PERIOPERATIVE BETA BLOCKADE FOR MAJOR VASCULAR SURGERY: A DESCRIPTIVE STUDY OF CURRENT INTENDED PRACTICE ACROSS SOUTH AFRICAN SPECIALIST TRAINING FACILITIES

Richard Barry Lawson

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Medicine in the branch of Anaesthesia

Johannesburg, April 2013

DECLARATION

I, Richard Barry Lawson, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Anaesthesia at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

_____

15th April 2013

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS STUDY

Publications

1. LAWSON, R. Perioperative Beta Blockade: A Practice in Need of Optimisation. *Southern African Journal of Anaesthesia and Analgesia* 2010;16(3):72-78

   Available at: http://www.sajaa.co.za/index.php/sajaa/article/view/602/568. Date accessed: 06 Aug. 2012.

2. LAWSON, R. Paper No: 897.00. Perioperative beta blockade at South African vascular surgery training facilities. *Br. J. Anaesth.* 2012;108(suppl 2):ii249-ii250.

   This article appears in: 15th WFSA WORLD CONGRESS OF ANAESTHESIOLOGISTS® ABSTRACTS

Presentations

1. South African Society of Anaesthesiologists (SASA) Congress 22-24 March 2010, Bloemfontein, South Africa. (Registrar communication prize entry)

   Perioperative beta blockade: A practice in need of optimisation.

2. 15th WFSA World Congress of Anaesthesiologists 25-30 March, Buenos Aires, Argentina. (Poster presentation)

   Perioperative beta blockade at South African vascular surgery training facilities.

3. Vascular Society of Southern Africa (VASSA) Congress 4-7 October 2012, Durban, South Africa.

   How we use perioperative beta blockers, and how we should use them.

4. Peri-operative Research Group: Recent advances in improving outcome in non-cardiac surgery. 6 October 2012. Department of Anaesthesia, Nelson Mandela School of Medicine.

   Suggestions for the appropriate use of prophylactic perioperative beta blockade.

ABSTRACT

BACKGROUND

Once lauded as one of the most valuable interventions across all fields of contemporary medicine, perioperative beta blockade (PBB) is a practice that has come under intense scrutiny. Publication of the PeriOperative ISchemic Evaluation (POISE) study forced a modification of recommendations for PBB in consensus guidelines. Practice in South Africa has not been previously reported.

OBJECTIVES

The primary objective of this study was to describe current intended practice, with respect to PBB, in patients undergoing major vascular surgery at South African specialist training facilities. Secondary objectives were describing participant satisfaction with current strategy, reporting suggested modifications to clinician responsibilities in the future, and identifying potential barriers to the intervention.

METHOD

One anaesthesiologist and one vascular surgeon from each of the seven recognised training facilities for vascular surgery in South Africa were included in a partially selective observational survey. Data was generated by the use of a semi-structured questionnaire specifically developed to address the objectives of the study.

RESULTS

The POISE study results and updated international consensus guidelines had not prompted a change in approach at most facilities. There was inconsistency in methods of risk stratification, treatment implementation, titration practices, and the timing of withdrawal of medication. Anaesthesiologist and vascular surgeon opinion on current intended practice correlated poorly. Opinions correlated least well at facilities where both clinicians claimed responsibility for PBB, implying that communication may be a problem. Similarities, where they did occur, were in keeping with recommendations that are widely supported in the literature.

Less than half of the participants were satisfied with current practice.

The involvement of the anaesthesiologists in the perioperative management of vascular surgery patients was less than reported in other countries. The participants supported a major role for anaesthesiologists in the future, and a move towards multidisciplinary involvement in policy development and patient management.

The need for appropriate monitoring was identified as one of many important barriers.

CONCLUSIONS

This study describes current intended practice at South African training facilities for vascular surgery. The variable practice across the country; the poor correlation of participant responses; widespread dissatisfaction with current strategy; suggested changes to clinician responsibilities; and the identification of multiple barriers to the implementation of strategy, highlight the need for review at all facilities. Further research is needed, since the optimal strategy for reducing risk in patients undergoing vascular surgery remains elusive.

ACKNOWLEDGEMENTS

I am grateful to the following people:

Professor AC Lundgren, for her dedication as supervisor to the successful completion of the research report, endless support and advice

Professor PE Cleaton-Jones, for his advice on aspects of study design and presentation of the results

Professor E Libhaber, for advice regarding statistical analysis

Professor E Grossman, for her advice regarding presentation of the results

The study participants, for willingly giving up their time to participate in the study, and for their ongoing interest in the results of the study

The University of the Witwatersrand, Department of Anaesthesia, for allowing me time out of theatre to conduct research

The University of the Witwatersrand, Faculty of Health Sciences, for funding the study through the award of a Faculty Research Committee Individual Research Grant.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ACRONYMS AND ABBREVIATIONS

ACCF/AHA- American College of Cardiology Foundation, American Heart Association Task Force on Practice Guidelines

ACE Inhibitor- Angiotensin Converting Enzyme Inhibitor medication

Anaes- Anaesthesia team

Anaes s- Specialist anaesthesiologist

Anaes r- Registrar/trainee anaesthetist

BBSA- Beta Blocker in Spinal Anaesthesia study

BP- Blood pressure

bpm- Heart rate in units of beats per minute

CAD- Coronary artery disease

CASS- Coronary Artery Surgery Study

Cardio- Cardiologist

CCF- Congestive cardiac failure

CF- Clinical Fellow/ Specialist vascular surgery trainee

CI- Confidence Interval

COPD- Chronic obstructive pulmonary disease

CPET- Cardiopulmonary Exercise Testing

CRF- Clinical risk factor

CRP- C-Reactive Protein

Crit care- Critical care specialist

DECREASE- Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group

DIPOM- The DIabetic PostOperative Mortality and Morbidity trial

DM- Diabetes Mellitus

dly- daily

ECG- Electrocardiogram

ESC- European Society of Cardiology

HMGCoA Reductase Inhibitor- Enzyme inhibitor in cholesterol synthesis pathway, also known as statin medication

HPCSA- Health Professions Council of South Africa

HR- Hazard ratio

ICU- Intensive Care Unit

IHD- Ischaemic heart disease

iv- Intravenous drug administration

MACE- Major adverse cardiovascular event

MaVS- Metoprolol after Vascular Surgery study

McSPI- Multicenter Study of Perioperative Ischemia Research Group

MDT- Multidisciplinary Team

mg- milligram

MRTD- Maximum recommended therapeutic daily dose

mmHg- millimetres of mercury

NNT- Number needed to treat

OR- Odds ratio

PAC- Pulmonary Artery Catheter

PAR- Population attributable risk

PBB- Perioperative beta blockade/ Perioperative beta blocker therapy

PCRRT- Perioperative Cardiac Risk Reduction Therapy protocol

PD- Pharmacodynamics

PK- Pharmacokinetics

PMI- Perioperative myocardial infarction

po- per os

POBBLE- PeriOperative Beta-BLockadE for patients undergoing infrarenal vascular surgery

POISE- PeriOperative Ischemic Evaluation Study Group

RCRI- Revised Cardiac Risk Index

stat- A medical abbreviation derived from the Latin word ‘statum’ meaning immediately

TEE- Transoesophageal Echocardiography

TIA- Transient Ischaemic Attack

VASSA- Vascular Surgery Society of Southern Africa

VS- Vascular surgery team

VSr- Vascular surgery registrar

VSs- Specialist vascular surgeon

CHAPTER ONE – INTRODUCTION

1.1 Problem Statement

The use of beta blocker medication as a tool to reduce perioperative adverse events in patients undergoing non-cardiac surgery is controversial. The current intended approach at South African specialist training facilities, in terms of perioperative beta blockade (PBB) in patients undergoing major vascular surgery, is not known.

1.2 Aim

The aim of this study is to determine how specialist training facilities in South Africa have chosen to implement PBB as a risk reduction strategy, and to assess the potential need for revision of their approach, in the light of ongoing controversy.

1.3 Objectives

1.3.1 Primary Objective

To describe current intended practice, with respect to the use of PBB as a tool for risk reduction, in patients undergoing major vascular surgical procedures at South African specialist training facilities for vascular surgery.

1.3.2 Secondary Objectives

a) To determine whether the anaesthesiologists and vascular surgeons included in the study are satisfied with their institution's current approach to the implementation of perioperative beta blockade, as a risk reduction strategy in the perioperative management of patients undergoing major vascular surgery.
b) To report suggested future modifications to clinician responsibilities in the implementation of perioperative beta blockade.
c) To identify potential barriers to the safe and effective implementation of perioperative beta blockade as an intervention.

1.4 Research assumptions and definitions

The following assumptions were made:

- It was assumed that the invited participants would be aware of current intended practice at their hospital.
- It was assumed that the specialist training facilities in the state sector are more likely to have a structured approach, to optimal perioperative care of major vascular surgery patients, than non specialist hospitals in the state sector.

The following definitions are important in the study:

Recognised training facility for vascular surgery - A hospital that is linked to a tertiary institution and is accredited as a site for the training of super-specialists in the field of vascular surgery. Accreditation is through the Health Professions Council of South Africa (HPCSA) and recognition is acknowledged by the Vascular Society of Southern Africa (VASSA)

Perioperative beta blockade/ Perioperative beta blocker therapy (PBB) - The introduction of beta adrenergic antagonist medication, around the time of surgery, as an intervention targeting a reduction in the risk of the patient suffering a major adverse cardiac event.

Procedures

- Major vascular surgery- Vascular surgical procedures consistently associated with >5% risk of a major adverse cardiac event. This includes procedures on the aorta and other major vessels, and peripheral vascular surgery. For the purposes of this study it does not include endovascular aneurysm repair, peripheral arterial angioplasty, surgery to the carotid arteries and limb amputations.

Personnel

- Anaesthesiologist- A fully qualified and registered specialist in the field of anaesthesia.
- Vascular anaesthesiologist - Anaesthesiologist with a special interest in vascular surgery. For the purpose of this study, this is defined as an anaesthesiologist who is involved in the provision of anaesthesia for vascular surgery patients on a regular basis, or who contributes to a multidisciplinary vascular surgery meeting, and who claims to have a special interest in the field.

- Vascular surgeon- A fully qualified and registered specialist in the field of vascular surgery.
- Clinical fellow in vascular surgery- A fully qualified general surgeon registered in a fellowship program for vascular surgery.
- Registrar- A fully qualified medical practitioner registered for training as a specialist.
- Paired participants- The anaesthesiologist and vascular surgeon participants employed at the same facility.

1.5 Study design

This is a descriptive study of current practice, based on the results of a semi-structured face-to-face interview and questionnaire.

1.6 Ethical considerations

1.6.1 Ethics clearance

The study was approved by the regional Ethics Committee – the Committee for Research on Human Subjects (Medical) of the University of the Witwatersrand. (**Appendix A**)

1.6.2 Post-Graduate approval

The study was approved by the Post-Graduate Committee of the University of the Witwatersrand. (**Appendix B**)

1.6.3 Participant approval

Participants were invited to participate in the study. Participants received a printed document (**Appendix C**) explaining the reason for the study, exactly what participation would involve, their right to refuse to participate without any repercussions, the assurance that their participation would not be revealed, that they would not be personally identified in the research report, and their right to withdraw from the study at any time without any repercussion.

A 24-hour contact number was supplied should they have required further information. Written informed consent was obtained from all participants agreeing to participate. (**Appendix D**)

Furthermore, written informed consent for the voice recording of the interviews was obtained from all participants. (**Appendix E**) Their consent was obtained after written and verbal explanation of the implications of the recording of the interview. It was explained that the recorded interviews would be processed in accordance with the regulations of the Health Professions Council of South Africa.[1] The need to retain the recordings for two years, before being destroyed, was explained to all of the participants.

1.6.4 Declaration of Helsinki

The research was conducted according to the principles described in the Declaration of Helsinki.[2]

1.7 Summary of methodology

The Vascular Society of Southern Africa (VASSA) was approached. The society identified seven hospitals as the only recognised facilities for academic training in the field of vascular surgery in South Africa. One anaesthesiologist and one vascular surgeon from each of the seven facilities were invited to participate in the study. A selective approach was used to identify appropriate candidates for inclusion in the study.

A semi-structured questionnaire (**Appendix F**) was developed to facilitate the gathering of information with potential relevance to the study objectives. The research tool was tailored to optimise the process of data collection by means of a face-to-face interview.

Appropriate anaesthesiologist candidates were identified by the Head of the Department of Anaesthesia at each hospital. VASSA helped to identify appropriate vascular surgeon candidates from each of the seven hospitals.

Interviews with the anaesthesiologist and vascular surgeon, at each of the hospitals, were conducted separately, and in no particular order. The order of recruitment into the study depended solely on the availability of the participant and investigator.

Data collection was simplified by the voice recording of the interviews. The data was coded from the outset to protect the participants from potential identification. Only the principal investigator has had access to the codes. The principal investigator was responsible for the conduct of all 14 interviews.

Data was analysed after consultation with a statistician.

The participants will receive feedback on the results of the study.

1.8 Importance of the study

Vascular surgery patients are a group of patients at high risk for perioperative mortality and morbidity. A large burden of cardiovascular risk factors makes vascular surgery patients prime candidates for perioperative risk stratification and optimisation. However, identifying patients that stand to benefit from PBB remains poorly defined, despite widespread interest in the practice.

This study was initiated shortly after the publication of a landmark trial[3] that has forced a change in international consensus guidelines.[4,5] This may imply a need to change the way in which the practice of PBB is implemented. With the current confusion and previously widely accessed guidelines being called into question, it was not known whether South African clinicians at academic institutions had reacted to recent developments. Neither was it known what the current practice was at these facilities.

This study is important in that it will be the first to describe and compare intended practice across South Africa.

It will highlight aspects of practice that are common to all facilities and aspects that may require review. Role players will be more accurately defined and an assessment of the degree of similarity, or difference, in opinion between the anaesthesiologists and vascular surgeons will help clarify responsibilities for policy development in the future. An assessment of the perceived barriers to PBB will identify areas requiring an improved allocation of resources.

The study is expected to facilitate discourse on controversies and raise awareness. Increased awareness may spark greater interest and subsequent improvement in the management of patients undergoing major vascular surgery.

Any improvements made at training facilities may influence practice at other hospitals, and can be expected to determine future practice of the clinicians that emerge from these centres. In addition, clinicians practicing outside of the specialist training environment may be interested in the approach of specialists at academic centres, as they seek direction on how to respond to differences in the recommendations of consensus committees and respected authors in the field.

South Africa has a large burden of cardiovascular disease. Strategies that appear to be effective elsewhere in the world may not translate into best practice in the South African environment. Defining current practice in South Africa, and particularly, at institutions where research is actively promoted, is an important first step towards more definitive research. It is envisaged that this report will foster improved communication between academic institutions, and will facilitate multicentre research in the future.

1.9 Limitations of the study

1.9.1 Sample limitations

The study method aimed for the inclusion of 14 participants. Although, the sample size is small, it is fully inclusive of a defined group of participants.

No power calculation, in an attempt to target statistical significance during data analysis, was necessary. Sufficient numbers of participating hospitals, to reach statistical significance, is not achievable in the South African environment, as a consequence of the markedly limited number of vascular surgery training facilities. In fact, even the private healthcare sector has a limited number of vascular surgeons practicing in the field of Vascular Surgery alone. The inclusion of this group would have created potentially prohibitive logistical challenges, and would likely have introduced bias that would have been difficult to avoid.

1.9.2 Timing of the study

Recommendation for changes in practice have materialised since the publication of a recent landmark randomised controlled trial.[3] This trial has had an effect on interpretation of the evidence for PBB as an intervention strategy. The most recent international consensus guidelines[4,5] were published less than six months before the conduct of interviews. Therefore, there had been a relatively short window period for a change in practice related to the shift of emphasis in the guidelines. The description of current practice may have preceded planned changes as a result of the inevitable lag in response to shifts in theory. The results of this study reflect opinion on current practice at the time of the interview only. The research tool was designed to further describe recent changes and opinion on the need to modify practice in the immediate future, but the focus of the study was on current practice and is, therefore, time sensitive.

1.9.3 Contextuality

The aim was to describe current practice at the recognised academic training centres. The findings of the study are subject to contextual limitation. The highly select population that was targeted may, or may not, reflect current academic opinion throughout South Africa. The likelihood of awareness of developments in the literature at academic institutions was one of the assumptions made in the study design. It is possible that the practice at training facilities will have an impact on the future approach of specialists emerging from these centres, but validity of the study is not dependant on this assumption.

In South Africa many contributions to academic medicine are initiated from the private medical sector. With hospitals in the private medical sector excluded from the study, there is no assumption made that the findings are a reflection of current practice at these hospitals.

Furthermore, it is possible that current practice at South Africa's recognised training facilities may not reflect best practice, and care will be required not to imply that the findings should be viewed as a standard of care.

Despite contextual limitation, the study remains valid. A large number of patients undergo major vascular surgery in the state sector, and addressing issues surrounding their management is important.

1.9.4 Quality of data collection

A disadvantage of survey research is that it may be difficult to gather detailed data, and that by attempting to cover too wide a range of questions, there may not be an adequate account of the relevant issues. In addition, limitations of the research tool are inevitable.

Attempts to reduce the impact of these potential limitations were actively pursued during study and research tool design. Participant comments obtained during the interview were recorded for assessment, in an attempt to increase the depth of data collected. Although the research tool has not been previously validated, it was carefully designed to meet the study objectives, and was piloted in an attempt to increase its' reliability.

The Head of the Department of Anaesthesia at each of the hospitals included in the study identified potential appropriate candidates for participation. VASSA helped to identify appropriate vascular surgeons for participation in the study. The identification of appropriate candidates was important, as the opinion of clinicians actively involved in the management of vascular surgery patients are more likely to reflect actual practice. Despite the selection process employed, it is possible that the role players in practice development, for major vascular surgery patients, may not have been the participants that were ultimately recruited into the study. In addition, the intended practice of the participant may not be a reflection of the intended practice of other clinicians practicing at the same hospital. The semi-structured interview attempts to establish whether this was a likely occurrence.

Finally, the study set out to describe intended practice and this may not be aligned with actual practice. Further research will need to be conducted to assess whether intended practice translates into actual practice at these hospitals.

1.10 Research report outline

This research report comprises the following chapters:

Chapter One – the introduction to the study, including the aim and objectives of the study, and a brief summary of the methodology used.

Chapter Two – a review of the literature pertinent to topics raised by the study.

Chapter Three – an in-depth description of the methodology used for the study.

Chapter Four – the results of the study.

Chapter Five – an interpretation and discussion of the results of the study.

Chapter Six – a summary of the study, and conclusions drawn from the study.

Chapter Seven – recommendations made for future development of perioperative beta blockade.

CHAPTER TWO – LITERATURE REVIEW

2.1 Introduction

It has been estimated that in excess of 200 million major surgical procedures are undertaken worldwide every year.[6] Cardiovascular complications, in particular, are a lead cause of morbidity and mortality, regardless of the type of surgery.[7,8] Cardiac death has an incidence of 0.5-1.5%, and major cardiovascular complications during the perioperative period affect 2-3.5% of all patients undergoing major non-cardiac surgery.[4]

The risk of suffering a major perioperative cardiac event is increased in patients with, or at risk of cardiac disease.[9] Patients presenting for vascular surgery have a high incidence of cardiac disease,[10-13] and those patients undergoing aortic surgery, other major vascular procedures, and peripheral vascular surgery, have a greater than 5% risk of suffering a major cardiovascular event (non fatal myocardial infarction or cardiac death).[4,5] Therefore, strategies aimed at the prevention of complications in the perioperative period have become a principle focus for clinicians involved in the management of patients undergoing major vascular surgery.

The introduction of beta blocker medication around the time of major non-cardiac surgery is a strategy that has been used to target a reduction in the incidence and severity of major adverse cardiovascular events (MACE).[3,14-19] However, the recommendations for use of beta blocker medication, solely to target a reduction in perioperative MACE, remain controversial.

2.2 The impact of perioperative major adverse cardiovascular events

Perioperative myocardial infarction (PMI), congestive cardiac failure (CCF) and arrhythmia are considered to be major adverse cardiovascular events (MACE).[9]

PMI is a powerful independent predictor of mortality and is the commonest cause of perioperative cardiac death.[3,9] It is associated with a 15-25% inhospital mortality.[9] Patients who initially survive a myocardial infarction in the postoperative period, have a significantly elevated independent risk of a further cardiac complication within two years of surgery (HR 20.0, 95% CI: 7.5-53.0).[20]

Myocardial ischaemia (particularly if it is sustained over a long period) and myocardial damage (elevated Troponin assay) predict an adverse effect on short, intermediate and long term cardiovascular outcome.[21,22] Myocardial ischaemia, as evidenced by ST segment depression on electrocardiogram, is common in the first 72 hours after vascular surgery, and has an association with worse outcome.[23]

Furthermore, patients who experience a cardiac complication are also more likely to experience additional non-cardiac complications, resulting in further risk as a result of prolonged hospitalisation.[24]

2.3 Pathophysiology of major adverse events and potential targets for beta blocker therapy

Although still incomplete, the understanding of the pathophysiology of PMI is critical to the development of appropriate strategies aimed at reducing perioperative cardiac morbidity and

mortality.[25,26] Efficacy of perioperative beta blockade (PBB), as a risk reduction strategy, depends on a reduction in the incidence of major perioperative cardiovascular events.

Myocardial infarction in medical patients is commonly related to plaque rupture (70%) in coronary vessels without significant stenoses.[27] In patients undergoing non-cardiac surgery, plaque rupture and imbalance between myocardial oxygen supply and demand are the two processes involved in myocardial infarction.[26,28] The overall contribution of each of these mechanisms is thought to be approximately equal.[26]

Almost 90% of PMI's occur within the first week of surgery, but events continue throughout the period of hospitalisation.[29] The majority of PMI's occur soon after surgery,[23,30] a period characterised by catecholamine levels that continue to rise.[31,32] Routine monitoring of postoperative Troponin assays, using new diagnostic criteria, suggests that the majority of PMI's occur within 12 – 32 hours of surgery.[33] This is earlier than previously realised.

Contemporary theories on the pathophysiology of PMI are not uniform.[26,30,33] A recent review[26] consolidates information gained from post-mortem studies, preoperative coronary angiography and inducible myocardial testing studies, perioperative Holter and haemodynamic studies, in addition to the studies of Troponin surveillance that have received the attention of other experts in the field.[30] The authors suggest that plaque rupture-type PMI occurs randomly throughout the perioperative period, but that imbalances between myocardial oxygen supply and demand, in patients with significant coronary artery stenoses, are responsible for the majority of PMI's in the first 3 – 4 days after surgery.[26] Derangements in flow (significant coronary artery stenoses and sustained periods of postoperative hypotension), hypercoagulability (platelet activation as a result of high shear stress and a thrombogenic blood profile as a result of the inflammatory

response), and endothelial priming or damage (regions of low shear stress allow pro-inflammatory cytokine upregulation and flow separation increases the contact between activated platelets and damaged endothelium), create the optimal milieu for stagnation and thrombus formation.[26] The increase in myocardial oxygen demand due to sympathetic activation associated with major surgery exacerbates the supply-demand mismatch.

Myocardial ischaemia is a likely precursor to many of the perioperative adverse events.[21] The development of myocardial ischaemia and myocardial infarction during the perioperative period has been associated with increases in heart rate.[21] However, the immediate beneficial effects of beta blockers, administered in this setting, are not restricted to the control of heart rate. Attenuation of the cardiotoxic effects of catecholamines limits the increase in myocardial oxygen demand related to heart rate, contractility and increased systolic blood pressure.[34,35] The antiarrhythmic properties of beta blockers are a further favourable effect.[28] Supply is enhanced by prolongation of diastole, and possibly by an improved distribution of coronary blood flow to the subendocardium.[36] Vessel patency is promoted by a reduction in shear stresses across vulnerable atherosclerotic plaque, and centrally mediated inhibition of platelet aggregation.[34,37]

Ventricular remodeling with improved coronary flow reserve,[38] changes in myocardial gene expression,[39,40] inhibition of catecholamine induced necrosis and apoptosis,[35] and a number of anti-inflammatory effects,[41] are potential delayed benefits of PBB. A recent meta-analysis shows that an elevated C-Reactive Protein (CRP) level predicts long term cardiovascular outcome in vascular surgery patients.[42] Lower levels of CRP in patients with coronary artery disease treated with beta blockers, implies a reduction in inflammation.[43,44] These anti-inflammatory effects may play a role in the stabilisation of atherosclerotic plaque.

2.4 Risk stratification and preoperative patient assessment

Quantifying the risk to a patient undergoing non-cardiac surgical intervention allows clinicians to consider the potential for benefit of introducing medical therapies, or of conducting further investigations that may ultimately lead to recommendation for pre-emptive coronary intervention. Appropriate counselling of patients provides further motivation for exploring methods of patient risk assessment.

Guidelines have been published with recommendations for the assessment of patients before non-cardiac surgery.[4,5] However, not all aspects of these consensus guidelines are universally accepted.

