South African patients. Appropriate thresholds for pre-operative systolic blood pressures, as well as appropriate guidelines to direct the acute pre-operative administration of β-blockers in South African vascular surgery patients is required, and should form the basis for future research.

No firm conclusions from this research can be drawn regarding the impact of hypertension on poor neurological outcomes following carotid endarterectomy. However, this outcome will in future be adequately described in sub-analyses from large, high-powered studies, such as the VISION study.[88] It is possible that South African vascular surgical patients may have less peri-operative morbidity if their co-existing hypertension is better managed and controlled.

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APPENDIX I:

Regulatory Documents

UNIVERSITY OF
KWAZULU-NATAL
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26 September 2014

Prof B Biccard
Dept of Anaesthetics
School of Clinical Medicine

Dear Prof Biccard

PHD PROTOCOL: "Perioperative studies of hypertension"
Student: Dr Y Moodley, Student number: 202511768 (Anaesthetics)

I am pleased to inform you that the abovementioned study has been approved for submission to the university Ethics Committee.

Please note:

- The Academic Leader: Research must review any changes made to this study.
- The study may not begin without the approval of the Biomedical Research Ethics Committee.

May I take this opportunity to wish the student every success with the study.

Yours sincerely

pp.

Dr VS Singaram
Academic Leader School Research
School of Clinical Medicine

Cc Dr Y Moodley

Biomedical Research Ethics Committee
Westville Campus

Postgraduate, Higher Degrees & Research
School of Clinical Medicine, NRMSM Campus
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Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

28 October 2014

Mr Yoshan Moodley
Department of Anaesthetics
Medical School Campus
UKZN

Dear Mr Moodley

RE: USE OF PUBLICATIONS TOWARDS A PhD

I refer to your application to BREC received on 10 October 2014 and wish to advise that the papers arising from the four BREC approved studies and one exempted study which are listed below has been noted and approved by a sub-committee of the Biomedical Research Ethics committee towards a PhD study titled: **"Perioperative studies of hypertension".**

1. BE019/12
2. BF068/07
3. BCA117/010
4. BE025/12
5. EXM077/14

This approval will be ratified at the Biomedical Research Ethics Committee meeting to be held on **09 December 2014.**

Yours sincerely

Ms A Marimuthu
Senior Administrator: Biomedical Research Ethics Committee

APPENDIX II:

Turnitin plagiarism report

Turnitin Originality Report

PhD Thesis by Yoshan Moodley
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Moodley, Yoshan, and Bruce M. Biccard. "The association between preoperative clinical risk factors and in-hospital strokes and death following carotid endarterectomy in South African patients", Southern African Journal of Anaesthesia and Analgesia, 2014.

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K P Pang. "Identifying patients who need close monitoring during and after upper airway surgery for obstructive sleep apnoea", The Journal of Laryngology & Otology, 08/2006