The course of management of three groups of patients is widely accepted:

i. Patients for whom the risk of delaying emergent surgery outweighs any benefit that may be achieved by further assessment, should not have surgery delayed. Active cardiac conditions and cardiovascular risk factors should be addressed concurrently and in the postoperative period.
ii. Patients that have active cardiac conditions, defined broadly as unstable coronary syndrome, decompensated or acute cardiac failure, significant cardiac arrhythmia, or severe/symptomatic valvular heart disease, require assessment and treatment before all but the most emergent indications for surgery.
iii. Patients at low risk, in terms of the type of procedure, risk factor burden, or functional status, should proceed to surgery without delay pending further cardiac investigation or introduction of beta blockade. Intervention in these low risk patients is unlikely to result in improved outcome.

The most useful assessment methods and perioperative management of the residual 'at risk' group of patients (group iv) is less uniformly accepted. The four groups of patients and suggested management of each group is illustrated in **Figure 2.1**.

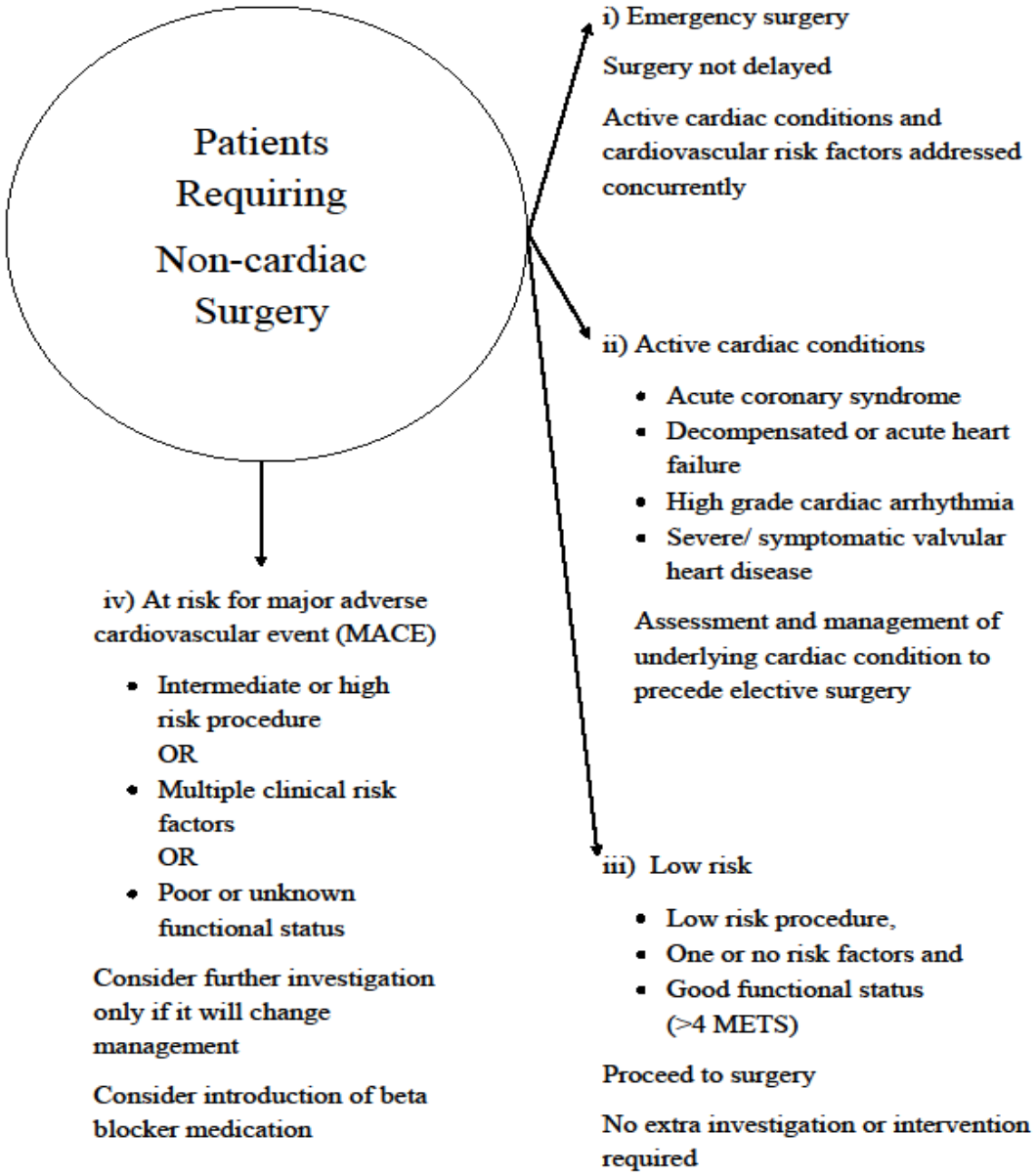

Figure 2.1 Diagram illustrating the process of risk stratification before non-cardiac surgery

2.4.1 Further assessment of the at risk group before elective non-cardiac surgery

There are two important considerations during the preparation of at risk patients before elective non-cardiac surgery. The need for further investigation to determine the presence or extent of cardiac disease should be considered, but only if the results will have an impact on subsequent management.[4,5] In addition, the potential to benefit from introduction of specific medical therapies should be contemplated. The desire to accurately predict which patients are likely to complicate in the perioperative period has become a major focus in modern day Anaesthesia, because both of these considerations rely on understanding patient risk. However, despite widespread interest in methods of risk stratification, the understanding of risk remains rudimentary.

A number of risk factors are associated with subsequent cardiac events, and stratification tools have been developed to aid clinicians in understanding the extent of risk.[7,11,45,46] The greater the number of risk factors that a patient has, the higher the chance is of suffering a perioperative cardiac event.[7] The balance between risk and benefit is biased toward intervention for those patients who are at higher risk of an adverse cardiovascular event. Therefore, clinical risk indices that allow prognostication have become an essential component of preoperative patient assessment.[4,5]

The use of the revised cardiac risk index (RCRI)[7] is currently favoured as a step in the process of determining the need for further assessment and patient suitability for PBB as a risk intervention.[4,5] This index assesses six factors; ischaemic heart disease (IHD), congestive cardiac failure (CCF), cerebrovascular disease, insulin requirement for the treatment of diabetes mellitus (DM), plasma creatinine >2mg/dl and high risk surgery.

Table 2.1 Revised Cardiac Risk Index and incidence of major cardiac complications

Number of risk factors	Rate of major cardiac events
0	0.4% (95%CI 0.05-1.5%)
1	0.9% (95%CI 0.3-2.1%)
2	6.6% (95%CI 3.9-10.3%)
≥3	11% (95%CI 5.8-18.4%)

(Adapted from Lee et al7) Revised Cardiac Risk Index risk factors:

High risk surgery; history of congestive heart failure; coronary artery disease; cerebrovascular disease, diabetes requiring insulin; preoperative creatinine ≥2mg/dl

The RCRI provides an accurate prediction of cardiovascular complication, and has been validated outside of the population in which it was derived.[47] However, the impact of different risk scores on management recommendations is inconsistent.[4,5] Concern has also been raised about the under-estimation of risk when the RCRI is used for prognostication in patients with multiple clinical risk factors,[12,47] and also reduced accuracy in patients undergoing vascular surgery.[11,12,47-49] A number of risk scores, specific to vascular surgery, have been reported,[50-52] but they are derived from small populations, they relate predominantly to aortic procedures, and also do not report on the spectrum of major adverse cardiac events assessed in the RCRI.

Other investigators have suggested that the addition of age as a risk factor, further stratification based on the type of vascular procedure, and adjustment for the presence of hypertension may improve the accuracy of risk assessment.[12] It has also been suggested that expanding analysis to all causes of mortality, and further inclusion of the use of beta blocker medication and statins, may improve prediction of overall perioperative mortality.[11] In 2010, subsequent to the publications cited above, the Vascular Study Group of New England published data

demonstrating that the RCRI performs poorly in risk prediction for patients undergoing major vascular surgery, and that a risk index derived and validated from their own cohort of patients performs better.[48] The Vascular Study Group Cardiac Risk Index (VSG-CRI) includes increasing age, smoking, an abnormal cardiac stress test, long term beta blocker therapy, and chronic obstructive pulmonary disease; this is in addition to four of the six risk factors assessed in the RCRI (insulin-dependent diabetes mellitus, coronary artery disease, congestive heart failure and renal impairment).[48] Previous cardiac catheterisation was noted to be protective.[48]

Data from a study conducted at Inkosi Albert Luthuli Central Hospital, suggests that indices derived in the western world may not be reliable in the South African environment.[53] This retrospective, single centre study has insufficient power to determine an association with a history of IHD, CCF, cerebrovascular accident (CVA) or DM, but identified a serum creatinine level of greater than 180µmol.l^{-1} (OR 3.02, 95% CI: 1.06-8.59, p=0.038) and a positive history of smoking (OR 3.40, 95% CI: 1.09-10.62, p=0.035) as statistically significant predictors of cardiac death.[53] Although a study conducted in American Veterans did not demonstrate an increased mortality in smokers,[54] the findings of Biccard et al[53] and the Vascular Study Group of New England[48] call for reassessment, both in South Africa and internationally, because a history of smoking was not previously evaluated as a risk factor in risk indices.[7,11,45,46]

Results of the Coronary Artery Surgery Study (CASS) suggested that there was merit in evaluation for the presence of coronary artery disease, and subsequent coronary revascularisation before high risk procedures.[55] On the basis of what is now considered to be misleading data from this particular study, that is subject to multiple limitations,[56] exercise or pharmacological stress testing was previously advocated for delineation of underlying coronary artery disease (CAD) in patients with risk factors undergoing high risk procedures.[57]

The negative predictive value of preoperative testing is consistently greater than 90%, and often approaches 100%, regardless of the testing method.[4,5] Therefore, a negative test result is helpful in excluding significant coronary artery disease (CAD), and is associated with low subsequent event rates.[58] However, the positive predictive value of preoperative testing is as low as 10% for exercise testing,[59] and ranges from 2-20% for radionuclide myocardial perfusion imaging techniques, to 0-33% for dobutamine stress echocardiography.[5] Therefore, many patients with a positive test result may not have significant CAD. The pre-test probability of the patient having CAD, and continuous rather than categorical assessment of test results, has an impact on the likelihood of a positive test result reflecting the presence of clinically significant CAD.[5] Clinical risk scoring, assessment of the severity and extent of ischaemia, and evidence of reversible as opposed to fixed perfusion defects, increases the reliability of a positive test result and allows a more accurate prediction of the risk for a myocardial infarct or cardiac death postoperatively.[4,5,60] Therefore, it is now recommended that testing, to define regional ischaemia and the potential for reversibility, should be restricted to patients at high risk for perioperative cardiac events, and only then if the results will alter the course of management.[4,5]

As a consequence of deficiencies in the recommended risk stratification processes,[4,5] particularly in patients undergoing vascular surgery,[11,12,47-49] there has been expanding interest in other investigations that may add valuable information. Biomarker assays for B-type Natriuretic Peptide (BNP),[61,62] and its precursor Pro-BNP,[63,64] have been advocated as preoperative and postoperative predictors of adverse cardiac outcomes. A meta-analysis published by Rodseth et al[61] suggests that intermediate risk groups can be more accurately reclassified on the basis of an elevated preoperative BNP result. However, a more recent publication questions the utility of the RCRI in reclassification of intermediate risk vascular surgery patients on the basis of an

intermediate BNP result.[62] Postoperative measurement of Troponin level also aids in the prediction of outcome.[65,66] Unfortunately these investigations have not yet been paired with interventions that have demonstrated more favourable outcomes. However, it is implied that they may have a role in risk stratification and perioperative decision making.

Similarly, the use of cardiopulmonary exercise testing (CPET), to gain better understanding of the likelihood of high risk patients coping with the stress of major surgery, continues to gain support.[67,68] However, the role of such testing in determining the need for preoperative intervention remains unclear.[69,70]

2.4.2 Management of the at risk group before elective non-cardiac surgery

i. Preoperative coronary revascularisation

It is uncommon for the results of preoperative testing in asymptomatic patients, to be used to assess suitability for preoperative revascularisation, as results of this practice have not shown increased benefit.[71,72] However, patients with extensive ischaemia may not be sufficiently protected by beta blockade alone.[73] A recent meta-analysis suggests that the chosen method of coronary revascularisation (CABG vs PCI with stenting) deserves consideration,[74] particularly as non-cardiac surgery was undertaken during a period of increased risk for stent thrombosis[75,76] in both of the randomised trials that currently influence recommendations for preoperative revascularisation.[71,72]

Furthermore, Monaco et al[77] recently demonstrated an improvement in survival and a reduction in major adverse cardiovascular events, in vascular surgery patients at intermediate-to-high risk, who were subjected to routine coronary angiography and offered coronary revascularisation on

the basis of the test result. The authors question the reliability of non-invasive testing in vascular surgical patients, highlight limitations in the CARP[71] and DECREASE-V[72] studies, and add to the ongoing debate with regard to the value of preoperative coronary revascularisation.[78-80]

Currently, there are no established recommendations for preoperative revascularisation that extend to patients that do not meet criteria for coronary revascularisation in general.[4,5] The absence of impressive survival benefit from management strategies associated with inevitable delays for preoperative testing (median of 30 days in DECREASE V[72] and 36 days in CARP[71]) are not supported.

ii. Less invasive procedure or avoidance of surgery

The results of preoperative testing may also allow more accurate counselling of high risk patients, and could be used to aid in the process of recommending a less invasive intervention, or avoidance of surgery altogether.[4,5] The risk of an adverse cardiovascular event in patients undergoing peripheral arterial angioplasty or endovascular aneurysm repair (1-5%), is lower than that for peripheral arterial bypass procedures or open aneurysm repair (≥5%).[4] However, the potential short term reduction in risk of a cardiac event,[81] does not necessarily translate into a long term survival benefit.[82-84]

iii. Optimal medical therapy and general measures

There is evidence to suggest that preoperative testing may delay surgery unnecessarily in patients at intermediate risk.[85] However, results may support a delay in surgery to allow optimisation of medical therapy in high risk patients booked for elective surgery.[4,5] A number of medical therapies have been investigated, but these medications have not received the same degree of attention that has been afforded to beta blockade. In addition to beta blockers, treatment may

include statins (HMGCoA reductase inhibitors), ACE (Angiotensin Converting Enzyme) inhibitors and aspirin. Concentrating on titration of beta blocker medication, introduction of statins, and other medical therapies may be more appropriate than pursuing strategies that support coronary intervention.[56]

There is growing evidence for the beneficial pleiotropic effects of statins.[86,87] The ESC and ACCF/AHA guidelines support the use of statins in patients undergoing vascular surgery, and also the continuation of chronic statin medication throughout the perioperative period.[4,5]

There is some evidence for a reduction in adverse cardiovascular events with the use of α2 receptor agonists in vascular surgical patients.[88] The potential for beneficial effects of acetyl-salicylic acid and clonidine on the perioperative outcome of cardiac patients undergoing non-cardiac surgery is currently being addressed in the POISE 2 multicenter randomised controlled trial (NCT01082874).

The evidence for perioperative beta blockade as a risk reduction strategy is discussed in **Section 2.5**.

General measures are also important. The management of tachycardia, in the perioperative setting, should always be directed at any potential underlying cause. Anaemia[89-91] and hypothermia[92,93] are associated with adverse perioperative cardiac events in at risk patients, and should be prevented. Beta blockade in the presence of anaemia may have a clinically significant adverse effect on cerebral oxygen delivery.[94,95] Lowering of the haemoglobin level for recommended blood transfusion may have an impact on outcome, although this has not been assessed in any of the randomised beta blocker studies.[96] Pain, hypovolaemia, infection and anxiety are further causes of increased myocardial oxygen demand that should be addressed.

2.5 Developments in perioperative beta blockade

2.5.1 The pre-POISE era

In the early 1970's it was not uncommon for beta blocker medication to be withheld before surgery.[97] A small study demonstrating beneficial effects of beta blockers at the time of laryngoscopy,[98] promoted a gradual increase in the number of patients continuing beta blocker medication during the perioperative period.

Initial interest in the use of beta blockers as a cardiovascular risk modification tool began in the late 1980's.[99-101] However, it was the publication of two randomised controlled trials towards the end of the 20th century that accelerated development in the field.[14,15] The Multicenter Study of Perioperative Ischemia Research Group (McSPI), under Mangano, published results of their study in 1996.[14] They claimed favourable effects of atenolol on the intermediate term outcome of patients with, or at risk for coronary artery disease (CAD). The Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) investigators, led by Poldermans in 1999, demonstrated such an impressive reduction in mortality and perioperative myocardial infarction, in patients treated with bisoprolol, that the trial was stopped early.[15]

The results of these two trials forged expert opinion through the early part of the 21st century. Limitations of these trials were widely publicised, and yet the findings were accepted by many with great enthusiasm.[102]

The practice of PBB developed rapidly, and was soon endorsed by expert consensus guidelines.[57] A 2001 critical analysis of supporting evidence for patient safety initiatives identified PBB, in selected patients, as 1 of the 11 most highly rated practices across all fields of medicine.[103] Scientists were so impressed that research interest broadened to include patient groups outside of those that had previously shown benefit. The expansion occurred despite an understanding that these recommendations were based on underpowered studies with potential methodological weaknesses. (**Table 2.2**)

In contrast, uncertainty among clinicians escalated, as a number of studies were unable to reproduce the findings of Mangano and Poldermans.[16-18] More importantly, significant concerns were raised about an increased risk of bradycardia and hypotension.[17,18,104]

Despite the premature introduction of quality of care initiatives at many hospitals across the United States of America,[105] the initiation of beta blockers in the perioperative period remained an under-utilised strategy.[106,107] This may reflect a lack of clinician confidence in the true benefit of the practice across all guideline recommendations. Concern for the potential adverse effects of beta blockers, was a major obstacle to widespread implementation of these guidelines.

Table 2.2 Table identifying limitations of the randomised controlled trials that assess the effect of perioperative beta blockade as an intervention strategy

	Limitation	Explanation
Mangano et al[14] McSPI Atenolol Study	Underpowered	-Small study, few events.
	Reliability	-Single centre.
	Potential bias due to randomisation	-Potential for increased events in the placebo group: Chronic beta blocker therapy withdrawn in eight patients, a trend toward more severe cardiac history, and more patients with diabetes mellitus in the placebo group. -Potential for decreased events in the treatment group: Increased use of ACE inhibitors at admission and discharge.
	Problems with data analysis	-Intention-to-treat analysis not followed. Deaths in the first 7 days were excluded. Data no longer significantly different if perioperative deaths are included.[108]
Poldermans et al[15] DECREASE-I	Underpowered	-Small study, few events.
	Study design	-Unblinded, no true placebo control.
	Selection bias	-High risk group likely to benefit from the intervention, but patients with the most severe ischaemic heart disease were excluded.
	Feasibility of results	-Trial stopped early. Treatment effect demonstrated is unprecedented in modern medicine.[102]
Brady et al[16] POBBLE	Underpowered	-Small study.
	Blinding	-Anaesthesiologists not blinded.
	Inclusion criteria	-Stringent criteria excluded many high risk patients.
	Reliability of results	-Unexplained very high event rate in both groups. Not consistent with other trials.
	Intervention	-Low doses of metoprolol without titration.
Juul et al[17] DIPOM	Underpowered	-Larger study, but still too small.
	Inclusion criteria/ Selection bias	-Heterogenous study population. Large number of patients with lower levels of risk. The predominant risk factor was diabetes mellitus. Patients with an independent indication for beta blockade were excluded. Study included youngest patients of all of the trials, and length of procedure >1 hour was used as a surrogate for perioperative stress.
	Intervention	-Low dose of metoprolol without titration.
Yang et al[18] MaVS	Underpowered	-Small study, very low event rate
	Intervention	-Modest weight adjusted doses of metoprolol two hours before surgery.
Zaugg et al[19] BSSA	Inclusion criteria	-Predominantly intermediate risk surgery with only one vascular surgery patient included. Spinal anaesthesia only.
Devereaux et al[3] POISE	Intervention	-Fixed, large dose of metoprolol on the day of surgery, without titration, and haemodynamic safety parameters not adjusted to individual patients.

2.5.2 The POISE Trial and beyond

A large multicentre randomised controlled trial was needed to help clarify best practice. As the largest randomised controlled trial ever conducted in the field, the PeriOperative Ischemic Evaluation (POISE) trial[3] was expected to deliver the final verdict on PBB.

The primary endpoint measure in POISE was a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal cardiac arrest. Administration of metoprolol 2-4 hours before surgery and continued for 30 days, demonstrated a decreased risk in the primary endpoint (Hazard Ratio 0.84, 95% CI: 0.70-0.99; p=0.0399) and a decreased risk of perioperative myocardial infarction (HR 0.73, 95% CI: 0.60-0.89; p=0.0017). The trial, however, also revealed an increased risk for all cause mortality (HR 1.33, 95% CI: 1.03-1.74; p=0.0317) and cerebrovascular accident (HR 2.17, 95% CI: 1.26-3.74; p=0.0053).

For every 1000 patients in the treatment group 15 PMI's were prevented. However, this was achieved at an unacceptable expense of 8 extra deaths and 5 strokes. Post hoc multivariate analysis pointed to significant hypotension as the largest population attributable risk for death (PAR 37.3%, 95% CI: 29.5-45.8).[3] Additionally, hypotension had a strong association with postoperative stroke. The numbers needed to harm were 130 and 190 for all-cause mortality and stroke respectively.[109] POISE exposed risks that were not revealed by the preceding smaller trials, and this illustrates the critical importance of conducting trials of sufficient statistical power to allow assessment of relatively uncommon, but important outcomes.

In essence, the POISE protocol achieves an unfavourable balance between efficacy and safety. The findings underline the dilemma that clinicians currently face. PBB, as administered in POISE, is effective at reducing perioperative myocardial ischaemia and its sequelae, but the safety of the practice remains in question. The benefits cannot be safely achieved if the POISE protocol is followed.

Despite the largest randomised controlled trial in the field not finding overall favour for the practice,[3] researchers and clinicians have found some encouragement in the results. Steadfast proponents of PBB voice concerns over the drug regimen and timing, indications for repeat dosing, and the inclusion of a number of lower risk individuals, as potential shortfalls in the POISE trial design.[110,111] It may be possible to balance efficacy and safety more favourably. As a result the focus has shifted to finding ways that may optimise the intervention. How best to initiate and titrate beta blocker medication has become a key consideration.[112]

2.5.3 Drawing conclusions from inconclusive evidence

The literature remains inconsistent and confusing as a result of fundamental differences in study design. Few reliable conclusions can be drawn from the currently available data. The marked heterogeneity and insufficient power of the small number of randomised trials, makes comparison difficult, if not inappropriate. (**Table 2.2**)

Attempts at clarifying best practice have received priority in the post-POISE era. Multiple reviews,[113-116] commentaries[117,118] and editorials[96,109] with suggested recommendations for PBB have been published. The European Society of Cardiologists (ESC) have published their first ever guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery.[4] In addition, the American College of Cardiology Foundation, American

Heart Association Task Force on Practice Guidelines (ACCF/AHA) were compelled to update their 2007 consensus guidelines with respect to the indications for the use of beta blockers in cardiac patients undergoing non-cardiac surgery.[5] Confusion is best illustrated by the differences in recommendations for PBB expressed within these sources of expert review.

The same body of literature was available for interpretation, and yet expert consensus guidelines differ on opposite sides of the Atlantic Ocean.[4,5]

The Europeans,[4] under the chairmanship of Poldermans, derive at least some of their recommendations from underpowered trials conducted within Europe.[15,73,85,119] Both groups consider the POISE findings, but the ACCF/AHA have recommended a more conservative and restricted approach.[5] However, concentrating on similarities, rather than differences, may select out more robust recommendations that promote an acceptable balance between efficacy and safety.[120]

Figure 2.2 helps to illustrate an approach that concentrates on common themes expressed in consensus guidelines and recent reviews.

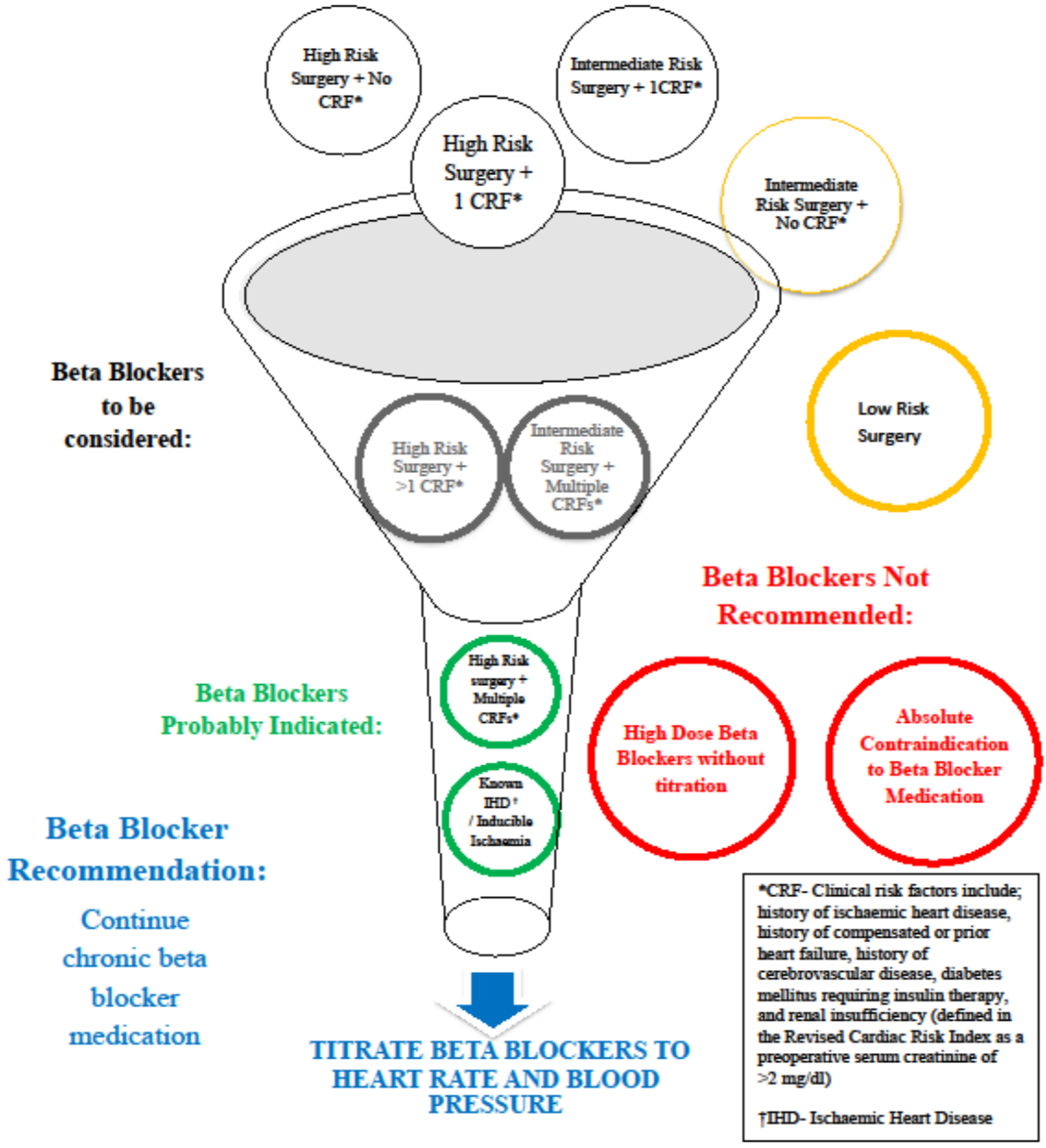

Figure 2.2 Illustration of current potential indications for perioperative beta blockade (Modified from Lawson R.[120])

2.6 Perioperative beta blocker therapy

2.6.1 Identifying appropriate candidates

PBB is not suitable for all patients. Even within the 'at risk' group of patients, described in **Section 2.4** and identified in **Figure 2.1**, it is necessary to individualise interventions.

2.6.1.1 The common ground in patient selection

Two widely accepted recommendations in the practice of PBB are indicated by blue text in **Figure 2.2**. There is also a degree of consistency in practices that are not recommended, and these are indicated by red text in **Figure 2.2**.

Recommended practice:

i. Continuation of chronic beta blocker therapy

Although no longer recognised as first line therapy for the treatment of hypertension,[121,122] the role of beta blockers in the secondary prevention of ischaemic events in patients with ischaemic heart disease (IHD),[123] and their accepted role in the management of congestive cardiac failure,[124] has led to an increase in the number of patients coming to surgery with a medical indication for their continued use.[125] Not only is it thought safe practice to continue beta blockers in the perioperative period, but it is apparent that withdrawal of beta blockers around the time of surgery is in fact harmful.[111,126-130]

The author of an editorial that reviews pertinent literature from the past 40 years, favours the continuation, and even optimisation, of beta blockade in the perioperative period, but highlights the limitations of the studies that have moulded opinion on the subject.[128] Although a randomised trial would be ideal to prove benefit in continuing beta blockade in this setting, current evidence indicating a significant harmful effect of beta blocker withdrawal in the perioperative period, makes such a study unethical.[125,126,128] Limited populations have been studied, but expert consensus from the small number of non-randomised studies, has resulted in the acceptance of continuation of beta blockade as a standard of care. [4,5,109,111-118]

Support for the continuation of beta blockers in patients undergoing vascular surgery has, until recently, relied on the results of two studies limited by sample size, methods of logistical regression, and confounding by indication.[126,127] A meta-analysis of these two studies shows an increased mortality in patients who do not continue to receive chronic beta blocker medication, throughout the perioperative period, when undergoing vascular surgery (OR 26.32, 95% CI: 8.95-77.44, $p<0.0001$).[130]

The use of patient-matching techniques rather than the multiple regression models, as used in the two studies mentioned above, may confer an advantage.[131] Biccard used a matched case-control technique, to identify predictors of mortality in those vascular surgical patients who do not continue to receive beta blockers throughout the perioperative period.[130] The study conducted at a single centre in South Africa, showed that an increase in the mean daily heart rate of $\geq$ six beats per minute, between the day of surgery and the third day after surgery (or death or discharge before the third day), was an independent predictor of inhospital mortality (OR 13.7, CI: 1.7-110; $p=0.014$). The small sample size (14 patients), high percentage of patient exclusions (33%) on the basis of incomplete data (4/21 patients) and inadequate matching (3/21 patients),

and the retrospective collection of data from a single centre, are important limitations of this study.

The affects of chronic beta blockade, and the perioperative management of such patients, has received little attention. An analysis of 18 studies that assess association between chronic beta blocker therapy and perioperative outcome, failed to demonstrate a protective effect.[125] As a result the authors proposed that chronic beta blocker therapy may not confer the same beneficial reduction in perioperative cardiovascular events that had been shown with acute administration of beta blocker medication.[125] In fact, meta-analysis of the five studies that reported on the incidence of myocardial infarction, demonstrated an association of chronic beta blocker therapy with an increased incidence of PMI (OR 2.14, 95% CI: 1.29-3.56).[125]

Upregulation of beta receptors in the setting of chronic beta blockade,[132,133] [132] and a reduction in the ischaemic threshold in patients treated with beta blockers,[134] may explain the insufficient protection afforded by chronic beta blocker therapy. A reduced threshold for the development of myocardial ischaemia has been shown to be dose dependent in one study.[135] The reduced threshold, and duration dependent relative increases in heart rate, may explain the episodes of myocardial ischaemia that occur more frequently, and at lower heart rates, in patients receiving chronic beta blocker medication.[136] When combined with the marked increase in catecholamine release postoperatively,[31,32] the increased risk of myocardial ischaemia is immediately evident.

In an attempt to reduce events in patients receiving long term beta blocker medication, experts have made the following suggestions;

- the use of supplementary beta blockade during the perioperative period to optimise heart rate control to a level below the ischaemic threshold[125,128,130]
- serial Troponin measurement and electrocardiogram surveillance in patients identified to be at increased risk[130]
- the use of alternative negative chronotropes to further reduce risk[125,130]
- consideration toward the use of other novel strategies that have not yet been extensively studied.[128]

More recently, and in contrast to the evidence reported above, Wallace et al have reported on patient outcomes in an epidemiological study conducted at a Veterans Affairs Hospital over a period of twelve years.[111] The study showed improved outcomes, at 30 days and at 1 year, in patients who had beta blockers added, or continued throughout the perioperative period.[111] Equivalent 1 year survival rates, in at risk patients who had beta blockers added to their treatment preoperatively, and those that had beta blocker medication continued, imply that chronic beta blocker therapy may be protective in a real world clinical setting.

Current international consensus guidelines give Class 1 recommendation to the continuation of beta blockers in the perioperative period.[4,5]

ii. Titration of beta blocker medication

The need to titrate beta blocker therapy to heart rate and blood pressure is a further area of agreement.[4,5] The limited evidence in support of the need for titration is discussed below. (**Section 2.6.2.2**)

Aspects of perioperative beta blockade that are to be avoided

i. Avoid high doses of beta blocker medication without titration

Both guidelines[4,5] specifically do not recommend high dose beta blockers without titration in the perioperative setting, because potential harm was demonstrated with this strategy in the POISE trial.[3]

ii. Avoid the use of beta blocker medication when contraindicated

Further agreement includes the avoidance of beta blockers in patients who have a contraindication to their use.[4,5]

- **Beta blockers should be avoided in the following situations;[137]**

- Severe conduction abnormalities (Second or third degree atrioventricular block)
- Symptomatic bradycardia
- Symptomatic hypotension
- Severe heart failure (Class IV or EF< 30%)
- Cardiogenic shock
- Severe COPD with strong reactive component, or severe asthma requiring steroids
- Known beta blocker intolerance

- **Conditions requiring careful consideration before introducing beta blockers**

- Emergency surgery

Analysis of all non-cardiac surgeries in a cohort of 108 693 patients, demonstrated a significantly elevated risk of cardiovascular mortality in the patients undergoing emergency procedures (6.1% vs 0.5%, $p<0.001$).[47] Emergent surgery was associated with mortality in POISE (Adjusted OR 3.71, 95% CI: 2.68-5.14).[3] However, no subgroup analysis was reported for a difference in outcome between the treatment and placebo groups.[3]

The safety of beta blocker initiation before emergency major vascular surgery is not known, and the decision to continue beta blocker medication in the emergency setting should be individualised.[4]

- Congestive cardiac failure

Beta blocker medication may improve myocardial performance. However, the use of beta blockers in perioperative haemodynamic optimisation should be individualised, and avoided in patients with decompensated heart failure.[138] Beta blockers should be avoided in patients reliant on sympathetic drive for cardiac output. This is because the oxygen extraction ratio is maximal and cannot be increased, and the effects of anaesthesia that obtund compensatory increases in stroke volume, are more apparent in the failing heart.[138]

Patients with congestive cardiac failure should have their surgery delayed to allow optimisation, if at all possible.[4]

- Peripheral vascular disease

Recent studies show that the symptoms of intermittent claudication do not occur more frequently in patients receiving beta blocker medication, as was previously claimed.[139]

- Cerebrovascular disease

A history of cerebrovascular disease (CVA or TIA) was the strongest independent predictor for perioperative stroke in POISE (PAR 30.5% 95% CI: 17.1-48.2).[3] The dose of metoprolol used, remains an important consideration,[140] and the underlying pathophysiology is not yet fully explained.[3] Consensus guidelines[4,5] continue to recommend the use of the RCRI[7] to stratify patient risk, and the index includes a history of a cerebrovascular event as an important clinical risk factor (CRF).

- Obstructive airways disease – Asthma and COPD

A Cochrane based systematic review updated in 2008, supports the use of cardioselective beta receptor antagonists in patients with cardiovascular disease and mild to moderate obstructive airways disease (asthma and COPD).[141] Cardioselective agents should be introduced gradually. Patients with COPD, who receive selective beta-1 receptor antagonists before vascular surgery, have been shown to have a reduced risk of death.[142] However, beta blockers should be avoided in severe persistent asthma.[143]

- Sepsis

Sepsis, as a cause of death, was the only cause that showed a significant difference between the treatment and control groups in POISE.[3] Caution is recommended in this setting. Theoretical

benefit of beta-1 receptor blockade in the modulation of the response to sepsis has received attention in recent literature, but currently remains experimental.[144,145]

- Diabetes mellitus and hyperlipidaemia

The adverse effects on insulin resistance and lipid profile that are associated with beta blocker medication are less pronounced with newer vasodilating agents,[146] but the newer agents do not currently have a role in PBB. A meta-analysis reports that the effects on the lipid profile are only modest with cardioselective agents, and may even be transient.[147] The benefits of beta blockers probably outweigh the adverse effect on glycaemic control and lipid profile in well selected patients.

- Advanced age

Cardiovascular comorbidities are common in the elderly, and elderly patients are probably at greater risk for perioperative adverse cardiac events.[11,12,137] Beta blockers should be considered in the elderly in the same way that they are considered for all patients undergoing surgery. However, awareness of drug interactions, altered drug handling, and reduced physiological reserve makes careful introduction prudent.[137] It is suggested that the dose should be limited to a dose that avoids adverse symptoms. Therefore, the optimal dose is reduced for many patients,[148] despite the decreased responsiveness to beta blocker therapy in the elderly.[149]

- Drug interactions

Important drug interactions include those that occur with calcium channel blocker medication. Non-dihydropyridine calcium channel blockers (verapamil and diltiazem), and beta blockers, have a significant effect on AV node conduction and increase the potential for significant

bradycardia and heart block. Heart rate and PR interval should be closely monitored, and the dose adjusted if administered concurrently.[150]

Furthermore, the adverse effects on cardiac contractility may be exacerbated.[151] The combined use of verapamil and metoprolol causes a reduction in hepatic blood flow, and competition for the same Cytochrome P450 isoenzyme leads to an increase in the bioavailability of metoprolol, and therefore, demands dose reduction.[152]

Interaction with antiarrhythmic agents and clonidine are further important considerations.[150]

2.6.1.2 Aspects of patient selection that are still debated

It is important to be aware that any further recommendations rely on interpretation of inconclusive evidence from a body of literature riddled with inconsistencies. Treatment algorithms differ because most of the available literature is subject to interpretation. For all other patients, the risks and benefits of PBB should possibly be evaluated on an individual basis.[120]

i. Patients at high risk for major adverse cardiac events

High risk patients, undergoing high risk procedures, are more likely to benefit from beta blockers than patients with intermediate or lower overall risk.[73,153,154]

Patients at the highest risk are those with known ischaemic heart disease (IHD) or inducible myocardial ischaemia on preoperative testing, as well as patients undergoing high risk surgery with multiple clinical risk factors (CRF's). The ESC guideline gives a Class 1 recommendation for beta blockers in these patients.[4] It is perhaps noteworthy that patients undergoing vascular surgery (high risk) who received beta blockers showed a beneficial reduction in the primary endpoint on subgroup analysis of the POISE data.[3] Patients with two risk factors present also

showed benefit, but those with three or four risk factors did not.[3] However, none of these subgroup analyses reached statistical significance,[3] and the POISE data cannot be interpreted as supportive evidence for these recommendations.

Although patients with evidence of inducible myocardial ischaemia on preoperative testing would probably benefit from PBB,[5] the ACCF/AHA are more reserved than the ESC in their judgement, and have allocated a class IIa recommendation for PBB in patients with known IHD or inducible ischaemia.[5]

In addition to the number of risk factors, used as a surrogate for overall disease burden, some of the CRF's within the RCRI may deserve individual attention.[155] Medical patients with IHD[123] or CCF [124] may have independent indications for beta blockade. Leibowitz et al imply that all such patients warrant beta blocker therapy.[155] Beta blocker medication may be prudent for most of these patients, but to assert that it is routinely indicated is misleading.

Not all patients with a positive non-invasive test result have significant CAD, although a negative test result helps to exclude significant disease.[4,5] In patients with a previous myocardial infarction, acute coronary syndrome, or left ventricular dysfunction in the presence of IHD, there is independent indication for beta blocker therapy.[123,156] In the absence of a previous myocardial infarction, proven beneficial effects are largely related to a reduction of symptoms in patients with known IHD.[58] Although chronic beta blocker therapy should be considered in all patients with IHD, especially if there is other vascular disease or diabetes mellitus,[156] the presence of IHD alone, without significant symptoms, is not an automatic indication for beta blockade.[123,156] This is currently accepted despite some evidence that beta blockers may be beneficial in the setting of silent ischaemia.[157]

Similarly, not all patients with heart failure are candidates for beta blocker therapy.[124]

Leibowitz et al also attribute a lower degree of risk to patients with insulin requiring diabetes mellitus, neurovascular disease, and renal dysfunction (creatinine > 2mg/dl), unless they occur in combination.[155] The DIPOM study did not show benefit with perioperative use of metoprolol in diabetic patients.[18] Patients included in the study had few risk factors other than diabetes mellitus. Leibowitz et al claim that the results support the omission of beta blockers if diabetes is the sole risk factor.[155]

Note: In **Figure 2.2** high risk patients are represented by green text and are situated closest to the exit of the funnel. Groups of patients depicted closest to the exit of the funnel warrant a low threshold for introduction of beta blockers preoperatively.

ii. Patients undergoing vascular surgery at intermediate risk (RCRI = 1 or 2)

The lower the risk of the patient, or the procedure, the lower the potential for significant benefit becomes. The point at which the risk outweighs potential benefit remains unknown. There is some evidence in favour of beta blockade in patients at intermediate risk,[73,85,158] but these studies are not adequately powered to assess important adverse events. A study by Biccard et al, showed possible benefit in patients at intermediate risk undergoing vascular surgery (NNT=68), but a reduced potential for benefit in those at intermediate risk undergoing intermediate risk surgery (NNT=833).[158] It is reasonable to consider PBB in patients at intermediate risk undergoing vascular surgery. However, it is important to note that this is a consideration rather than a recommendation.

Patients undergoing vascular surgery, who have no CRF's, score only one point on the RCRI, and consensus guidelines differ in the recommendations for beta blockade in this setting.[4,5]

Lindenhauer's retrospective analysis showed no benefit, and even potential for harm, associated with beta blocker administration in patients with less than two risk factors.[153] It is not known, however, whether beta blocker medication was introduced in response to adverse cardiac events, rather than in an attempt to prevent such events.[159] The ACCF/AHA guideline suggests that the benefit to be gained from beta blockers is uncertain in this setting (Class IIb recommendation, level of evidence B).[5] The ESC are more proactive, and recommend beta blockade in patients undergoing high risk surgery, even in the absence of any other clinical risk factor (Class 1, level of evidence B).[4] The lack of benefit demonstrated by the DIPOM[18], MaVS[17] and POBBLE[16] trials, adds support for the omission of beta blockade in patients at low risk, even if they are undergoing vascular surgery. It may be prudent not to subject patients with no clinical risk factors to the potential risks of PBB until further favourable evidence is obtained.[120,155]

Note: Patients for whom PBB can be considered are illustrated in bold black text within the funnel, and those for whom the benefit is uncertain are illustrated in fine black print and hover above the funnel in **Figure 2.2**.

2.6.2 Implementation of perioperative beta blockade

There are no studies that have been designed to determine the optimal type, dose, preoperative timing, postoperative duration, or the need for titration of beta blockers in patients undergoing non cardiac surgery.[5] Expert opinion draws on evidence gathered from studies addressing non-cardiac surgery, with positive or negative outcomes, that are potentially attributable to specific aspects of the intervention undertaken in the treatment group, or the evidence is extrapolated from other fields of medicine.

2.6.2.1 Specific beta blocker

The trials associated with mortality benefit used atenolol[14] or bisoprolol,[15] but comparisons are not necessarily informative because the methodology used in these trials is so diverse.

The use of metoprolol was effective in terms of a reduction in cardiac events and myocardial ischaemia in the POISE trial.[3] However, a meta-analysis assessing the effect of tight heart rate control with beta blockade, showed that patients receiving metoprolol had less effective reduction in heart rate than patients receiving other beta blockers (atenolol, propanolol, bisoprolol and esmolol), or calcium channel blockers in combination with beta blockers.[160]

CYP2D6 is responsible for 70-80% of metoprolol metabolism.[161] Badgett et al suggest that reliance on the CYP2D6 isoenzyme of Cytochrome P450, for the majority of drug metabolism, may explain a reduced benefit with the use of metoprolol, particularly if medication is not titrated before surgery.[162] The authors also hypothesise that the beta-1 receptor selectivity, that is considerably higher for bisoprolol (β1:β2 affinity ratio is 13.5) than metoprolol (β1:β2 affinity ratio is 2.3),[163] may confer an advantage by improving cardiac protection without increasing cerebral ischaemia during periods of hypotension.[162]

A Veterans Affairs Study analysing data accumulated over a 12 year period demonstrates a significant difference in mortality, at 30 days and at 1 year, associated with the specific beta blocker medication that was prescribed.[164] After propensity matching and correcting for risk factors, the authors found a statistically significant increased risk of mortality when metoprolol use was compared with that of atenolol (OR = 2.1 [95% CI 1.5-2.9], $p<0.0001$).[164] An epidemiological analysis of 37,151 elderly patients receiving atenolol or metoprolol before surgery also reported lower mortality in the atenolol group.[165] Acute withdrawal of shorter acting

metoprolol was offered as a possible explanation for the increased mortality in sicker patients who may miss doses of chronic medication in the postoperative period.[165]

Atenolol has not shown the same benefits in the treatment of heart failure that are associated with carvedilol, sustained release metoprolol and bisoprolol.[124] Therefore, if beta blockers are initiated in patients with heart failure it may be prudent to use an agent with proven long term benefit in the medical setting.

The only independent predictor for adverse outcome in vascular patients randomised to receive placebo or bisoprolol, in the Swiss Beta Blocker in Spinal Anesthesia (BBSA) trial, was the presence of an adrenergic receptor polymorphism.[19] The optimal beta blocker may ultimately require assessment of the indication for use, underlying comorbid disease, and patient genetic profile. The route of administration of beta blocker medication may also have an impact on efficacy.[166]

Current recommendations favour the use of cardioselctive beta-1 receptor antagonists.[4,5] It is suggested that agents with a long half life, and no intrinsic sympathomimetic activity, should be used.[4,5]

2.6.2.2 Dose and titration

Effective control of heart rate with beta blocker medication may be a critical determinant of cardioprotection. One study even suggests that tight control of heart rate, in intermediate risk patients undergoing vascular surgery, negates the need for preoperative testing.[85] However, overall benefit related to heart rate manipulation with beta blockers, remains unproven.[167,168] One meta-analysis of eight trials,[15-18,169-172] designed to determine the effect of beta blocker adjusted

heart rate on cardiovascular outcome, did not confirm short term benefit.[167] The same eight trials were included among ten randomised trials[15-18,169-174] assessed in a meta-analysis conducted by Beattie et al.[160] Beattie's meta-analysis demonstrated a proportional reduction in risk with tight control of heart rate, but benefit could only be shown for studies that achieved maximal heart rates of less than 100 beats per minute. The use of higher doses of beta blocker medication with tight control of heart rate,[175] or maintaining the heart rate below the ischaemic threshold,[171] may be important determinants of efficacy.

Attempting to introduce beta blocker medication at high dose increases the risk of side effects, and may have an impact on outcome. Both meta-analyses,[160,167] and an increasing number of trials,[3,16,17] have reported an increase in the development of significant bradycardia and hypotension in patients randomised to receive beta blockers. The negative impact of bradycardia and hypotension on patient outcome, may explain the inconsistent evidence of benefit gained by the implementation of PBB.[168]

Significant hypotension had the highest population attributable risk of all assessed independent predictors of mortality in the POISE trial (PAR 37.3%, 95% CI: 29.5-45.8).[3] Current understanding of the pathophysiology of PMI identifies an important contribution of hypotension to the underlying process.[26] Furthermore, clinically significant hypotension was second, only to a previous history of cerebrovascular accident or transient ischaemic attack, as an independent predictor for stroke (PAR 14.7%, 95% CI: 5.2-35.4).[3] More than 75% of the strokes recorded in the POISE trial were ischaemic, and may have been related to periods of hypotension.[155] The cause for stroke was, however, unexplained in almost half of the cases, and data must be considered with this limitation in mind.[3] The association between significant haemorrhage and death or stroke in POISE,[3] combined with demonstrated,[94] or theoretical[95] reductions in cerebral

oxygen delivery, in the presence of beta blockade and acute haemodilution, highlight the likelihood that the pathophysiology of adverse events depends on many factors and not hypotension alone. The level below which the blood pressure should be defended is not known, but the need to avoid sustained periods of reduced blood pressure is apparent.

One suggestion is to reduce the dose of drug administered. The POBBLE[16] and MaVS[17] studies used lower doses of metoprolol without a significant period of preoperative titration, but neither of these studies showed outcome benefit. Some experts have suggested that the dose of metoprolol used in POISE was too high.[117] The Perioperative Cardiac Risk Reduction Therapy (PCRRT) protocol, followed at a Veterans Affairs clinic, showed survival benefit by implementing a strategy more in keeping with the dosing regimens of the DECREASE[15,119] and McSPI[14,170] studies.[111] The POISE protocol, on the other hand, allowed for up to 100% of the maximum recommended therapeutic daily dose (MRTD) of metoprolol to be administered to beta blocker naïve patients on the day of major surgery.[140] This is much higher than the recommended starting dose for metoprolol in the non-surgical setting.[176] Devereaux, as the lead investigator in POISE, believes that the potential for such high doses is a theoretical possibility that would seldom have been realised.[177] Lower doses of bisoprolol (10-20% MRTD), titrated over a minimum of 7 days appears to be a safer strategy.[140,178] The incidence of stroke in the DECREASE trials was not significantly increased (OR 1.16, 95% CI 0.4 to 3.4),[140] unlike the increased risk demonstrated in the POISE trial (OR 2.2, 95% CI 1.3 to 3.8).[3]

Feringa et al showed that higher doses and tighter control of heart rate were predictors of improved outcome.[175] The reported decrease in myocardial ischaemia, Troponin release and long term outcome in association with tight control of heart rate and higher doses of beta blocker medication, highlights the potential benefit of optimal dosing. However, the patients that

received beta blockers were well established on treatment before surgery. In the DECREASE-I trial, which showed an unprecedented reduction in the incidence of perioperative cardiac death and myocardial infarction (3.4% bisoprolol group vs 34% placebo group; $p<0.001$), bisoprolol was titrated to a heart rate of less than 60 beats per minute over a mean of 37 days (range 7-89 days), and heart rate control at less than 80 beats per minute was continued postoperatively for a minimum of 30 days.[15] In addition to allowing time for potentially important anti-inflammatory and plaque-stabilising effects of beta blockers, that may take several days to develop,[44] a longer lead-in period may allow tighter heart rate control, with a reduced risk of clinically significant bradycardia and hypotension.[113,178] Conversely, fixed doses of beta blocker medication do not reliably reduce heart rate in all patients.[160] Fixed doses are likely to be too high for some patients, and do not allow adjustment for dynamic changes that may be pronounced in the perioperative setting.[5]

It is unclear whether the potential benefits of titration relate to efficacy or safety. Subgroup analysis conducted during a meta-analysis of trials including the POISE data, points towards an increased efficacy in studies that practiced titration of beta blockade, and an increase in safety if beta blockade was introduced more than one day before surgery.[154] However, among other limitations in the six studies that allowed titration to heart rate, blinding was either not reported,[179] not effective[171] or non-existent,[15,172,174] in all of the studies except for the Beta Blocker in Spinal Anesthesia (BBSA) trial.[19] If benefit is related to efficacy, then a prolonged titration phase may be necessary to allow time for all beneficial effects. If related to safety only, then provided due attention is paid to potential adverse effects, it seems feasible that titration could be achieved over a much shorter interval.

Consensus guidelines[4,5] differ slightly in the recommended targets of titration, and the period over which this titration should occur. It is also recommended that beta blockade should be titrated, and reassessed throughout the perioperative period, as requirements are likely to fluctuate with changes in sympathetic activity.[4,5]

In summary, the proposed benefits of titration are not proven, they rely on limited data[15,119], and further investigation is essential.

2.6.2.3 Duration and withdrawal of perioperative beta blockade

Avoidance of the withdrawal of chronic beta blockade during the perioperative period is advised.[4,5] There are no evidence based recommendations for optimal timing of withdrawal of beta blockade when it is used solely as a risk intervention strategy.

A recent review suggests that beta blockers should be commenced at least seven days before planned major surgery, and continued for a minimum of seven days after surgery.[155] The positive findings of DECREASE-I[15] and the Mangano Atenolol study,[14] are cited as supportive evidence for the recommendation. However, in POBBLE (7 days),[16] DIPOM (7 days)[18] and MaVS (5 days),[17] beta blockers were withdrawn within a week of surgery, and none of these trials showed benefit. POISE and DECREASE-I, on the other hand, showed a reduction in cardiovascular events, and the patients in both of these studies continued beta blocker medication for at least thirty days.[3,15] Reports of cardiac events several months after surgery may suggest a lower threshold to continue medication for even longer periods.[4] Specific groups of patients, such as those with a positive non-invasive stress test, should probably continue beta blockers in the long term.[4,106]

2.7 Potential barriers to the implementation of perioperative beta blockade as a strategy

Barriers to the implementation of PBB as a risk reduction strategy are multifactorial.

i. Inconsistent evidence

A survey of Canadian anaesthesiologists in 2003 suggests that controversies in the literature, and practical considerations, rather than awareness of recent literature, were the principal barriers to widespread implementation of guideline recommendations.[180] However, a further study conducted in Canada one year later, suggested that anaesthesiologists at one tertiary centre would benefit from further education on this topic.[181] Price suggests that the need to extrapolate data from alternative populations, limitations of the available evidence, concern for adverse effects, insufficient resources, and lack of agreement between specialties, are the potential reasons for lower than expected administration of beta blockers in the perioperative setting in Australasia.[182]

Surveys have shown that only approximately 10% of clinicians make use of specific department protocols for PBB.[180,182,183] The use of a protocol has been suggested as a method of increasing the number of appropriate candidates for PBB that will go on to receive beta blockers perioperatively.[180,182,184] However, cognisant of the recent controversies in PBB, one review has not recommended the introduction of a protocol.[185] Similarly, another review highlighted that a change in their suggested approach will almost certainly be required at some point.[155] In addition to inconsistent evidence of benefit and concern about potential harm, there is no clear data to suggest appropriate implementation regimens or required monitoring.[182]

ii. Staffing

A survey conducted by Ellis et al in the United States showed that although anaesthesiologists were aware of the importance of PBB as a risk intervention, recommendation for the introduction of beta blockade in a hypothetical scenario was more closely related to the anaesthesiologists' level of training, site of training, and practice setting, than patient specific risk factors.[186]

From a practical point of view, the specialty responsible for PBB is not widely reported. Internal Medicine (89%) and Anaesthesiology (86%) were most commonly identified as the departments responsible for implementation of PBB in a Canadian survey.[180] Only 21% of survey responders indicated that the surgeons were involved in the administration of beta blocker medication as a prevention strategy. In London's Veterens Affairs survey,[183] once again, the surgeons were not commonly identified as being responsible for this aspect of patient management. The cardiologists were more inclined to identify themselves as being responsible for the development of strategy. However, coordination of PBB in the setting of a preoperative anaesthetic screening clinic was favoured by all specialties, and it was most common for no single specialty to have control over PBB.[183] An Australasian survey showed that the anaesthesiologists were more commonly involved in PBB than the intensivists, cardiologists and surgeons.[182] The authors explain that the complexity of risk stratification has seen a necessary increase in the involvement of anaesthesiologists in assessment clinics, and a shift toward decision making at a more senior level.

iii. Monitoring

Post POISE a greater emphasis must be given to the monitoring of patients. There is no instructive evidence from previous studies that directs how, where and when these patients should be monitored.[5] Although more than half of the respondents in Price's survey indicated that the patients receiving PBB are managed in an intensive care unit (ICU) or a high dependency unit (HDU) postoperatively, more than 40% of respondents indicated that the patients are managed unmonitored on the general ward within the first 24-48 hours.[182]

Potentially effective monitoring may not necessarily require a more invasive approach. More regular assessment of simple measurements of haemodynamic status, such as non-invasive blood pressure and heart rate, when combined with a greater level of awareness of the potential for adverse events, may be sufficient to optimise safe practice both pre- and postoperatively.

The Biccard group has published a model for prediction of all cause inhospital mortality in South African patients undergoing vascular surgery.[187] The value of this model is limited by retrospective data collection from a hospital database, and the inclusion of continuous data (age and physiological data) that complicates the scoring of risk. Early warning systems may improve outcome,[188,189] and the use of the postoperative model, developed by Biccard, may allow early identification of patients at increased risk of complication on the basis of physiological variables.[187]

iv. Cost Analysis

The complications associated with high risk patients undergoing major non-cardiac surgery present an increasing burden on health systems.[6] Strategies to reduce these complications must remain a research priority.

One study suggested that the development of a practice guideline for PBB would realise significant cost savings.[190] A cost analysis completed in 2006, favoured the use of PBB in the South African environment.[191] However, the risk was extrapolated from international data due to the lack of reliable data from within South Africa, and the intervention was only favourable if the patient's risk of an adverse cardiac event was at least 10%.[191] With opinion on the risk and benefit of PBB still being so diverse, and the literature so inconclusive, the validity of costing studies is questionable.

2.8 Other literature pertinent to the study

2.8.1 Studies describing practice across multiple facilities

PBB was previously suggested as a performance measure,[105] but poor compliance with guidelines and under use of the strategy has been widely reported.[107,181,192,193] A quality improvement project demonstrated increased utilisation of PBB across multiple centres, but did not result in a reduction in the incidence of postoperative myocardial infarctions.[194] Once again, this highlights the need to more accurately define the population that will benefit from PBB as an intervention.

Surveys have been conducted to assess current practice across multiple institutions or practitioners in many countries around the world,[107,180-183,195,196] but no studies have been published describing practice throughout South Africa.

2.8.2 Risk associated with vascular surgery in South Africa

The perioperative risk of patients undergoing vascular surgery in South Africa has not been widely studied, and the long term outcome of patients after vascular surgery is not known.

In South Africa racial groups differ in terms of the clinical and pathological presentation that is most commonly encountered.[13] Biccard suggests that environmental and socioeconomic factors are largely responsible for the discrepancy.[13]

In the general medical setting, the African INTERHEART study showed that the major risk factors for acute myocardial infarction in sub-Saharan Africa are the same as those that underlie risk globally.[197] However, the relative contribution to overall risk, by each of the independent risk factors differs between racial groups, and may be a consequence of an epidemiological transition.[197] When compared with results from the rest of the world,[198] the age at presentation of patients with first time acute myocardial infarction was significantly lower in all three racial groups in the African INTERHEART study.[197] In addition, the odds ratios (OR) and population attributable risk (PAR) calculations were significantly higher for many of the risk factors in African patients. Prevention, screening, and management of risk factors are seemingly inadequate in sub-Saharan Africa, and the overall management of cardiovascular risk is less effective.[197]

Published[53] and unpublished data, from vascular surgical patients treated at Inkosi Albert Luthuli Central Hospital between 2003 and 2006, indicate that South African patients present for vascular surgical intervention at a younger age, but suffer a significantly higher cardiovascular burden[13] than patients presenting for vascular surgery at a European centre.[11] The South African cohort[13] demonstrated a significantly higher all-cause (10.8% vs 6.7%; $p<0.01$) and non-cardiac mortality (6.4% vs 5.1%; $p<0.01$) than the European cohort.[11] The cardiac mortality was very low in the black South African group (0.7%) and very high in the Indian group (7.2%), but across all groups the cardiac mortality was no different to the European cohort (4.4% vs 3.3%; $p=0.2$).[13]

Biccard's analysis of mortality data was restricted to patients older than 39 years of age, in an attempt to reduce bias introduced by the analysis of patients requiring vascular surgery for trauma or HIV associated vasculopathy.[13] HIV vasculopathy is a common cause of vascular disease in South Africa,[199] and is associated with high perioperative mortality.[200] The use of perioperative risk reduction strategies in this group of patients has received little attention, but may require a different approach.

Race specific risk profiles, and the increased burden of cardiovascular risk factors, implies that the use of risk indices derived elsewhere in the world may not be appropriate for prognostication in the South African vascular surgery population.[13]

2.9 Summary

The optimal approach to risk reduction in patients undergoing major vascular surgery remains elusive. PBB is a not a benign intervention, and evidence of overall benefit is inconclusive. Guidelines have moved away from a notion of beta blockers for all at the turn of the century, to a realisation that a more measured approach is indicated. The POISE study has raised important concerns about how to administer beta blockers, in such a way as to minimise the adverse effects, yet capitalise on their proven benefit in terms of a reduction in perioperative myocardial ischaemia. Unless alternative effective and safe strategies are found to modify risk, beta blockers must be considered as an optional intervention in patients at high risk for perioperative cardiovascular events.

The large burden of cardiovascular disease in South Africa makes this an important area to target in future research. To date very little research has emerged from South Africa, despite its potential as an ideal setting to investigate methods of risk reduction.

CHAPTER THREE – METHODOLOGY

3.1 Study design

This study is descriptive. A partially selective, observational survey, facilitated by the use of a semi-structured questionnaire and voice recorded face-to-face interview, was conducted.

Descriptive: participant responses were documented and then described in the results section of the research report.

Partially selective: the study includes participants from each of the recognised facilities for specialist training in the field of vascular surgery. However, it does not include the opinions of all the potential role players in perioperative beta blockade (PBB) at each of these facilities. The participants were invited to participate after being identified as key role players in the perioperative management of vascular surgery patients.

Observational: the data was collected without any intention of intervening in any aspect of the current approach at each of the hospitals.

The benefits of the chosen study design are that it facilitates collection of a large amount of data, in a finite time span, and at a relatively low cost.

A non-validated, goal directed research tool was designed to meet the study objectives. Research tool development included a piloting process involving anaesthesia and vascular surgery trainees, not involved in the study. The purpose of the pilot was to identify areas of inconsistency and ambiguity, in order to optimise the generation of good quality data and fluency of the interview process.

The chosen topic is very complex and extra comments or explanations have the potential to add greater clarity and understanding. Allowance was made for the notation of any extra comments made by the participants. In addition, the study design allowed for subsequent telephonic or electronic mail correspondence, for the purpose of clarification, where there were any gross inconsistencies in answers obtained during the interview. Participants were encouraged to contact the investigator with any additional information deemed to be of importance. Any delayed information received from the participants was to be identified as such in the results section of the research report.

3.2 Study sites

The Vascular Society of Southern Africa (VASSA) identified seven hospitals as accredited specialist training facilities for vascular surgery in South Africa. Representatives from all seven hospitals were invited to participate in the study. It was not necessary to conduct the interview process at the specific sites, and interviews were arranged at a time and place that was most convenient for the participant.

Description of intended current practice is not linked to named hospitals in the research report. A coding system protects the identity of the participants and hospitals. Codes were generated to allow linking of the anaesthesiologist and vascular surgeon responses at each hospital. Each hospital was randomly assigned a letter (V,A,S,C,U,L or R). Anaesthesiologist responses are identified by the number ‘1’ and vascular surgeon responses identified by the number ‘2’. The anaesthesiologist and vascular surgeon, representing the same facility, are described as ‘paired

participants' in the results chapter of the report. Only the principal investigator of the study has had access to the codes.

The following seven hospitals are the recognised facilities for specialist training in vascular surgery, and all seven were included in the study:

i. Charlotte Maxeke Johannesburg Academic Hospital, University of the Witwatersrand
ii. Chris Hani Baragwanath Academic Hospital, University of the Witwatersrand
iii. Groote Schuur Hospital, University of Cape Town
iv. Inkosi Albert Luthuli Central Hospital, University of Kwa Zulu Natal
v. Steve Biko Academic Hospital, University of Pretoria
vi. Tygerberg Hospital, Stellenbosch University
vii. Universitas Hospital, University of the Free State

3.3 Study period

The data were collected over a period of one month, between 04 February 2010 and 04 March 2010.

3.4 Study population

The study population includes potential role players in the practice of PBB as a risk intervention strategy. The population is restricted to anaesthesiologists and vascular surgeons employed at recognised facilities for specialist training in vascular surgery.

3.5 Sample population and sampling method

There was a proposed sample of 14 participants, which included one anaesthesiologist and one vascular surgeon from each of the seven hospitals meeting the criteria for inclusion in the study.

While this is a small sample, it is sufficient for this study. The sample size is not an issue in terms of allowing conclusions that are statistically significant. All of the recognised state sector training facilities for vascular surgery are included, and the sample is not selected to represent a larger population. The inclusive nature of the study negates the need for randomisation.

A partially selective approach to the identification of suitable candidates was performed. This was necessary as the study required opinion of current practice, specific to a super-specialised area in the management of vascular surgery patients during the perioperative period. Therefore, the study required the participation of an appropriate participant who was likely to have knowledge about a very specific aspect of current practice.

VASSA identified appropriate contacts in the Department of Vascular Surgery at each of the hospitals. An explanation sheet (**Appendix C**) was sent to each of the contacts after a telephonic conversation to assess interest in their unit's participation in the study. Appropriate candidates for participation were identified by the principal contact. One of the identified candidates at each facility was invited to participate in the study.

There was no Anaesthesia Society that could be identified that represented a body of anaesthesiologists with a dedicated interest to vascular anaesthesia, and this made it necessary to identify potential candidates by contacting each of the Anaesthesia Departments individually. The explanation sheet (**Appendix C**) was sent to the Head of the Anaesthesia Department at

each of the included hospitals. The Heads of Department were asked to identify potential candidates best suited to the objectives of the study. One of the identified candidates was then contacted, and invited to participate in the study. The Heads of Department were not informed of any individual candidate's decision to participate.

A high response rate is an essential component of a descriptive study with a relatively small number of participants. The methodology was structured in such a way as to minimise inconvenience, in an attempt to facilitate a more complete response. A favourable response rate was further promoted by the already healthy relationship between the academic institutions, and a topic that is notorious for controversy, and therefore, likely to be of interest to the targeted population.

3.6 Exclusion criteria

i. **Hospitals not recognised as specialist training facilities for vascular surgery**
   - Private hospitals.
   - Training facilities without specialist vascular surgery training accreditation.
   - State hospitals not accredited for specialist training.

ii. **Participants**
   - Refusal to participate.
   - Request to withdraw from the study at any stage.
   - Non-specialists.

3.7 Data collection

Data collection involved a face-to-face voice recorded interview and an investigator assisted written completion of a semi-structured questionnaire. (**Appendix F**) The interview was recorded on a standard voice recording device to facilitate accurate collection of data that could be reviewed. In addition, this reduced the time taken for data collection during the interview. It was decided to encourage explanation and extra comments during the interview in order to promote greater insight into the complexities of practice and its potential barriers.

Data collection was not commenced before the participant read and fully comprehended the explanation sheet (**Appendix C**), and provided written informed consent for participation in the study. (**Appendix D**) Completion of a separate consent form was required for voice recording of the interview. (**Appendix E**)

The invitation to participate was free of any coercion. It was made clear to all participants that their inclusion in the study was entirely of their own free will, and that there would be no penalty or disadvantage for any participant who wished to withdraw from the study at any stage.

An interview sheet was generated for each of the participants. Hospital and individual participant information have remained confidential. The front page of the research tool (**Appendix F**) has been kept separate from the rest of the document, and all documentation has been coded. The interview recordings were given different codes to the questionnaire and have been kept separate. The code is only known to the principal researcher.

The recording device was not concealed. The recorded interviews will be kept safely locked away for a period of 2 years, after which they will be destroyed in accordance with Health Professions Council of South Africa regulations.

3.8 Data analysis

The quantitative data obtained during the interview was extensively reviewed with respect to the potential for statistical testing. A biostatistician was consulted for assistance.

In the absence of data that allows meaningful statistical analysis, the results were discussed individually with emphasis placed on areas of consistency and areas of disagreement.

The extra comments and explanations offered by the participants are discussed individually in the results section of the research report, but only if they were thought to add value in terms of understanding or hypothesis generation.

3.9 Funding

The study was funded by means of a Faculty Research Committee Individual Research Grant provided by the University of the Witwatersrand.

CHAPTER FOUR – RESULTS

4.1 General Data

4.1.1 Study conduct

The potential candidates for participation in the study were identified in accordance with the methodology set out in **Chapter Three**. Semi-structured interviews were conducted at all seven recognised centres for academic training in the field of vascular surgery in South Africa. One anaesthesiologist and one vascular surgeon from each hospital participated in the study. The study included 14 participants.

In order to conceal the identity of the participants, each of the seven hospitals was allocated a code letter, known only by the principal investigator. The anaesthesiologist and vascular surgeon representing the same facility have the same code letter, and are distinguished on the basis of a number. Anaesthesiologists are identified by number '1' adjacent to the allocated hospital code letter, and vascular surgeons by the number '2'. The coding system facilitates the demonstration of similarities and differences in participant responses within a given hospital, and across the country. The anaesthesiologist and vascular surgeon representing the same facility are referred to as 'paired participants' in the results that follow.

The data were collected over a period of one month, between 04 February 2010 and 04 March 2010. All interviews were completed during the first nine days of data collection, except for one interview which was delayed due to problems with availability of the participant. The anaesthesiology and vascular surgery participants from each hospital were interviewed

separately. They were interviewed on the same day in all but two cases. The order of interviews was determined solely by availability in the schedules of the participants and the principal investigator. There was no difference in the conduct of interviews related to the order in which they were scheduled.

Two anaesthesiologists were identified as potential candidates for inclusion in the study at Hospital C. Both of these candidates were invited to participate in the study. Only one of these candidates replied to the invitation, and was subsequently included.

Informed consent was obtained from all participants before the interviews were conducted, and all participants consented to a voice recording of the interview.

4.1.2 Characteristics of the sample population

In addition to the number of elective surgery lists that were allocated to vascular surgery on a weekly basis, **Table 4.1** shows the participants' reponses for the number of specialists that were regularly providing a service at each of the hospitals, and the extent of anaesthesiologist interest.

There were 20 allocated vascular surgery lists each week at training facilities across South Africa.

Anaesthesiologist and vascular surgeon responses for the number of vascular surgeons employed at the hospital, matched at all hospitals except two of the seven. It seems more likely that the vascular surgeon responses would be correct, and that a total of 14 specialist vascular surgeons were operating on a regular basis across the seven recognised facilities for specialist training in the field of vascular surgery.

At the time of the study, six surgeons were undergoing training to become specialist vascular surgeons. One of the hospitals did not have a trainee.

Table 4.1 Table illustrating participant responses for staff numbers, specialist involvement, and the number of lists at each hospital

	Number of elective vascular surgery lists per week	Number of specialist vascular surgeons operating on a regular basis (Clinical fellow or equivalent)	Number of anaesthesiologists covering the elective vascular surgery list at least once per week	Number of anaesthesiologists known to have a special interest in anaesthesia for vascular surgery
V1	3	3 (1)	1	1
V2	3	3 (1)	1	Unsure – 1
A1	2	1 (1)	1	1
A2	2	1 (1)	2	Unsure – 2 or 3
S1	2	1 (1)	1	3
S2	2	1 (1)	0	1
C1	3	2 (1)	1	3
C2	3	2 (1)	1	2
U1	3	3 (2) +2 Part Time	2	3
U2	3	4 (1) +2 Part Time	2	2
L1	4	2	5	5
L2	4	2	2	2
R1	3	2	4	4
R2	3	1 (1)	3	3
Total - Anaes	**20**	**14 (6)**	**15**	**20**
Total - VS	**20**	**14 (6)**	**11**	**13 ± 1**

The number of anaesthesiologists that were regularly involved in the management of patients for vascular surgical procedures, or that had a special interest in this field, is not clear.

At two of the hospitals the vascular surgeons acknowledged that they were unsure about the number of anaesthesiologists with a special interest in anaesthesia for vascular surgery. At the remaining five hospitals the anaesthesiologist indicated more widespread interest than that which was appreciated by the vascular surgeon. It was apparent that not all of the anaesthesiologists with a special interest in the field had the opportunity to be involved on a regular basis. At one

hospital the vascular surgeon indicated that there was not a single anaesthesiologist that took responsibility for the elective vascular surgery list on a regular basis.

Paired participant responses for the number of anaesthesiologists regularly involved in vascular surgical procedures matched at only three of the hospitals. At two of these hospitals there was agreement that only one anaesthesiologist regularly fulfilled the role.

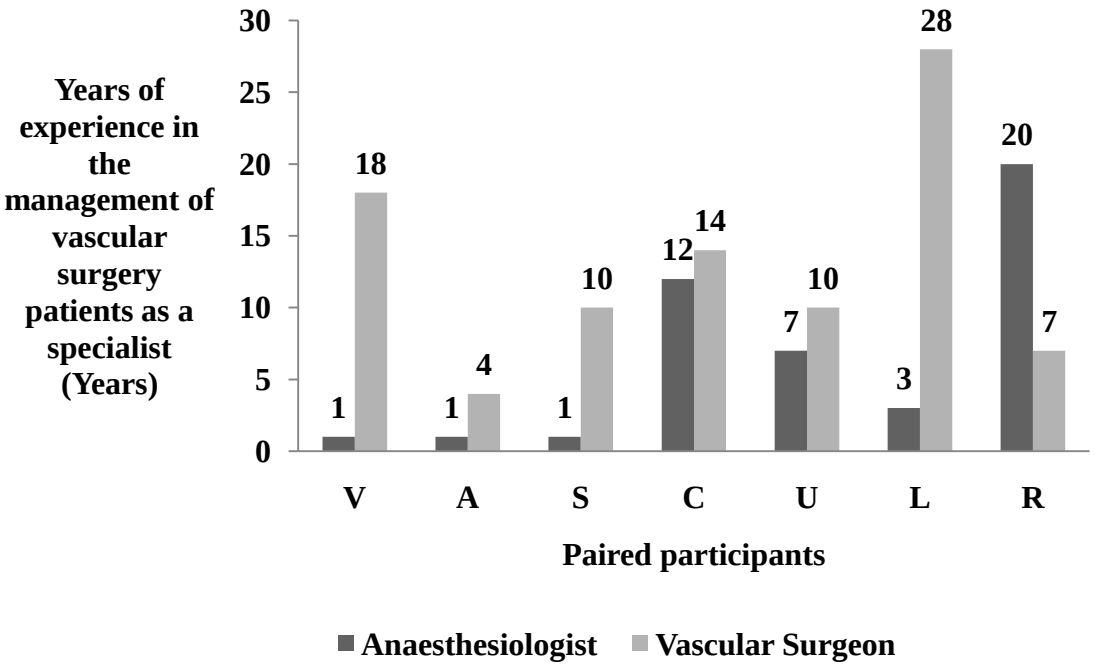

Figure 4.1 Bar graph comparing the years of experience as a specialist in the management of vascular surgery patients

The vascular surgeons had more years of experience in the care of vascular surgery patients. Cumulative experience was more than twice that of the anaesthesiologists (91 years vs 45 years). The greater experience of the vascular surgeon at all hospitals, except Hospital R, is demonstrated in **Figure 4.1**.

Only two of the anaesthesiologists had more than ten years of experience. In contrast, only two of the vascular surgeons had been specialists in the field for less than ten years, and only one of them had less than five years experience. Three of the anaesthesiologists had less than one year of experience as a specialist.

The vascular surgeon at Hospital R had been employed in his current role for only one year. However, the participant had previously accumulated seven years of experience as a vascular surgeon at another hospital.

4.1.3 Data reproducibility

Table 4.2 shows participant responses with respect to standardisation of approach and the processes used to aid decision making.

Grey shading has been used to highlight differences in response between participants from the same hospital. Despite claims suggesting similarity in the approach of other clinicians within the same hospital, a difference in the processes used to aid the decision to commence beta blocker medication was a common finding.

4.1.3.1 Standardisation of approach

Eleven of the participants indicated that they thought the current practice of the anaesthesiologists and/or the vascular surgeons at their hospital was essentially the same as they had reported. However, there was agreement at five of the hospitals that there was no standardised approach to the identification of candidates likely to benefit from perioperative beta blockade (PBB).

Table 4.2 Table showing opinion on the degree of consistency in approach, and the processes relied upon in the decision to introduce beta blocker medication

	Degree of similarity in the approach used by other clinicians	Use of a standardised approach to PBB	Processes used to aid the decision to commence beta blockers
V1	Essentially the same	No	Discretion of vascular surgeon, anaesthesiologist or cardiologist
V2	Essentially the same	Yes "Unit Specific Approach"	Department protocol at discretion of vascular surgeon
A1	Essentially the same	No	Unsure
A2	Essentially the same	No	Discretion of vascular surgeon or multidisciplinary team
S1	Unsure	No	Discretion of vascular surgeon or anaesthesiologist
S2	Essentially the same	Yes	Defined guidelines from the literature
C1	Unsure	No	Defined guidelines from the literature
C2	Some overlap	No	Discretion of vascular surgeon or anaesthesiologist
U1	Essentially the same	No	Discretion of anaesthesiologist
U2	Essentially the same	No	Discretion of anaesthesiologist
L1	Essentially the same	No	Defined guidelines from the literature
L2	Essentially the same	No	Discretion of cardiologist or anaesthesiologist
R1	Essentially the same	No	Discretion of cardiologist
R2	Essentially the same	No	Discretion of cardiologist

(Grey shading highlights inconsistent responses of paired participants)

No protocols were available despite one participant reporting the presence of a "unit specific approach." This participant was one of only two participants who indicated that a standardised approach was used to identify suitable candidates for PBB. At both of these hospitals, where a

standardised approach was reported, the anaesthesiologist was unaware of any such standardisation.

The processes identified as aids in the decision to commence beta blockers were consistent between paired participants at only two of the seven facilities.

4.1.3.2 Recent modification to approach

Table 4.3 shows the reported motivation for any change in approach, and the timing of any modifications that were reported to have taken place. The publication of the Perioperative Ischaemic Evaluation (POISE) trial, and updated guidelines published by both the European Society of Cardiologists (ESC), and the American College of Cardiologists Foundation and American Heart Association (ACCF/AHA), were used as reference points to aid in the understanding of motivation for any recent changes in approach.

There was very little consistency in paired participant responses. Changes in policy, where they had been instituted, had been initiated in response to developments in the literature. None of the participants indicated that policy had been recently modified by personal experience, hospital experience, or the inability to institute a protocol.

Despite eight participants attributing importance to evidence in international literature, it appears that the publication of the POISE study (May 2008) and the latest revised guideline recommendations (November 2009), did not lead to changes in approach at many South African training facilities. At least three institutions (Hospitals S,C and R) had not made any recent change to their practice in response to the most recent developments in the literature.

Table 4.3 Table showing timing of any modification to approach, and the motivation for any reported modification made

	When was the approach to perioperative beta blockade last modified?	What was the reason for the most recent change?
V1	No standard approach	-
V2	After May 2008 (POISE)	Evidence in International Literature
A1	Unsure (Not following current guidelines)	-
A2	Recurrently updated but no standard approach	Evidence in International Literature
S1	No standard approach	-
S2	Before October 2007 (Never been modified – new practice in previous 5 years)	Evidence in International Literature
C1	Before October 2007	Departmental lecture based on evidence in international literature
C2	No change in past 2-3 years	Evidence in International Literature
U1	After May 2008 (POISE)	Evidence in International Literature
U2	No standard approach	Evidence in International Literature
L1	Recurrently updated but no standard approach	Evidence in International Literature
L2	Before October 2007	-
R1	No recent change	-
R2	No recent change	-

Three of the participants reported a lack of standardisation as a reason for the absence of any recent change in approach. One participant specifically indicated that current guidelines were not being followed. One participant indicated that practice had not changed in the past 2-3 years. Another reported that practice had not changed in five years, despite identifying evidence in international literature as a reason for the initial approach. Both participants at hospital R indicated that there had been no recent change, and a further two participants reported that the

approach was last modified before the ACC/AHA guideline recommendations for the management of the cardiac patient for non-cardiac surgery published in October 2007.

Four participants specifically reported changes in response to literature published since the POISE study. Two of these participants indicated that the approach to the management of patients was recurrently updated, despite a lack of standardisation. The other two participants specified that the POISE results were directly responsible for the most recent change in policy.

4.2 Description of current intended practice

This section of the results chapter sets out to demonstrate three important components of the study. Most importantly, intended practice is described. In addition, the regularity of poor correlation of responses obtained in the study from paired participants representing the same hospital, and the variable practice reported across the country, are highlighted.

Clinician roles, patient selection for perioperative beta blockade (PBB), and some of the specifics of PBB are considered. For each of these components, participant responses are presented, and the most likely practice at each hospital is reported.

Determining the most likely practice is straight forward when both the anaesthesiologist's and vascular surgeon's responses demonstrate agreement. In areas where agreement was not present, unless both participants claimed responsibility, the response of the participant who made a claim of responsibility for that aspect of practice is assumed to be most likely to represent intended practice. Multiple aspects of practice were unclear, and the most likely practice could not always be determined.

4.2.1 Clinician roles

Table 4.4 summarises participant responses for which clinicians assumed responsibility for various aspects of PBB. The anaesthesiologist response, vascular surgeon response, and most likely scenario are shown in three rows for each of the hospitals. The rows are consolidated for simplicity wherever possible. The clinician most likely to have been responsible for the specific component of practice at each hospital is indicated by bold text.

Any inconsistency in the responses of the anaesthesiologist and vascular surgeon representing the same hospital is indicated by grey shading. The extent of grey shading in **Table 4.4** demonstrates the poorly defined clinician roles at most of the hospitals.

The following abbreviations apply:

VSs - Specialist vascular surgeon

VSr - Vascular surgery registrar

VS – Vascular surgery team

CF – Clinical Fellow/ Specialist vascular surgery trainee

Cardio – Specialist cardiologist

Anaes – Anaesthesia team

Anaes s – Specialist anaesthesiologist

Anaes r – Registrar anaesthetist

Crit care – Critical care specialist

? – Participant unsure

Table 4.4 Table showing participant opinion on which clinicians were responsible for various aspects of perioperative beta blockade

	Policy Development	Preoperative Management				Intra-operative	Post-operative
		Patient Identification	Decision to commence	Prescription	Titration	Initiation/ Titration	Withdrawal
V1	**VSs**	**VSs**	**VSs**	VSs?	VSs +/- Cardio	**Not PBB Specific**	Unsure
V2				**VSr**	**VSr**		**VS**
V							
A1	**VSs**	**VSs**	**VSs**	VSr	**VSr/ VSs**	**Not PBB Specific**	Unsure
A2				**VSr/ Junior doctor**			**VS**
A							
S1	No Policy	Unsure (VSr/ VSs)	PBB Not Practiced			**Not PBB Specific**	PBB Not Practiced
S2	**VSs**	**VSs**	**Physician> VSs/ CF**	**VSr**	**VSs**		**VS (Not continued on discharge)**
S							
C1	Anaes s	Anaes s/ VS	Anaes s	Anaes (s/r)	Anaes (s/r)	**Anaes s**	**VS**
C2	VSs	VSr	VSr	VSr	Intra/ Postop only		
C	**Unclear – Proactive approach of VS not supported by Anaes**						
U1	Anaes s	Anaes s	Anaes s	Anaes r	Not in acute setting	**Anaes s**	Anaes s decision, VS practical role
U2	Anaes s> VSs, Crit Care	Anaes s/VSs	VSs-Ward Anaes s-Clinic	VSr/ Anaes	VSs		VS
U	**Anaes lead agreed, VS role unsupported by Anaes**						**VS**
L1	VSs > Anaes s	VSs	VSs > Anaes s/ Cardio	VSr	VSs	**Anaes s**	**Beta blockers not withdrawn**
L2	VSs	VSs/Anaes s	Cardio	Cardio/ Anaes s	Anaes s/ Crit Care	?	
L	**VSS lead**	**VSs>Anaes**	**Unclear- Important role for Cardio**		**Unclear**	**Anaes s**	
R1	**VSs**	VSs/Anaes s referral to physician	**Cardio**	**Cardio**	**Cardio**	**Anaes s**	**Beta blockers not withdrawn**
R2		VSs				?	
R		**VSs >Anaes**				**Anaes s**	

(Any inconsistent response between anaesthesiologist and vascular surgeon from the same hospital is indicated by grey shading. The most likely clinician responsible at each hospital is indicated by bold text.)

The most likely current practice at each hospital is shown below in a series of horizontal bar graphs (**Figure 4.2 – Figure 4.8**). These bar graphs clearly illustrate the variable practice across South Africa.

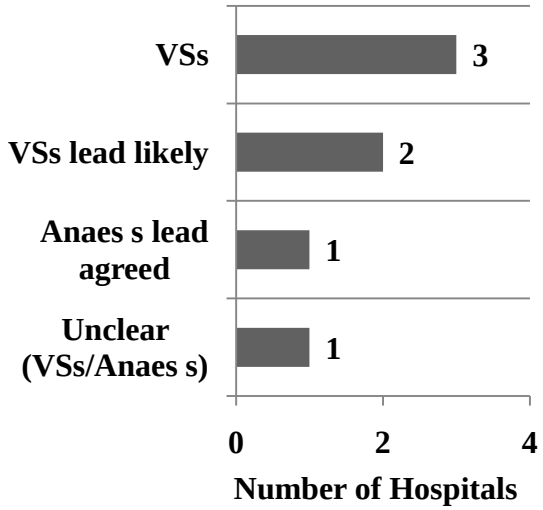

Figure 4.2 Horizontal bar graph showing the most likely clinician responsible for policy development at South African training facilities for Vascular Surgery

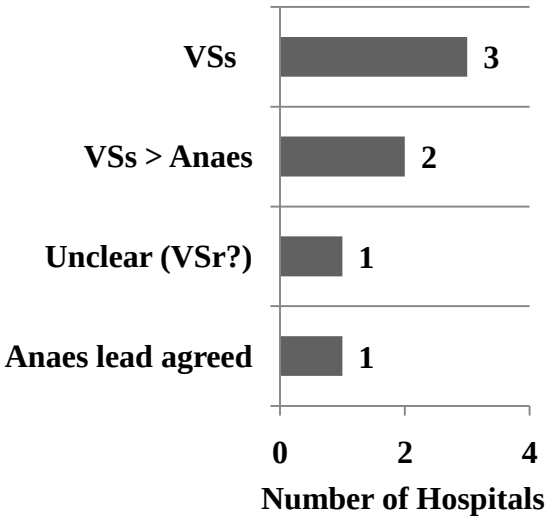

Figure 4.3 Horizontal bar graph showing the most likely clinician responsible for identifying potential candidates for perioperative beta blockade

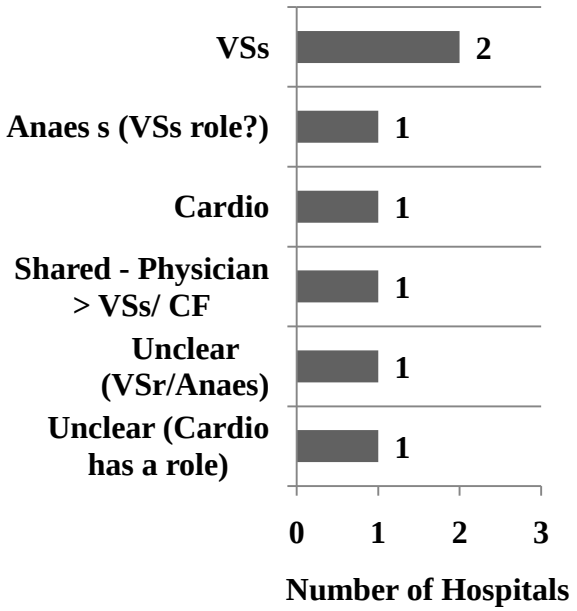

Figure 4.4 Horizontal bar graph showing the most likely clinician responsible for the decision to institute perioperative beta blockade

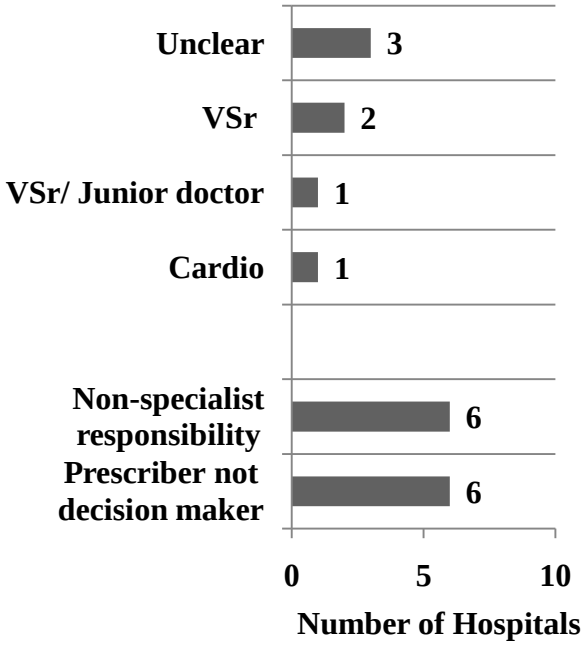

Figure 4.5 Horizontal bar graph showing the most likely clinician responsible for beta blocker prescription

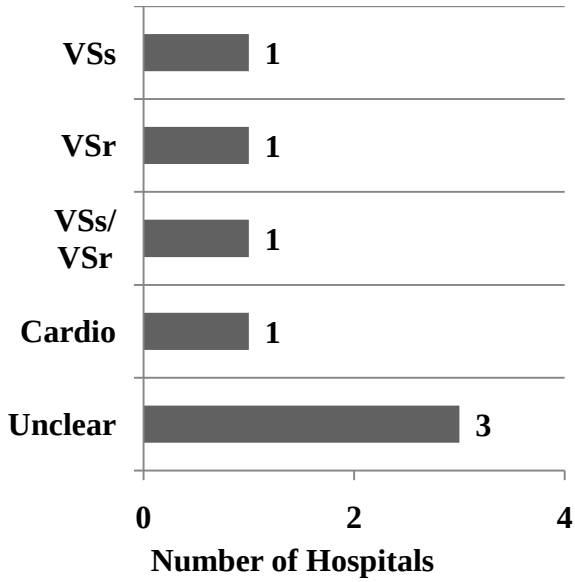

Figure 4.6 Horizontal bar graph showing the most likely clinician responsible for the titration of beta blocker medication before major vascular surgery

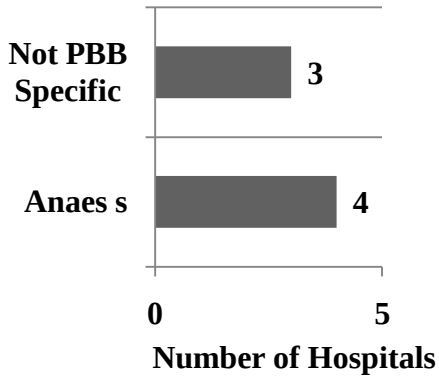

Figure 4.7 Horizontal bar graph showing the most likely clinician responsible for intraoperative beta blocker initiation and titration

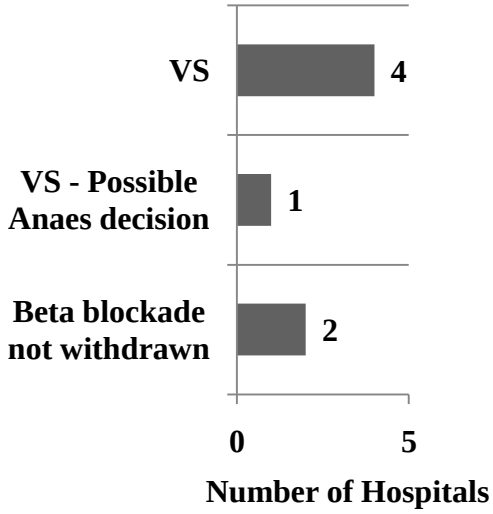

Figure 4.8 Horizontal bar graph showing the most likely clinician responsible for beta blocker withdrawal after vascular surgery

4.2.1.1 Policy development

In South Africa the vascular surgeons have taken the lead role in perioperative patient management, and in policy development, at most of the training facilities. (**Figure 4.2**) The anaesthesiologists control policy at only one of the hospitals (Hospital U), and the extent of the anaesthesiologist's role at another hospital (Hospital C) was unclear.

There is little consistency in clinician roles across other components of practice. However, closer inspection of the data allows the hospitals to be grouped, thus categorising the variable practice across the country.

4.2.1.2 Grouping of hospitals based on similarities in reported clinician responsibilities

The hospitals can be divided into three groups on the basis of similarities in reported control of intended practice.

i. Hospitals reliant on vascular surgeons with limited involvement of other clinicians

Three hospitals (V,A and S) relied on the vascular surgeons for almost all aspects of perioperative management. These three hospitals were characterised by the regular involvement of very few anaesthesiologists, and a comparatively low reported level of interest in vascular anaesthesia. (**Table 4.1**)

The anaesthesiologist at each of these facilities had been involved in an overall management role for less than one year. (**Figure 4.1**) These participants were commonly unsure of the current approach to perioperative beta blocker administration, and perioperative management in general. They played no role in the initiation or titration of beta blockers.

The vascular surgeons were responsible for all aspects of perioperative management at these three hospitals. This included the withdrawal of beta blockade in situations where there was no independent indication for continued therapy.

The vascular surgeon at Hospital V fulfilled the lead role in policy development. The vascular surgeon's opinion is likely to be an accurate reflection of intended practice at Hospital V.

Both the anaesthesiologist and the vascular surgeon indicated that the vascular surgeons controlled current practice at Hospital A. As the only specialist vascular surgeon employed at Hospital A at the time of the study, the opinion of the vascular surgeon in most instances is likely to be an accurate reflection of intended practice.

The anaesthesiologist at Hospital S did not think that there was any policy for perioperative patient optimisation, and hence, added very little to the understanding of current practice. Furthermore, the vascular surgeon, as the sole specialist vascular surgeon at Hospital S, possibly provides a more reliable reflection of intended practice.

ii. Hospitals where both vascular surgeon and anaesthesiologist claimed major roles

At two of the hospitals (Hospital C and U) both the anaesthesiologist and vascular surgeon claimed significant roles in current practice. The poor correlation of opinion is clearly illustrated in **Table 4.4** by the high proportion of grey shaded boxes.

The anaesthesiologists attached to these two hospitals were the only two participants in the study who reported that the vascular surgeons did not have a role in policy development.

Identification of likely intended practice at Hospital C, when participant responses differ, is complicated by inconsistent identification of a dominant clinician. Both participants claimed the

lead role in policy development and overall responsibility for PBB. Appreciation and awareness of cross-discipline responsibility and intended practice was lacking.

The only areas of correlation in participant responses were restricted to anaesthesiologists' responsibility for intraoperative introduction or titration of beta blockers, and the vascular surgeons' responsibility for effecting withdrawal of beta blockade.

The reported intention of the vascular surgeon to initiate beta blocker medication in almost all patients undergoing major vascular surgery implies a reduced opportunity for anaesthesiologist involvement. It was reported that the anaesthesiologist's involvement was partly restricted to the cases deemed to be of the highest risk. A different anaesthesiologist at Hospital C was more regularly involved in the routine management of patients undergoing vascular surgical procedures. Current intended practice is, therefore, unclear.

Hospital U was the only hospital where PBB and perioperative optimisation was controlled by the anaesthesiologists. It was accepted that the anaesthesiologists were responsible for perioperative risk stratification in vascular surgery patients, and that they would decide on appropriate risk reduction strategies for implementation in these patients. However, the clinician responsibilities within each of the aspects of practice were reported differently. The vascular surgeon indicated that a collaborative team derived approach was employed, and claimed that beta blockers were occasionally initiated by the vascular surgeons in some of the more straightforward patients. The anaesthesiologist, on the other hand, specifically denied preoperative introduction of beta blockers by the vascular surgeons. Again, clinician responsibilities were not well defined.

The opinion of the anaesthesiologist probably reflects intended practice. The opinion of the vascular surgeon, where it differs from that of the anaesthesiologist, may reflect a breech of policy, and also highlight a difference in intended and actual practice at this hospital.

iii. Hospitals that relied on the cardiologists with some anaesthesiologist involvement

The vascular surgeons at Hospitals L and R led policy development and also retained their status as the principal treating physician in the perioperative care of patients with vascular disease. However, they were not directly responsible for the decision to commence beta blockers. The cardiologists played the major role in cardiovascular risk assessment and patient optimisation at these two facilities. (**Table 4.4**)

Beta blockers were usually only commenced when there was a medical indication for medication introduction, independent of the potential for benefit to be gained from beta blockade as a risk reduction strategy around the time of major vascular surgery. Therefore, beta blocker medication was generally commenced with the intention of continuing the medication in the long term. PBB per se, was largely restricted to the intraoperative use of beta blockers administered by the anaesthesiologist.

At Hospital L, the anaesthesiologist identified the vascular surgeons, and concurrently the vascular surgeon identified the anaesthesiologists, as the clinicians responsible for aspects of care that neither accepted as being their own responsibility. The paucity of agreement on intended current practice was immediately apparent. (**Table 4.4**) This reflects both a lack of consensus on control of current practice, and the presence of more than one potential pathway to beta blocker introduction.

The opinion of the anaesthesiologist probably has greater value with respect to practices related to intraoperative use of beta blockers and preoperative assessment clinic practices. The opinion of the vascular surgeon may be a more accurate report of aspects of practice related to policy and cardiology referral.

The participants at Hospital R revealed greater agreement for a process that relies on cardiologist referral. The anaesthesiologist involvement in initiation of beta blockers at Hospital R was largely restricted to intraoperative titration. The anaesthesiologists did not initiate beta blockers preoperatively, but did suggest cardiology referral for patients that they believed could gain benefit from beta blockade perioperatively.

The appropriate weight of responses can be interpreted on a situation-specific basis. The fact that the vascular surgeon had been employed at Hospital R for only one year is noteworthy.

4.2.2 Patient selection for perioperative beta blockade

First the dominant determinants of patient selection for PBB as a risk reduction strategy are reported. Important patient risk factors are then addressed. Finally, the contraindications to PBB, and factors that demand careful consideration, are dealt with.

4.2.2.1 Determinants of patient selection

Table 4.5 shows the important determinants of patient selection for PBB before major vascular surgery. Participants reporting on their own practice, having claimed control over this aspect of patient management, are indicated by bold text in the table.

Differences of opinion are once again highlighted by grey shading in **Table 4.5**.

Table 4.5 Table showing the important determinants of patient selection

	Patient risk factors affect selection for PBB	Type of procedure determines need for PBB	Dominant determinants for selection of patients to receive beta blockers preoperatively
V1	Yes	No	*Number of patient risk factors
V2	**Yes**	**No**	***Patient risk factors** ***Baseline physiological values which can be manipulated by beta blockers** ***Other – Total atherosclerotic load**
A1	No	No	*Baseline physiological values which can be manipulated by beta blockers
A2	**Yes**	**Yes**	***Type of procedure – Principle determinant** ***Patient risk factors** ***Baseline physiological values which can be manipulated by beta blockers**
S1	Yes	Yes	Unsure
S2	**Yes**	**Yes**	***Type of procedure – Principle determinant** ***Patient risk factors**
C1	**Yes**	**Yes**	***Type of procedure** ***Patient risk factors** ***Number of patient risk factors** ***Baseline physiological values which can be manipulated by beta blockers**
C2	**No**	**Yes**	***Type of procedure – Only determinant**
U1	**Yes**	**Yes**	***Patient risk factors** ***Number of patient risk factors** ***Baseline physiological values which can be manipulated by beta blockers**
U2	**Yes**	**Yes**	***Type of procedure** ***Other – Nature of disease, Physiological reserve of patient**
L1	**Yes**	**Yes**	***Type of procedure** ***Patient risk factors** ***Number of patient risk factors**
L2	Yes	No	*Patient risk factors
R1	**Yes**	**No**	***Patient risk factors**
R2	Yes	No	***Patient risk factors** *Number of patient risk factors

The anaesthesiologists at Hospitals V,A and S reported their understanding of a vascular surgeon led process. The vascular surgeons at Hospitals L and R reported their understanding of a process under cardiologist control. The anaesthesiologist's intended practice at Hospitals L and R reflect intraoperative introduction of PBB only.

There were three main contributions to the selection of candidates to receive PBB;

i. Patient Risk Factors
ii. Baseline physiological values which can be manipulated by beta blocker therapy
iii. Type of Procedure.

The variability in determinants of patient selection at South African training facilities is illustrated in the horizontal bar graphs that follow. (**Figure 4.9 – Figure 4.11**)

i. Patient Risk Factors

Although participant reports differ at two of the hospitals, where clinician roles are not entirely clear, **Figure 4.9** illustrates the widespread acceptance that patient risk factors were important determinants of patient selection strategies across the country.

Referral to the cardiologist at Hospitals L and R relied upon risk factors or evidence for ischaemic heart disease (IHD), congestive cardiac failure (CCF), or the presence of an arrhythmia. Each of these conditions was viewed as a potential independent indication for beta blocker medication. In keeping with this intended practice, the vascular surgeon at Hospital L, and the anaesthesiologist at Hospital R, indicated that patient risk factors were the sole determinant of the need for beta blocker medication.

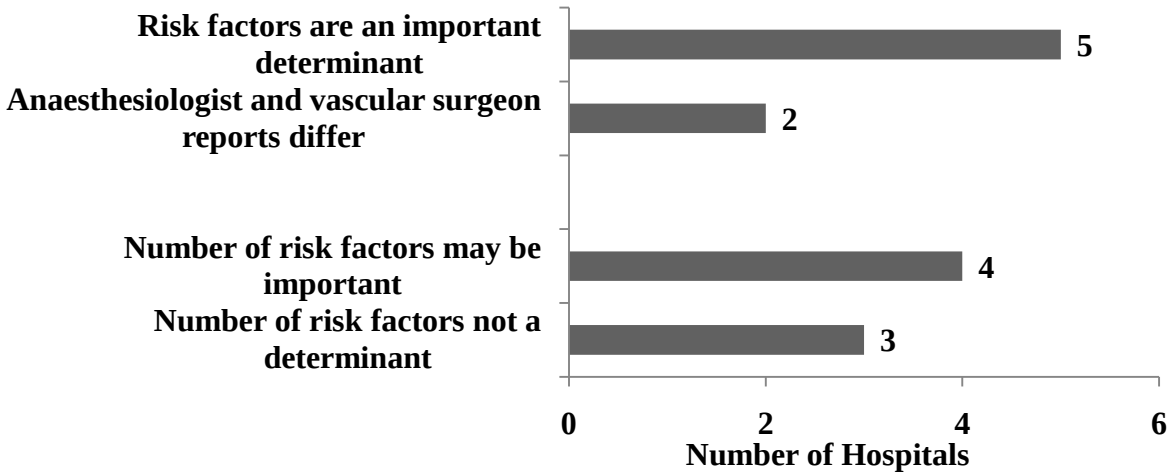

Figure 4.9 Horizontal bar graph showing the importance of patient risk factors, and the number of such factors, in the process of determining candidates for perioperative beta blockade

Figure 4.9 also highlights the variable importance of the number of risk factors in determining patient selection. The three hospitals primarily under vascular surgeon control did not report the number of risk factors as an important tool. In contrast, the number of patient risk factors was an important consideration for the anaesthesiologists involved in patient selection. The vascular surgeon at Hospital R was the only vascular surgeon who attributed value to the number of risk factors in the decision to commence beta blocker medication. However, this reflects the approach of the cardiologist at Hospital R, rather than the participant's own practice.

ii. Baseline physiological values which can be manipulated by beta blocker therapy

As shown in **Figure 4.10**, heart rate control was of variable importance to clinicians in patient selection for PBB. It was not the sole determinant of selection at any hospital. Control of heart rate was an important determinant at two of the hospitals, and was also a feature in the management of patients under the care of the anaesthesiologists at two of the hospitals where clinician roles were unclear.

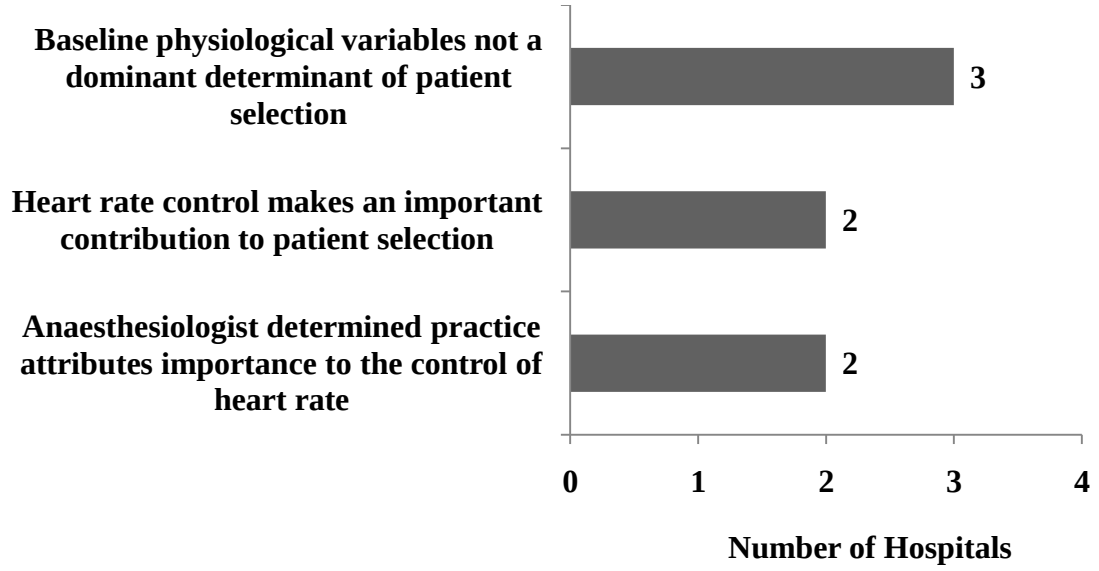

Figure 4.10 Horizontal bar graph showing the importance of physiological variables in patient selection for perioperative beta blockade

iii. Type of procedure

Figure 4.11 illustrates the variable importance attributed to the type of procedure in patient selection at hospitals across South Africa.

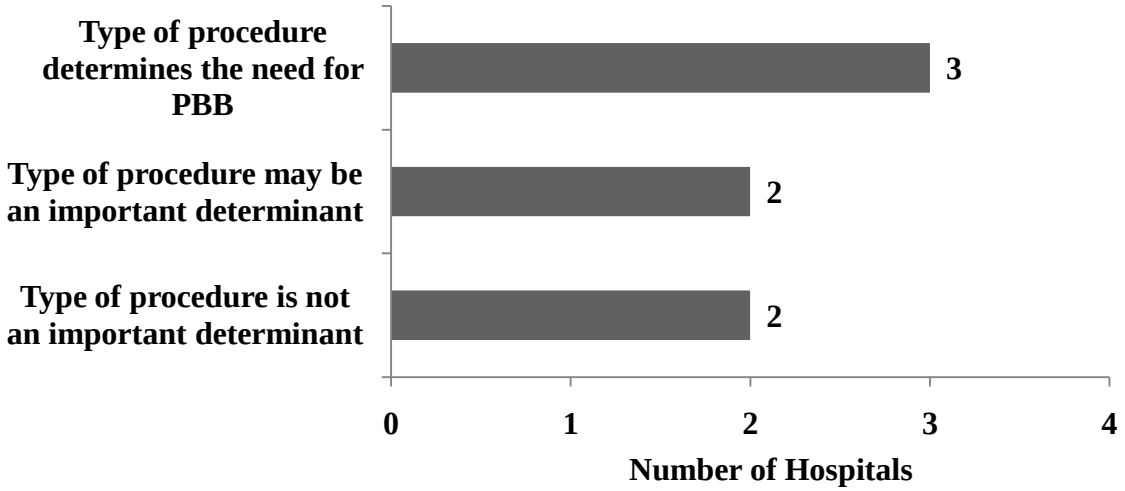

Figure 4.11 Horizontal bar graph showing the importance of the type of procedure in deciding whether to introduce perioperative beta blockade at South African training facilities

The type of procedure was reported as the principal determinant of patient selection by three of the vascular surgeons. The vascular surgeons controlled patient selection at two of these three hospitals (Hospitals A and S). Practice at the remaining facility (Hospital C) was less clear. The vascular surgeon claimed that the type of procedure was the sole determinant of a need to introduce beta blockade. The anaesthesiologist reported a more selective approach, with the type of surgery used as an aid in the decision, rather than an absolute indication for PBB.

The type of procedure may be of major importance in patient selection for PBB at two further hospitals (Hospitals U and L). However, it was not the principal determinant at either of these hospitals. At Hospital U it played a role in how patients were assessed preoperatively. The anesthesiologist's intention was to distinguish between targeting prevention of perioperative myocardial infarction (PMI), and the perceived need to optimise myocardial performance. This was a distinction made on the basis of infrainguinal versus suprainguinal major vascular procedures. At Hospital L, the possibility of the type of procedure having an impact on the decision to introduce PBB was based only on the occasional initiation of beta blockers by the anaesthesiologists. The anaesthesiologist involvement in the decision was restricted to the intraoperative period, and to a minority of cases referred onto the preoperative anaesthetic assessment clinic. In this setting, the type of procedure was an important determinant of an overall risk assessment.

There was agreement between the anaesthesiologist and vascular surgeon that the type of procedure was not a dominant factor in the decision to institute PBB at the remaining two hospitals (Hospitals V and R).

The indications for beta blockade, when assessed by the cardiologist at Hospitals L and R, were assessed independent of the background of proposed major vascular surgery.

4.2.2.2 Important patient risk factors

Table 4.6 identifies the patient risk factors that were potential targets for intervention with preoperative introduction of beta blocker medication. It reflects the opinion on current practice of the nine participants who claimed involvement in the introduction of beta blockers perioperatively. Their responses are shown in bold text in the table.

There were five participants not certain of the factors that promoted the use of beta blockers at their hospital. The anaesthesiolgists at Hospitals V and A, and the vascular surgeon representing Hospital R, identified the patient risk factors that they would use to aid selection of candidates for PBB, in the event that they been responsible for this aspect of practice. The anaesthesiologist representing Hospital S indicated that safety concerns prevented the use of PBB as a risk reduction strategy. The vascular surgeon from Hospital L highlighted the risk factors that prompted cardiology referral. The anaesthesiologists representing Hospitals L and R reported their own approach to introduction of PBB, rather than the approach of the cardiologist at their respective facilities.

The grey shading in **Table 4.6** is used to draw attention to the similarity of approach recommended by the anaesthesiologists. The difference in responses between anaesthesiologists and vascular surgeons are clearly evident.

Table 4.6 Table showing important risk factors in patient selection

	Current beta blockade	Inducible myocardial ischaemia	Unacceptable heart rate	Revised cardiac risk index (RCRI)						Other
				Type of Procedure	IHD	CCF	CVA	DM on insulin	Renal dys-function	
V1	Yes	Yes	-	Yes	Yes	Yes	Yes	Yes	Yes	-
V2	**Yes**	**-**	**>90 bpm**	**-**	**Yes**	**-**	**-**	**-**	**-**	**Hypertension**
A1	Yes	Yes	-	Yes	Yes	Yes	Yes	Yes	Yes	-
A2	**Yes**	**-**	**>70 bpm**	**Yes**	**-**	**-**	**-**	**-**	**-**	**Hypertension, Obesity**
S1	Perioperative beta blockade not practiced.									
S2	**Yes**	**-**	**Target 60-80 bpm**	**Yes**	**Yes**	**-**	**-**	**-**	**-**	**Hypertension, Family History IHD**
C1	**Yes**	**Yes**	**Not specified**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Hypertension, Family History IHD**
C2	**Beta blockers administered to all patients undergoing major vascular surgery**									
U1	**Yes**	**Yes**	**Not specified**	**Yes**	**Yes**	**Yes**	**-**	**Yes**	**Yes**	**-**
U2	**Yes**	**Yes**	**-**	**Yes**	**-**	**-**	**-**	**-**	**-**	**-**
L1	**Yes**	**Yes**	**>90 bpm**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**-**
L2	Yes	Yes	Not specified	-	Yes	-	-	Yes	-	-
R1	**Yes**	**Yes**	**>80 bpm**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Hypertension**
R2	Yes	Yes	Not specified	-	Yes	-	-	Yes	Yes	-

(Grey shading highlights similarities in the approach of anaesthesiologists. Bold text identifies the participants who claimed a role in policy development.)

Figure 4.12 illustrates the most important patient risk factors. The figure also highlights an interesting difference of intended approach between anaesthesiologists and vascular surgeons at South African training facilities.

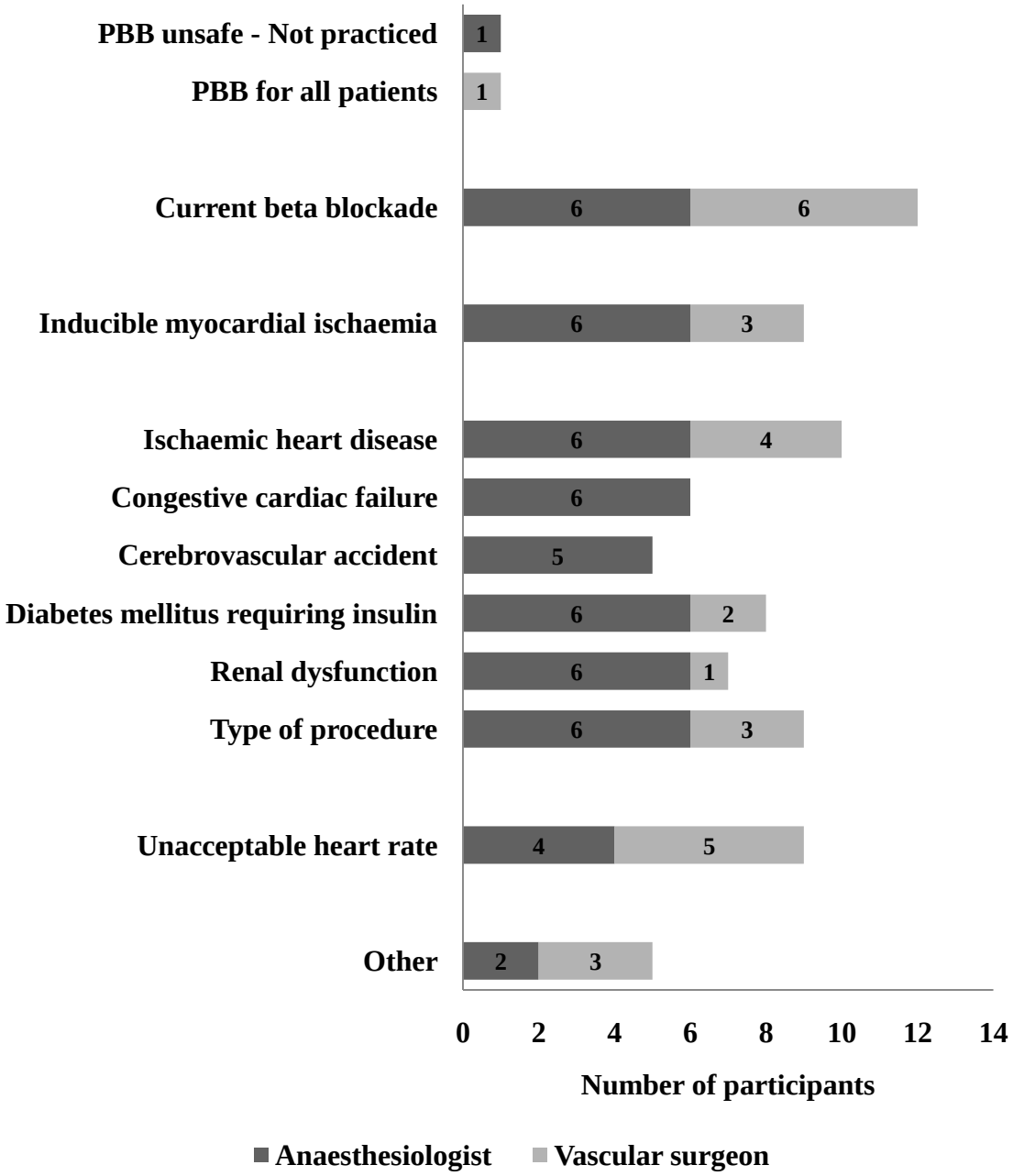

Figure 4.12 Horizontal bar graph illustrating the patient risk factors that make a contribution to the decision to introduce perioperative beta blockade

The opinion of the anaesthesiologist at Hospital S (PBB unsafe and not practiced) and the intended practice of the vascular surgeon at Hospital C (PBB for all patients undergoing major vascular surgery) represent the extremes of a variety of responses recorded from the participants included in the study. Despite the marked variability in intended practice, a few consistencies are worth highlighting.

The continuation of beta blocker medication, in the absence of limiting haemodynamic compromise, was an accepted recommendation. The introduction of beta blockers in patients with inducible myocardial ischaemia, or a history of ischaemic heart disease (IHD), was also widely supported. However, these risk factors were not uniformly supported as indications to commence beta blockers by all of the vascular surgeons.

The actual or recommended approaches of each of the anaesthesiologists were very similar. The anaesthesiologists attributed importance to risk factors included in the Revised Cardiac Risk Index (RCRI). However, the handling of congestive cardiac failure (CCF) and cerebrovascular accident (CVA), as risk factors, was inconsistent. The individual components of the RCRI were sometimes deemed to be of greater importance than just the number of these criteria.

Of the risk factors not included in the RCRI, the targeting of an unacceptable heart rate was a common recommendation for introduction of beta blockers. Control of heart rate was a stronger focus for the vascular surgeons than individual components of the RCRI. The rate that would promote initiation of medication was variable, and commonly not specified despite specific enquiry.

None of the participants indicated that age was an indication for beta blockade, neither as part of a risk index, nor as an individual risk factor.

4.2.2.3 Contraindications to PBB and situations that demand careful consideration

Data was collected addressing patient characteristics that demand careful consideration or avoidance of beta blocker medication around the time of major vascular surgery. Again the paired participant responses were inconsistent. The responses of all participants are important irrespective of clinician roles in the introduction of beta blockers, because the presence of a contraindication to beta blockade, or the need for careful consideration, should supercede any intended approach of another clinician. The anaesthesiologist at Hospital S reported that PBB was not specifically practiced. Therefore, a total of 13 participants gave an indication of situations in which careful consideration or avoidance of beta blockade was considered prudent.

The data are grouped under three themes;

i. Emergency surgery
ii. Potential major adverse effects of beta blockers
iii. Other potential adverse interactions with beta blockers.

Figures 4.13 – 4.16 illustrate the degree of concern reported by the participants for introducing beta blockers under a variety of circumstances.

i. Emergency Surgery

Figure 4.13 shows the extent of participant concern about the safety of introducing beta blocker medication before emergent major vascular surgery. Only two of the participants did not indicate that emergency surgery had an impact on their decision to commence beta blockers perioperatively. Three participants believed that emergency surgery was a specific reason not to commence beta blockers.

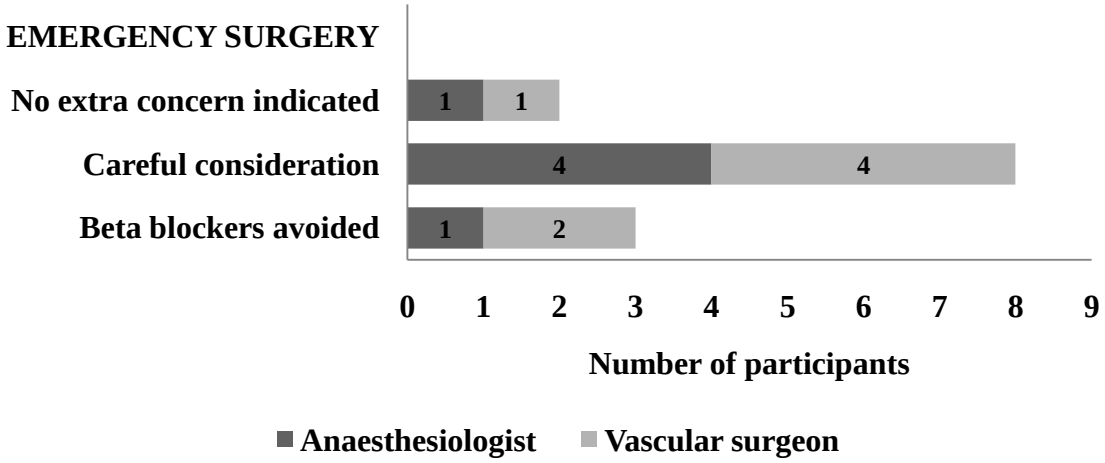

Figure 4.13 Horizontal bar graph illustrating the extent of participant concern about the safety of introducing beta blocker medication before emergent major vascular surgery

ii. Potential major adverse effects of beta blocker medication

Deciding whether beta blocker medication was likely to be safe in patients with compromised cardiovascular or respiratory function was important. Responses for the impact that an abnormal cardiovascular or respiratory system had on the decision to commence beta blockers are summarised in **Figure 4.14** and **Figure 4.15**.

- **Cardiovascular effects**

The most common recommendations for the avoidance of beta blockade were due to slow heart rate (10 participants) and low blood pressure (9 participants). The identified heart rate that precluded administration of beta blockers was not consistent, but the anaesthesiologists generally accepted lower heart rates than the vascular surgeons. Three of the anaesthesiologists, each with a responsibility for intraoperative beta blocker initiation and titration, still considered careful titration of beta blocker medication under these conditions. Their practice was highly selective and the patient response was closely monitored.

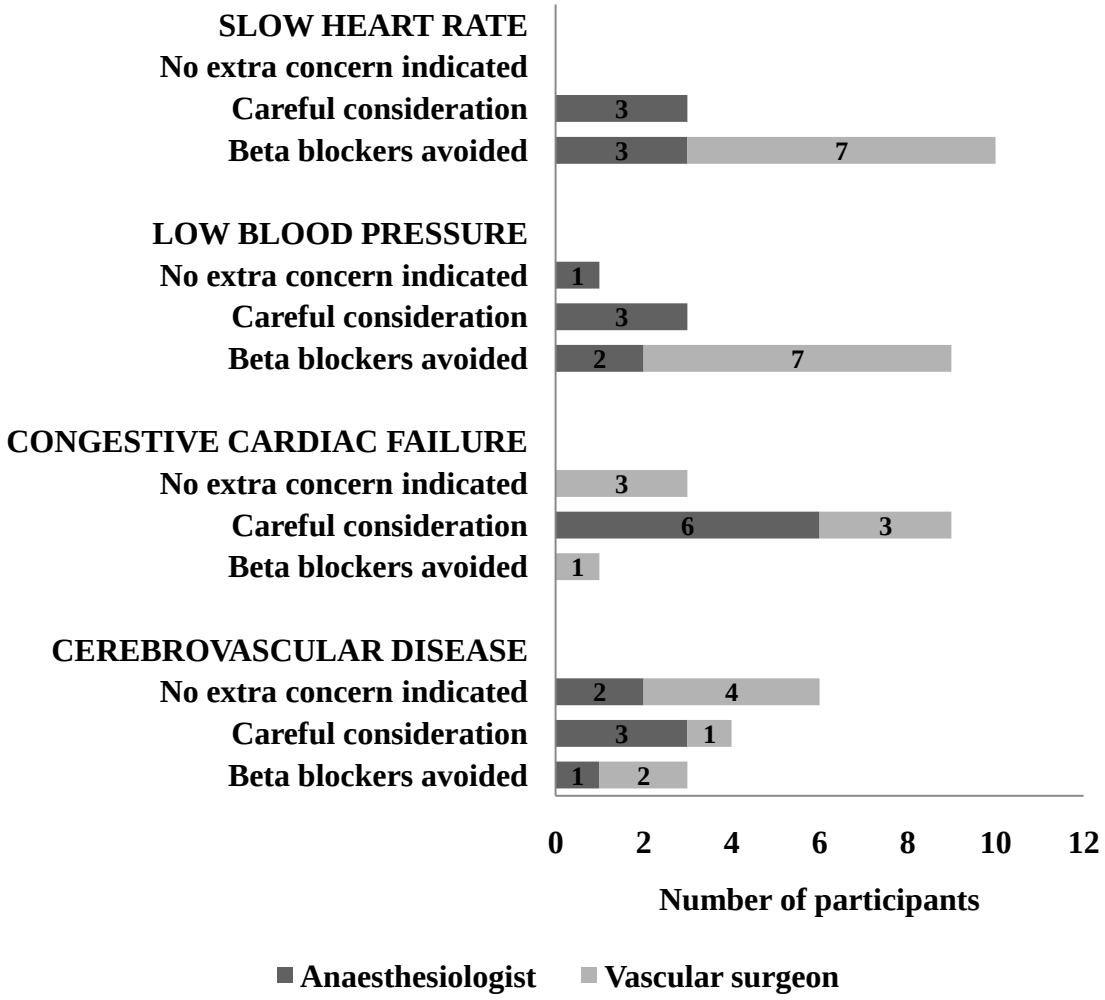

Figure 4.14 Horizontal bar graph illustrating the effect that abnormalities of the cardiovascular system had on the decision to introduce beta blockers before major vascular surgery

The need for careful consideration was commonly indicated as being necessary for patients with congestive cardiac failure (CCF). All of the anaesthesiologists recognised a need for careful consideration before the introduction of beta blockers in patients with CCF. Three of the anaesthesiologists indicated that even a history of CCF warranted careful consideration. Only one participant believed that beta blockers were contraindicated in the setting of CCF.

A history of cerebrovascular disease was highlighted as a contraindication to PBB by three participants, and also as a condition requiring careful consideration by a further four participants.

- **Respiratory effects**

Careful consideration before commencing beta blockers in patients with asthma or chronic obstructive respiratory disease (COPD) was common practice. Only one participant did not indicate the need for careful consideration in patients with asthma or COPD.

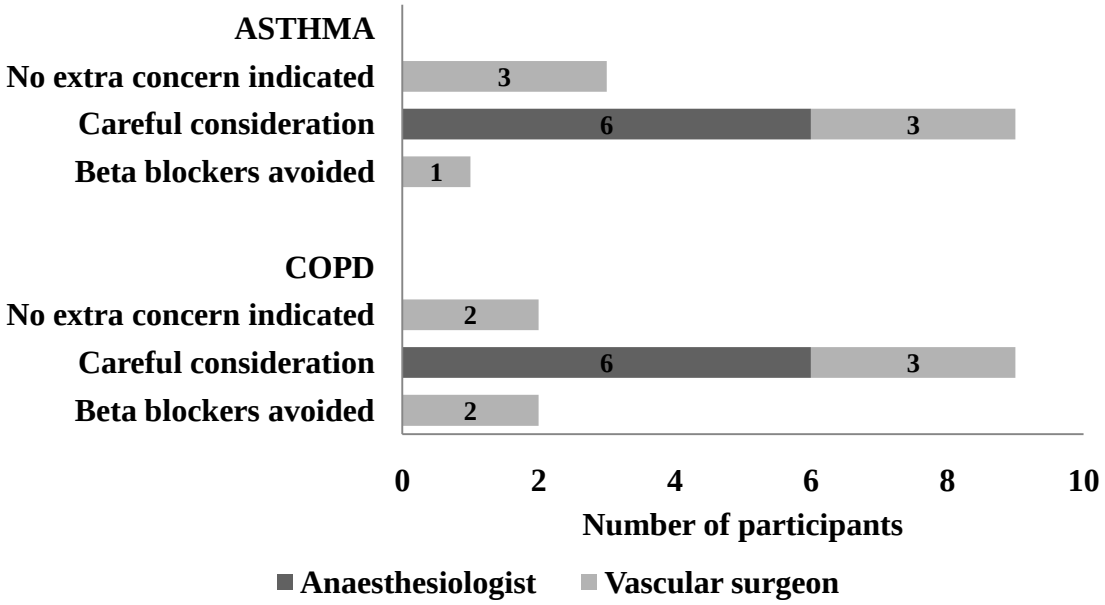

Figure 4.15 Horizontal bar graph illustrating the effect that respiratory disease had on the decision to introduce perioperative beta blockade

Complete avoidance was not commonly recommended. None of the anaesthesiologists recommended routine avoidance. The severity and reversibility of airway obstruction were important considerations. There was a difference in the way asthma and COPD were viewed by three of the vascular surgeons. Two had a greater degree of concern for COPD than for asthma.

iii. Other potential adverse interactions of beta blocker medication

Few participants reported that the presence of sepsis or diabetes mellitus, advanced age, or the concurrent use of calcium channel blocker (CCB) medication, were important reasons for additional concern. The extent of their concern is shown in **Figure 4.16**.

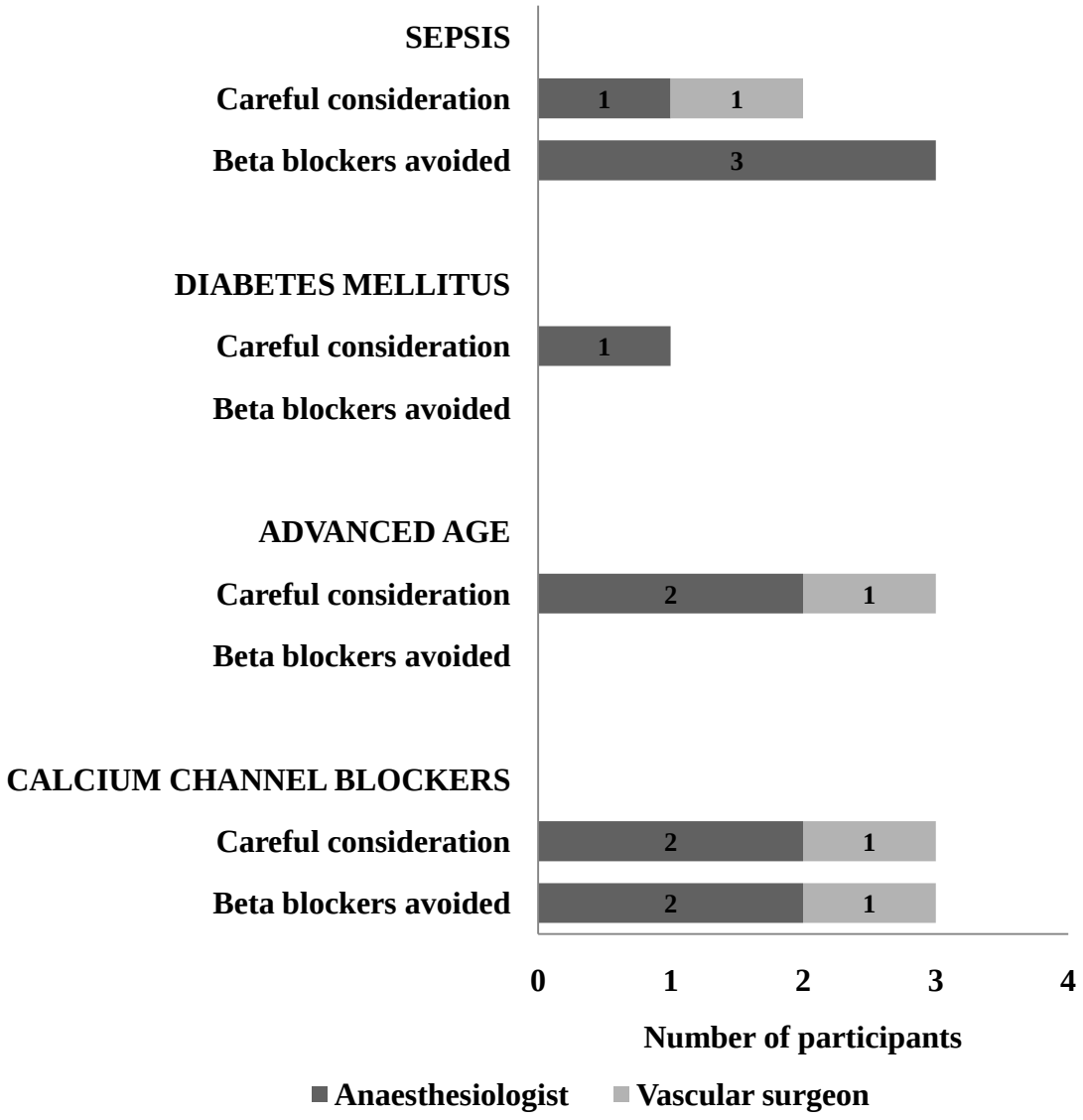

Figure 4.16 Horizontal bar graph illustrating the effect that sepsis, diabetes mellitus, advanced age and calcium channel blocker medication had on participant concern for commencing beta blocker medication

- **Sepsis**

Three participants believed that beta blockers were to be avoided in patients with systemic sepsis. Only one of these participants had concerns about the use of PBB in the setting of localised sepsis.

- **Diabetes Mellitus**

Only one participant identified the potential adverse effects of beta blockade on glycaemic control as a cause for careful consideration before selecting patients to receive beta blockers perioperatively.

- **Advanced age**

The implementation of PBB in elderly patients was not specifically avoided, and only three participants viewed advanced age as a cause for careful consideration in the selection of patients.

- **Drug interactions**

Three participants indicated that the use of calcium channel blocker (CCB) medication precluded the use of beta blockers. A further three participants indicated that the concomitant use of these medications called for careful consideration.

No other drug interactions were highlighted as a cause for additional consideration.

4.2.3 Specifics of perioperative beta blockade

4.2.3.1 Frequency of perioperative beta blockade and intraoperative use of beta blockers

Table 4.7 shows responses for the frequency with which PBB as a risk reduction strategy was utilised at South African training facilities for vascular surgery. Where responses differed between participants representing the same hospital, the response that is most likely to reflect practice is indicated with bold text. Areas of inconsistency in paired participant responses are highlighted by grey shading. The marked lack of consistency within hospitals across the country is clearly demonstrated by the extent of grey shading.

Table 4.7 Table showing the participant responses for the frequency of perioperative beta blockade and intraoperative beta blocker use

	Frequency of perioperative beta blocker use	Intraoperative use of beta blockers
V1	Occasional	**Very rare (<1%) Not for PBB**
V2	**Regular (Used to be always)**	**Very rare (<1%) Not for PBB**
A1	Almost always in the absence of a contraindication	**Very rare (<1%) Not for PBB**
A2	**Regular (Used to be always)**	Unsure – (Very rare/ Sometimes)
S1	Unsure - Not used as perioperative risk intervention	**Very rare (<1%) Not for PBB**
S2	**Regular (70%)**	Never
C1	Regular	**Unsure -Liberal use recommended**
C2	Almost always in the absence of a contraindication	Sometimes (<5%)
U1	Occasional	**Regular (<25%)**
U2	Regular	Very rare (<1%) Under anaesthesiologist control
L1	Regular	**Regular (<33%)**
L2	Occasional (Less than10%) Not used as perioperative risk intervention	Unsure – (Very rare/ Sometimes)
R1	Regular	**Regular (Up to 30%)**
R2	Occasional (Not common) Not used as perioperative risk intervention	Unsure – (Very rare/ Never)

(The response that is most likely to reflect actual practice is indicated by bold text. Inconsistent responses within a hospital are highlighted by grey shading.)

Perioperative beta blockade is practiced at all training facilities across South Africa. However, it is unclear how frequently this occurs. One participant from each hospital indicated that the practice occurred regularly. However, no two participants from the same hospital were in agreement on the frequency of the intervention.

The vascular surgeon led practice at Hospitals V, A and S supported a proactive approach to PBB.

The lack of consistency in the reports of the participants representing Hospitals C and U make it difficult to draw any firm conclusions. The anaesthesiologists at these two hospitals reported a more selective approach.

A cardiology referral based, restrictive approach to the introduction of beta blockers was reported by the vascular surgeons at Hospitals L and R. Both participants explained that patients only received beta blocker medication if there was an independent medical indication for beta blocker use. In this setting the intention was to continue beta blocker medication in the long term. The anaesthesiologists at Hospitals L and R reported titration of beta blockers intraoperatively. The vascular surgeons were unaware of the extent of their involvement.

PBB was initiated or titrated during surgery by the anaesthesiologists at four of the facilities. Intraoperative beta blocker use at the other facilities was restricted to very few cases, and was not initiated specifically as a risk reduction strategy.

4.2.3.2 Beta blocker medication

The anaesthesiologist at Hospital S did not believe that PBB was being practiced. The vascular surgeon representing Hospital R was unsure about the medications and details of the

cardiologists' practice. Reports on the beta blocker medication commonly used in the perioperative period, and the reasons for the choice of the remaining twelve participants, are summarised in **Table 4.8**.

All of the hospitals included in the study prescribed oral atenolol when implementing PBB. Availability of the medication was the chief reason for the choice, and the availability of atenolol was commonly attributed to the favourable cost of the medication. Two participants cited favourable pharmacodynamic properties of atenolol as a reason for the choice, but they failed to mention whether they believed these favourable effects were more pronounced with the use of atenolol when compared with other beta blockers.

Two institutions imported intravenous atenolol for intraoperative use. Three other agents were sometimes used for intraoperative titration, or in the immediate perioperative period. Carvedilol was sometimes prescribed, but its use was largely under the control of the cardiologists. Labetolol (4 participants) and esmolol (5 participants) were the other agents only occasionally used.

Bisoprolol and metoprolol may have advantages, but they were not available for use in the state health sector. Although not specifically asked, six participants indicated that they would prefer to use another drug not available to them for use at their hospital.

4.2.3.3 Initial prescription of beta blockers

The initial prescription of beta blockade was variable, both within each hospital, and in general across the country. The extent of grey shading in **Table 4.8** highlights the lack of consistency in the anaesthesiologist and vascular surgeon reports at each of the hospitals.

Table 4.8 Table showing the agents used, the reason for the choice of agent, and the initial prescription

	Most commonly used beta blocker and the reason for its use	Initial Prescription
V1	**Atenolol (po) -** Availability + Other (Always been used) **Esmolol (iv) -** Intraoperative titration but not for PBB **Carvedilol (po)** (Cardiology)	Unsure Low dose followed by titration
V2	**Atenolol (po)** - Availability + Cost **Bisoprolol (po)** (Private Sector) - Favourable PK/PD + Evidence of benefit in the literature	**Low dose followed by titration (Atenolol 12,5mg po od/ Bisoprolol 2,5mg po od)**
A1	**Atenolol (po)** - Availability	Patient specific adjusted dose followed by titration (Atenolol 12,5-100mg po dly)
A2	**Atenolol (po)** - Availability	**Standard dose followed by titration (Atenolol 25mg po od)**
S1	**Esmolol (iv) -** Intraoperative titration but not for PBB	Not Practiced
S2	**Atenolol (po)** - Availability **Labetolol (iv) -** Control of BP in ICU **Metoprolol (po/iv)** (Unavailable) - Most studies used this medication	**Low dose followed by titration (Atenolol 25mg po bd)**
C1	**Atenolol (po/iv) -** Availability + Cost + Favourable PK (Long duration of action) **Bisoprolol (po)/ Metoprolol (po/iv)** (Private Sector) - Current practice not based on evidence - These agents may be better	**Low dose followed by titration**
C2	**Atenolol (po)** - Availability + Cost + Favourable PD	**Standard dose (Atenolol 25mg po od)**
U1	**Atenolol (po)** – Availability (Not convinced it is the correct agent to use) **Labetolol (iv)** (Intraoperative titration) - Only available intravenous agent with beta blocker activity **Carvedilol (po) -** Favourable PD (Remodelling) **Metoprolol (po/iv)** (1st choice- unavailable) **-** Favourable PK/PD + Evidence from the literature	**Standard dose (Atenolol 50mg po stat on morning of surgery)**
U2	**Atenolol (po)** - Availability + Cost **Labetolol (iv) -** Control of BP in ICU	**Standard dose followed by titration (Atenolol 25-100mg po dly) (Only if time allows)**
L1	**Atenolol (po) -** Availability + Favourable PD **Labetolol (iv) -** Availability (Lack on Atenolol iv) + Familiarity **Esmolol (iv) -** Favourable PK - Intraoperative Titration **Bisoprolol (po)** (Private Sector)	**Patient specific adjusted dose followed by titration (Only if time allows)**
L2	**Atenolol (po)** - Availability + Cost **Esmolol (iv)** **Carvedilol (po)** (Cardiology) **-** Favourable PD – CCF	Low dose followed by titration (Only if time allows)
R1	**Atenolol (po/iv) -** Availability **Esmolol (iv) -** Favourable PK – Intraoperative Titration **Carvedilol (po)** (Cardiology) **Metoprolol (iv)** (Unavailable) **-** Favourable PK	Unsure – Patient specific adjusted dose followed by titration (Cardiologist)
R2	Unsure	Unsure (Cardiologist)

In **Table 4.8** grey shading highlights inconsistent responses between paired participants, and the following abbreviations apply:

po – per os

iv –intravenous

PK – pharmacokinetics

PD – pharmacodynamics

mg – milligram

od – once daily

bd – twice daily

stat – term derived from the latin word ‘statum’ meaning immediately

dly – daily

BP – blood pressure

ICU – intensive care unit

Among the nine participants that claimed direct involvement in the initiation of PBB, standard initiation doses (4 participants) were more commonly reported than low initiation doses (3 participants) and patient specific adjusted doses (2 participants). The reported initial prescription was consistent at only one of the hospitals (Hospital V). However, the anaesthesiologist was not certain of current practice at that hospital.

4.2.3.4 Duration of beta blockade before surgery, the intention to titrate medication, and the targets of titration

Table 4.9 shows the widespread lack of consistency in paired participant responses (indicated by grey shading). It also highlights the reality of not achieving that which was considered to be ideal practice, and the variable and often ill-defined targets of titration.

The anaesthesiologist and vascular surgeon did not share exactly the same opinion, on actual or ideal duration of beta blocker therapy before surgery, at any of the hospitals.

Longer duration of beta blockade before surgery was thought to be beneficial, but delaying surgery for preoperative titration was not standard practice. Only two participants claimed that surgery was delayed to allow optimal titration. The reports of these two vascular surgeons were not shared by the anaesthesiologists at either of these hospitals.

All of the participants agreed that beta blockers should ideally be commenced more than one week before surgery (range: 1-6 weeks). However, this probably only occurred at two of the hospitals. The vascular surgeon at one of these hospitals was the only participant who indicated that ideal and actual practice was matched with respect to the timing of beta blocker therapy. The anaesthesiologist believed that surgery was not specifically delayed to allow potential benefits related to duration of beta blocker therapy, but that the duration of therapy before surgery was an entirely fortuitous consequence of logistical delays within the hospital system.

The introduction of beta blocker medication on the day of surgery, or less than one week before surgery was not uncommon.

Table 4.9 Table showing participant responses for ideal and reported actual duration of beta blocker medication before surgery

	Duration of beta blockade before surgery		Titration of beta blockers intended	Surgery delayed to allow titration	End point targets of titration
	Ideal practice	**Actual practice**			
V1	2 weeks	3-5 days	Yes	Unsure	Unsure (Managed by VS) Personal Practice: HR<60bpm
V2	4 weeks (Longer duration is better)	2-4 weeks	Yes	No	HR 70-90bpm
A1	At least 2 weeks	2-4 weeks	Yes	No	Unsure (Managed by VS)
A2	1-2 weeks with titration	7-10 days	Yes	Yes	HR 60-70bpm
S1	>1 week	Perioperative beta blockade not practiced			
S2	4-6 weeks	<1 week	Yes	No	HR 60-80bpm
C1	4-6 weeks	<1 week	Yes	No	HR 60-70bpm Not done effectively Proactive intraop
C2	Unsure - 1-2 weeks	Often day before surgery (Up to 1 week)	No	No	Unsure (Managed by anaesthesiologist)
U1	1-2 weeks	Administered on the morning of surgery (4-6 weeks before suprainguinal procedures)	No	No	Clinically acceptable heart rate or resolution of ischaemia
U2	2-4 weeks	1-2 days	Yes	No	Patient specific absolute heart rate
L1	2-4 weeks	<1 week	Yes	No	Limited heart rate response to exercise
L2	No fixed time Await titration	No fixed time Await titration	Yes	Yes	Unsure (Managed by anaesthesiologist)
R1	Longer duration is better. Still beneficial if given acutely	Day before surgery	Yes	Unsure	Unsure (Managed by cardiologist) Personal Practice: Resting HR 60-80bpm Titrate to ST changes and Cardiac Output
R2	>4 weeks	Few days before surgery	Yes	Unsure	Unsure (Managed by cardiologist)

(The intention to titrate medication, the targets of such titration, and whether surgery was delayed until targets were achieved, are also shown)

Most of the participants conceded that titration was suboptimal or even non-existent. The anaesthesiologists representing three of the hospitals had access to select groups of at risk patients, weeks before major vascular surgery, at a preoperative anaesthetic assessment clinic. Two participants, each with an important role in PBB, indicated that there was no intention to titrate beta blockers before surgery.

End point targets in the titration of beta blockade were inconsistent. Six participants indicated that they were unsure of the targets of titration. Absolute heart rate targets over a wide range (60-90 bpm) were advocated. Patient specific heart rate and a clinically acceptable heart rate were further ill-defined targets that were recommended. The conditions under which the heart rate was measured, varied from a limited response to exercise, to heart rate measured at rest.

4.2.3.5 Continuation of beta blocker medication after surgery and the manner in which medication was withdrawn

Aspects of beta blocker withdrawal after major vascular surgery are shown in **Table 4.10**. The participant responses that most likely represent intended practice are identified by bold text. Inconsistencies within a hospital are identified by grey shading.

The recommended duration for continuing beta blockers when used as a risk intervention varied, and was often poorly defined. None of the anaesthesiologists could accurately identify how beta blockade was withdrawn.

Therapy was abruptly withdrawn at all facilities, except Hospitals L and R. At these two hospitals medication was continued, because beta blockade was only initiated in patients with long term indications for beta blocker therapy. One participant believed that the medication

should be tapered before being stopped completely. Another participant questioned the potential benefit of withdrawing the medication gradually, and believed that tapering would be impractical.

The most likely practice at Hospital U was unclear.

Table 4.10 Table showing participant reports on when and how beta blockers were withdrawn after surgery

	Duration of continued beta blocker therapy after major vascular surgery	Method of withdrawal of beta blocker medication
V1	Unsure - No recommendation	Unsure
V2	**4 weeks Not done well, relies on outpatient prescription on hospital discharge**	**Abrupt withdrawal Tapering is of questionable benefit and impractical**
A1	Unsure	Unsure
A2	**On discharge from hospital (Previously continued indefinitely)**	**Abrupt withdrawal**
S1	PBB Not Practiced	
S2	**<72 hours On return to ward from High Care/ ICU**	**Abrupt withdrawal**
C1	Usually continued long term Reviewed at 4 weeks post hospital discharge	Tapered
C2	**Reviewed at 4 weeks post hospital discharge**	**Abrupt withdrawal**
U1	7 days In absence of indication to continue long term	Abrupt withdrawal
U2	Up to 6 weeks Relies on referral hospital continuation of medication - Not an area of focus	Unsure – Defer to anaesthesiologist
L1	Unsure - **Continue long term**	**Beta blockers not withdrawn**
L2	**Continue long term** Very few without indication for continued use	**Beta blockers not withdrawn**
R1	Unsure – **Continued long term**	**Beta blockers not withdrawn**
R2	**Continued long term**	**Beta blockers not withdrawn**

(Bold text identifies most likely practice. Grey shading highlights inconsistent responses between paired participants.)

4.2.3.6 Additions to standard care related to the decision to initiate PBB

The participants indicated that the introduction of beta blockers alone made no difference to the routine level of care or monitoring that the patient received. (**Figure 4.17**)

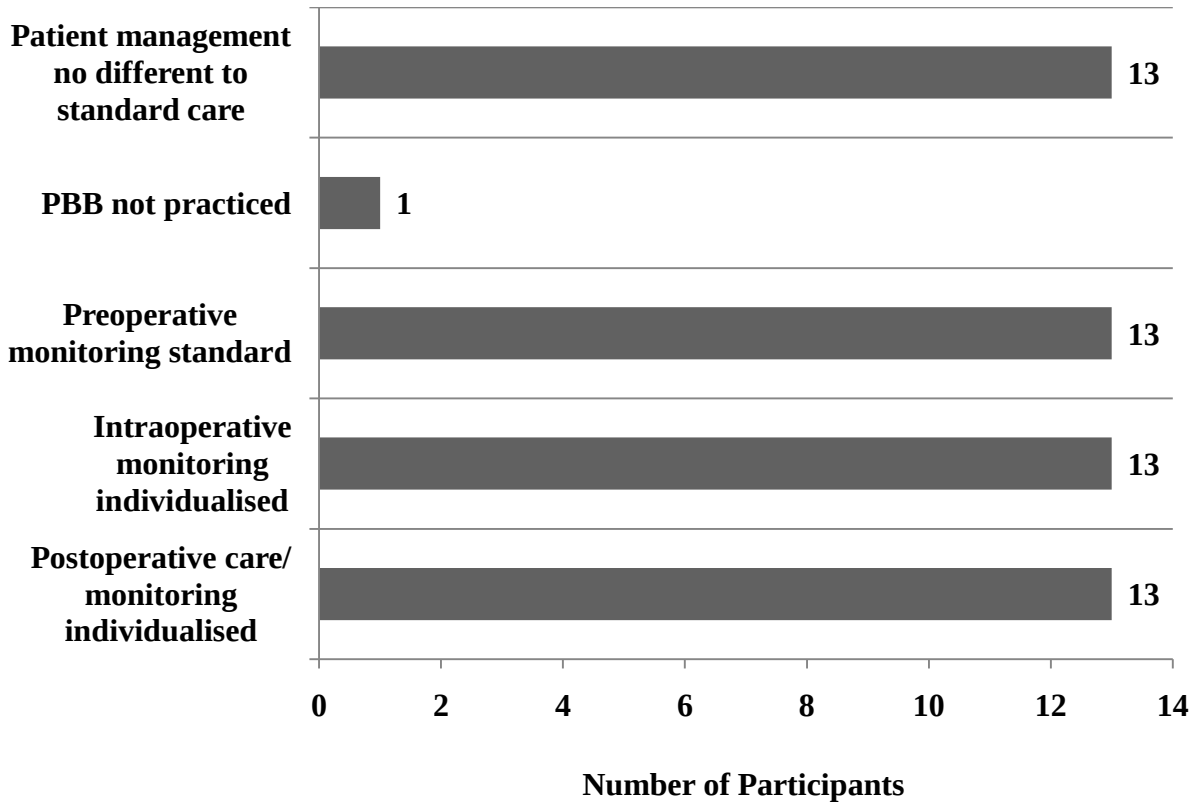

Figure 4.17 Horizontal bar graph illustrating the lack of a change in the way that patients were managed and monitored when perioperative beta blockade was implemented

The simple measurements of blood pressure and heart rate were not more frequently assessed. Patients commenced on beta blockers were not routinely nursed at a higher level of dependency. There was neither a specific change in anaesthetic technique, nor a lower threshold for invasive monitoring in patients selected for PBB. The decision to monitor invasively, related to the physiological status of the patient and extent of the planned procedure, rather than the use of beta blocker medication. Patients were not hospitalised for a longer period, preoperatively or

postoperatively, to facilitate the safe introduction, titration or withdrawal of beta blocker medication. The patients who received PBB were not followed up at a clinic sooner than would ordinarily have been arranged.

Figure 4.18 shows the intention for routine use of statin medication (HMGCoA reductase inhibitors) in patients requiring major vascular surgery, the frequent prescription of aspirin, and an apparent difference in focus between anaesthesiologists and vascular surgeons across the country.

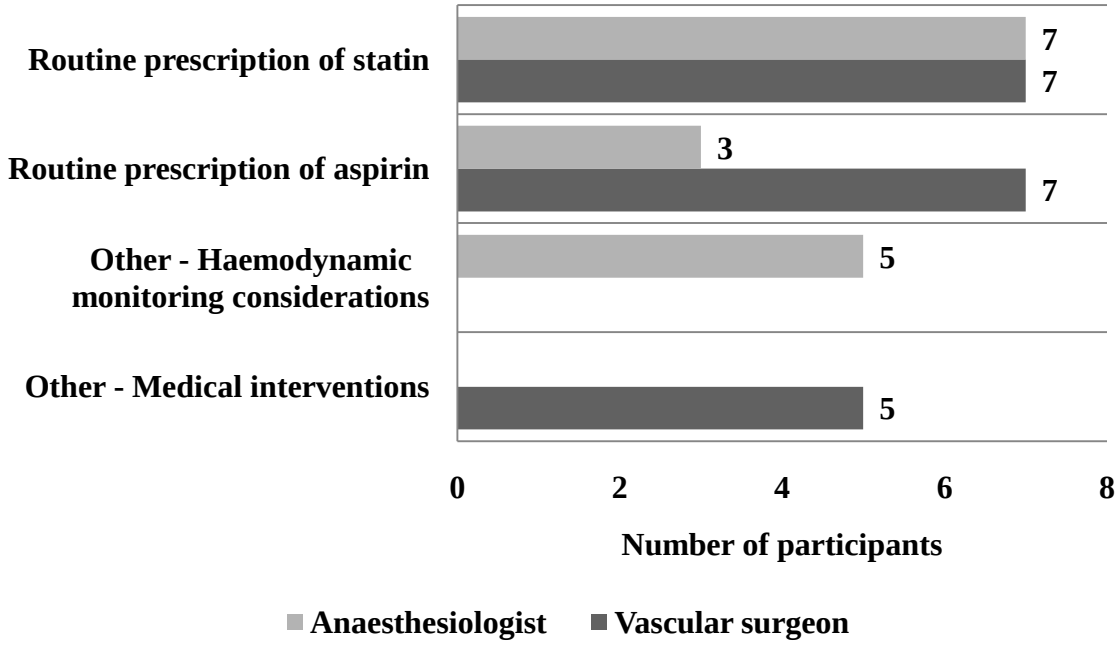

Figure 4.18 Horizontal bar graph illustrating the routine prescription of statin medication, and the different areas of focus of anaesthesiologists and vascular surgeons in patients requiring major vascular surgery

Other important monitoring considerations and medical interventions were not specifically related to the decision to institute PBB. The detail of the participants additional considerations are shown in **Table 4.11**.

Table 4.11 Table identifying further routine and commonly considered practice in patients undergoing major vascular surgery

	Haemodynamic monitoring	Medical interventions
V1	-	-
A1	Modified ECG Invasive blood pressure monitoring	-
S1	-	-
C1	Modified ECG Invasive cardiac output monitoring considered (PAC)	-
U1	Routine ST segment monitoring	-
L1	Transoesophageal Echocardiography considered (TEE)	-
R1	Routine ST segment monitoring Cardiac output monitoring considered	-
V2	-	Blood pressure and glycaemic control, Cessation of cigarette smoking, Inflammation control
A2	-	Control of Diabetes Mellitus, ACE Inhibitor
S2	-	ACE Inhibitor (Not for patients with renal impairment)
C2	-	Preoperative ACE Inhibitor (Especially in patients with Diabetes Mellitus)
U2	-	-
L2	-	-
R2	-	ACE Inhibitor (Proactive)

The anaesthesiologists expressed consideration for the use of modified ECG, ST segment analysis, invasive blood pressure monitoring, and the measurement of cardiac output. The vascular surgeons as a group were more concerned about medical interventions. They attributed importance to blood pressure and glycaemic control, to reduction of inflammation, to cessation of cigarette smoking, and to the introduction of ACE (Angiotensin Converting Enzyme) inhibitors.

4.3 Participant satisfaction with current strategy

Participant satisfaction with current practice is shown in **Figure 4.19**. Less than half of the participants were satisfied with current practice at their hospital.

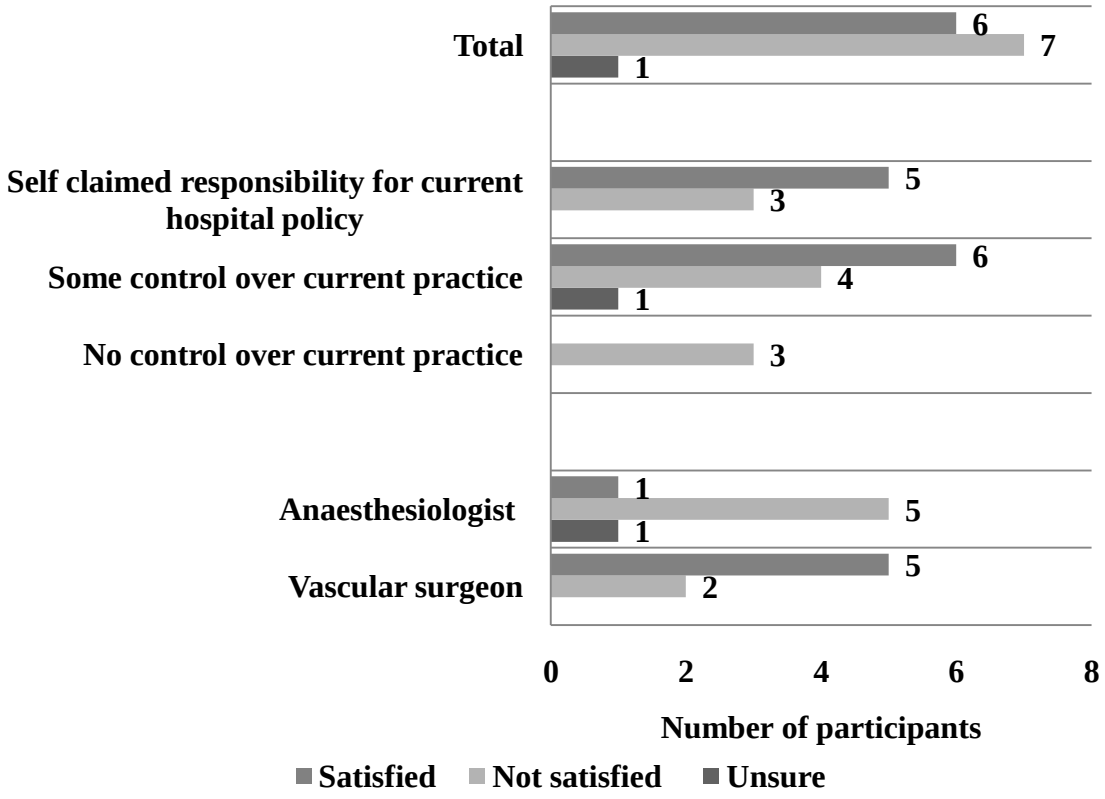

Figure 4.19 Horizontal bar graph illustrating participant satisfaction with the current perioperative beta blockade strategy being implemented at their respective hospitals

All of the participants who had no control over any aspect of intended practice indicated that they were not satisfied with current strategy. All of the participants that were satisfied had a degree of control over practice at their hospital. However, control over some aspect of practice, or a claim of complete control, did not necessarily translate into participant satisfaction.

Only one of the anaesthesiologists was satisfied with current practice. This was the only hospital (Hospital U) where both participants indicated that current practice was satisfactory, and it was accepted that the anaesthesiologist led processes at this hospital. However, the timing of initiation of beta blocker medication, and the way patients were monitored, remained a concern. The vascular surgeon at this hospital believed that good communication was a favourable aspect of their current practice, but inconsistent responses were common. It is possible that both participants may not have been satisfied had actual practice been determined.

Two of the anaesthesiologists indicated that they had access to vascular surgery patients at a preoperative anaesthetic assessment clinic. Another of the anaesthesiologists occasionally assessed patients, deemed to be at particularly high risk, a few weeks before planned surgery. The vascular surgeons at all of these facilities indicated that they were satisfied with practice, which possibly suggests that the involvement of another clinician in the preoperative optimisation of patients for vascular surgery increased overall satisfaction.

Only two of the vascular surgeons were not satisfied with the approach to the practice of PBB at their facility. There was agreement that practice was unsatisfactory at both of these hospitals. The dissatisfaction of one of the vascular surgeons was due to a lack of support from other disciplines (Anaesthesia and Cardiology). Similarly, the vascular surgeon and the anaesthesiologist at another hospital identified a shortage of cardiologists as an important limitation of current practice. The restrictive approach to PBB under the direction of a limited number of cardiologists prevented the introduction of beta blockers in some patients who may have gained benefit from the intervention.

Problems with current practice related to logistics, to the focus of different specialties, and to ignorance. Logistical problems, which posed the greatest challenge, related to workload, staffing, clinic availability, bed availability, and hospital management policy.

There was agreement at only one of the hospitals that the development of a protocol for PBB would be potentially useful.

4.4 Suggested changes to clinician roles and responsibilities

The participants made numerous suggestions for changes to the current clinician roles in the management of patients around the time of major vascular surgery. Irrespective of a participant's satisfaction with current practice, a greater role for the anaesthesiologists in the future was widely supported. (**Table 4.12**)

Only three of the participants did not indicate the need for greater involvement of the anaesthesiologists. These participants all claimed that the anaesthesiologists were already involved. Another participant was undecided, and pointed out the potential for problems related to feasibility of the intervention, should the reliance on the anaesthesiologist significantly increase. The participant's concern for a lack of resource to facilitate greater involvement was shared by others, and the possibility of increasing delays was another important consideration that was highlighted.

Table 4.12 Table showing the desire for a greater role for anaesthesiologists irrespective of participant satisfaction with current practice

	Satisfied with current practice	Greater role for anaesthesiologists
V1	No	**Yes**
V2	Yes	**Yes**
A1	No	**Yes**
A2	Yes	**Yes (May cause delays)**
S1	No	**Yes**
S2	No	**Yes**
C1	No	No (Already involved)
C2	Yes	**Yes (Resources do not allow)**
U1	Yes	No (Already involved)
U2	Yes	No (Already involved)
L1	Unsure	**Yes**
L2	Yes	**Yes**
R1	No	Unsure (Concern for extra burden and workload)
R2	No	**Yes**

4.4.1 Suggested future roles in policy development

Twelve of the participants believed that the roles of specialists in the development of policy should be modified. **Figure 4.20** illustrates suggested changes to the control of policy development.

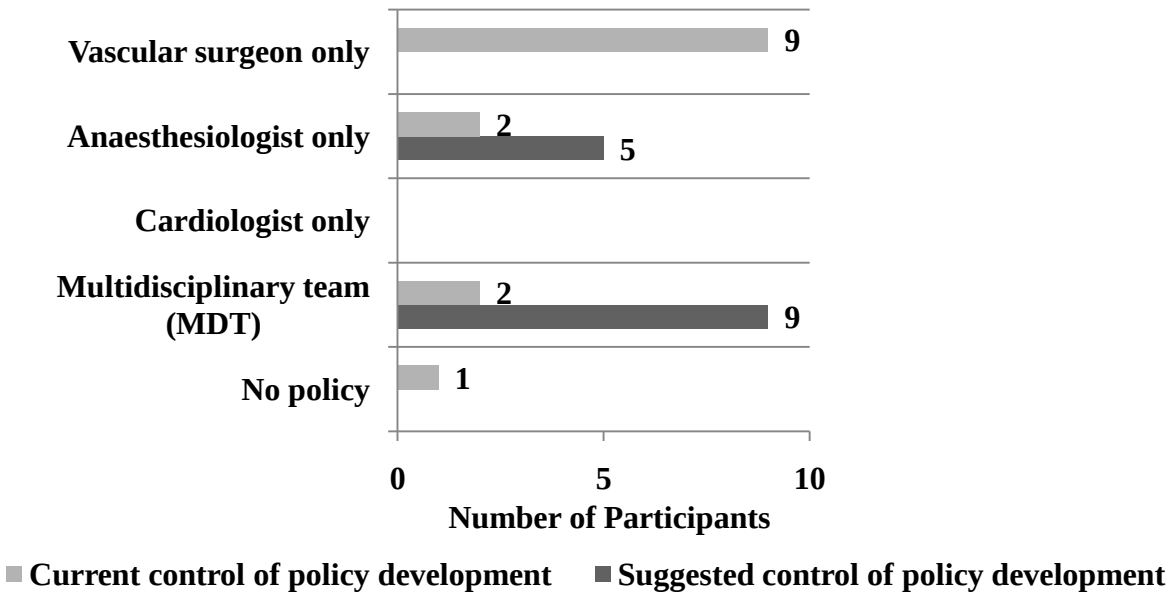

Figure 4.20 Horizontal bar graph illustrating the suggested changes to clinician responsibility for policy development

There was a desire to shift from widespread vascular surgeon led practice, to policy developed by a multidisciplinary team (MDT), or anaesthesiologists. None of the participants believed that vascular surgeons should be entirely responsible for policy, and only three indicated that vascular surgeons should take a lead role in an MDT. (**Figure 4.22**)

Nine participants indicated that they believed an MDT should determine practice in the future. They all indicated that vascular surgeons and anaesthesiologists should be included, and all but one believed that cardiologists should also be included. (**Figure 4.21**) Few attributed further value to the inclusion of a critical care specialist. However, continuity of care was identified as an important component of any successful intervention. The suggested lead role in an MDT was variable. (**Figure 4.22**)

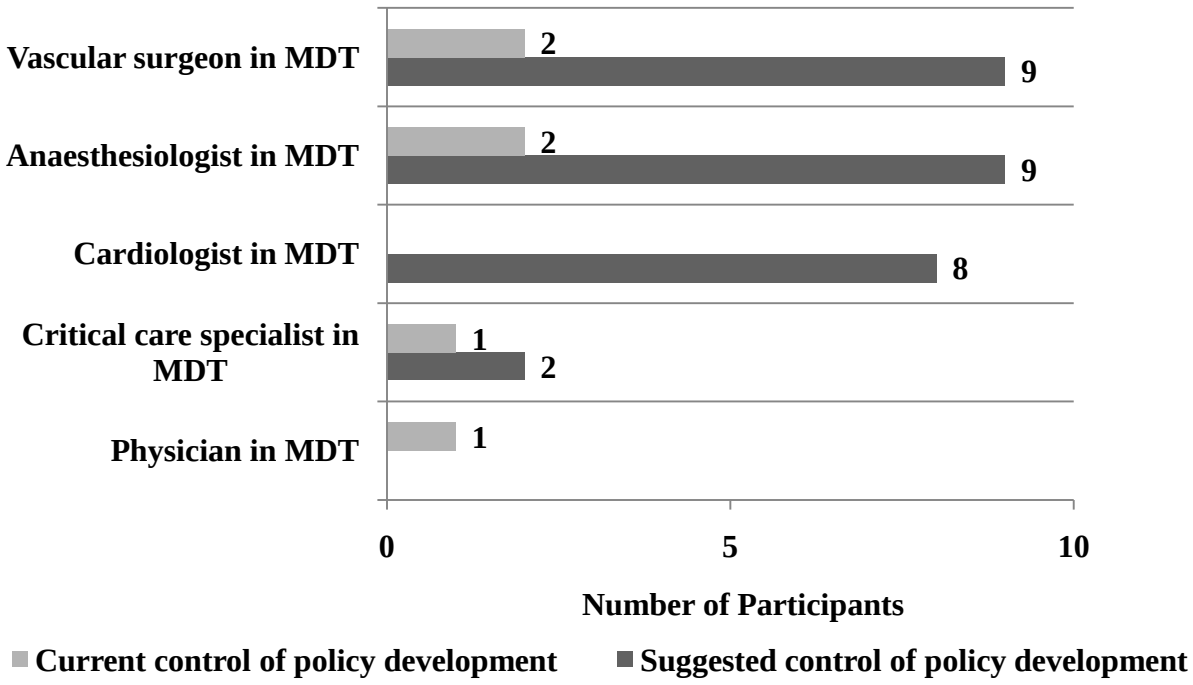

Figure 4.21 Horizontal bar graph showing the specialties that should be included in policy development when controlled by a multidisciplinary team

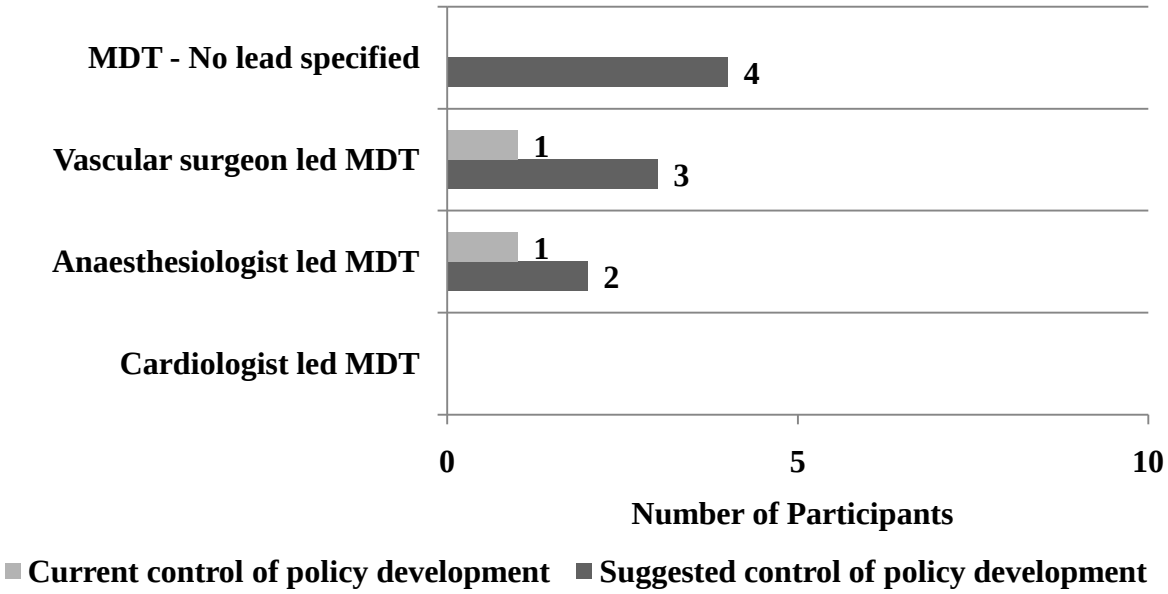

Figure 4.22 Horizontal bar graph showing the variety of recommendations for a lead clinician in the event of a multidisciplinary team approach to policy development

All of the participants indicated that anaesthesiologists should play a role in future policy development. Overall anaesthesiologist control was recommended by the anaesthesiologists at five of the hospitals. Two of the vascular surgeons indicated that anaesthesiologists should lead an MDT. The remaining participants recommended that anaesthesiologists should play a role as part of an MDT, but not necessarily as the lead clinician.

All seven of the vascular surgeons believed that an MDT should be formulated to develop management policy for vascular surgery patients. However, only one of the participating vascular surgeons specifically indicated that vascular surgeons should lead the team. The two anaesthesiologists who did not believe that they themselves should take overall responsibility, both indicated that vascular surgeons, as the entry point to the system, should take control of an MDT determined approach.

4.4.2 Suggested future roles in beta blocker initiation

Figure 4.23 illustrates current and suggested clinician responsibility for beta blocker initiation before major vascular surgery.

Half of the participants did not recommend a change to current responsibility for the initiation of beta blockers. Ten of the participants indicated that they believed vascular surgeons should be at least partly responsible for the initiation of beta blockade in the perioperative period. The support for vascular surgeons carrying sole responsibility increased from five participants to eight participants. For half of these participants this represents a change in favour of increasing the responsibility of vascular surgeons. Feasibility and the perceived benefit of early introduction of beta blockade were the major reasons for a shift in favour of vascular surgeon control.

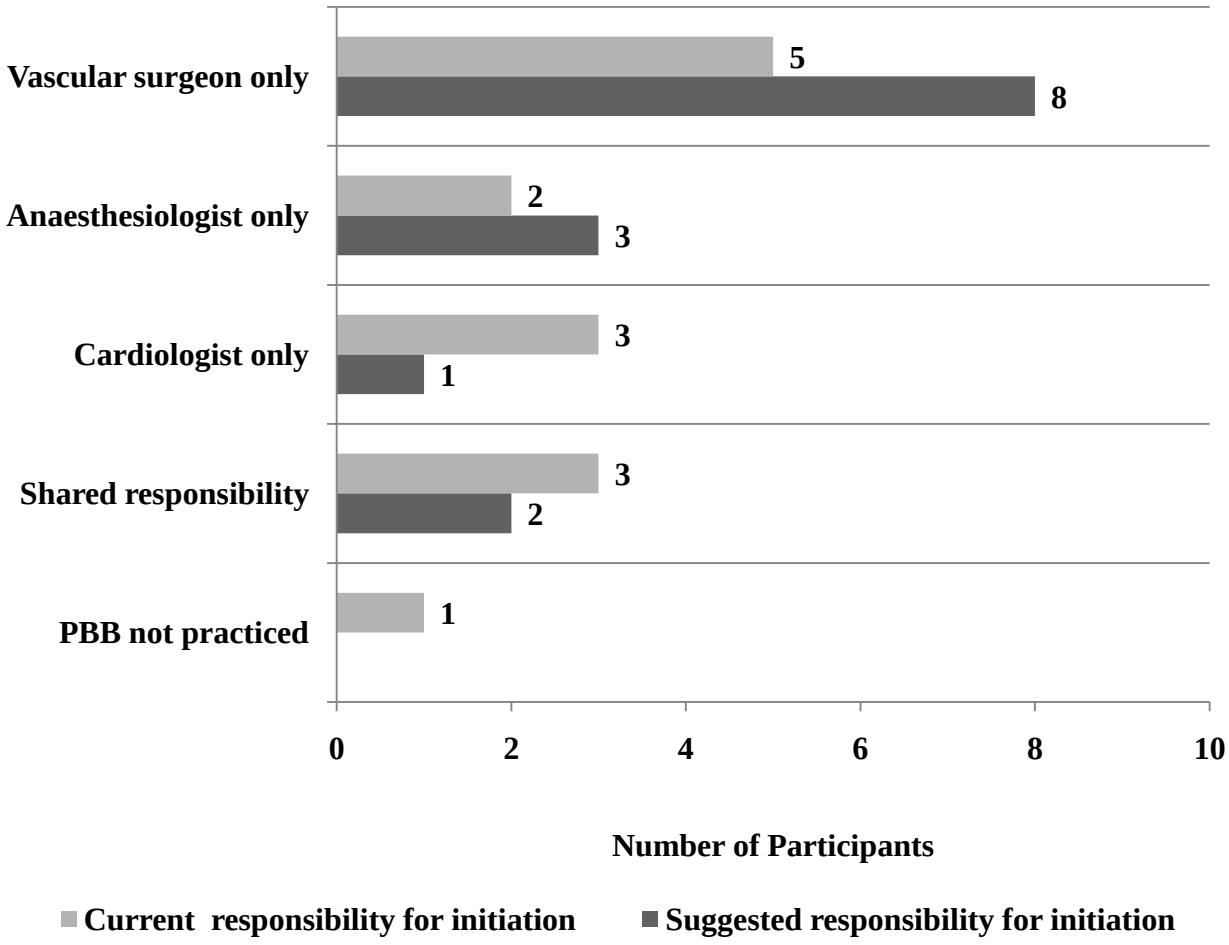

Figure 4.23 Horizontal bar graph showing the suggested changes in responsibility for initiation of beta blockers in the perioperative period

Two of the anaesthesiologists recommended that vascular surgeons should take overall responsibility for the initiation of beta blockers. Another two anaesthesiologists indicated that vascular surgeons should be responsible for the straightforward cases, and that anaesthesiologists should be responsible for the decision in patients attending a preoperative assessment clinic, and the challenging cases that would warrant specialist referral. One of the remaining anaesthesiologists believed that a sharing of responsibility would be helpful, but did not think that sharing responsibility would be safe.

Five participants suggested an ongoing role for anaesthesiologists in the initiation of PBB. Three of these participants identified initiation as a role specifically for the anaesthesiologist. One of the vascular surgeons thought that anaesthesiologists should take a more active role in all aspects of PBB when implemented as a perioperative risk reduction strategy. Ultimately, there was some support for a principal role for anaesthesiologists at four of the Hospitals.

There was a desire to move away from reliance on cardiologists for beta blocker initiation in the perioperative setting. This was due to the cardiologists' reluctance to introduce beta blocker therapy as a risk reduction strategy, and the shortage of cardiologists, which limits the number of patients that can be referred for assessment. Only one participant believed that cardiologists should retain responsibility for the initiation of therapy.

4.4.3 Suggested future roles in the titration of beta blocker medication

Recommended changes to clinician responsibility for titration of beta blockers are illustrated in **Figure 4.24**.

One of the participants recommended retention of the policy of no titration before surgery. This participant indicated ongoing concern for the safety of titrating beta blocker medication in the general ward, and highlighted the logistical difficulties of anaesthesiologists having to assess patients at a time that they would not usually be available to do so. Furthermore, although the participant thought that titration would be the ideal, it was not believed to be critical for risk reduction.

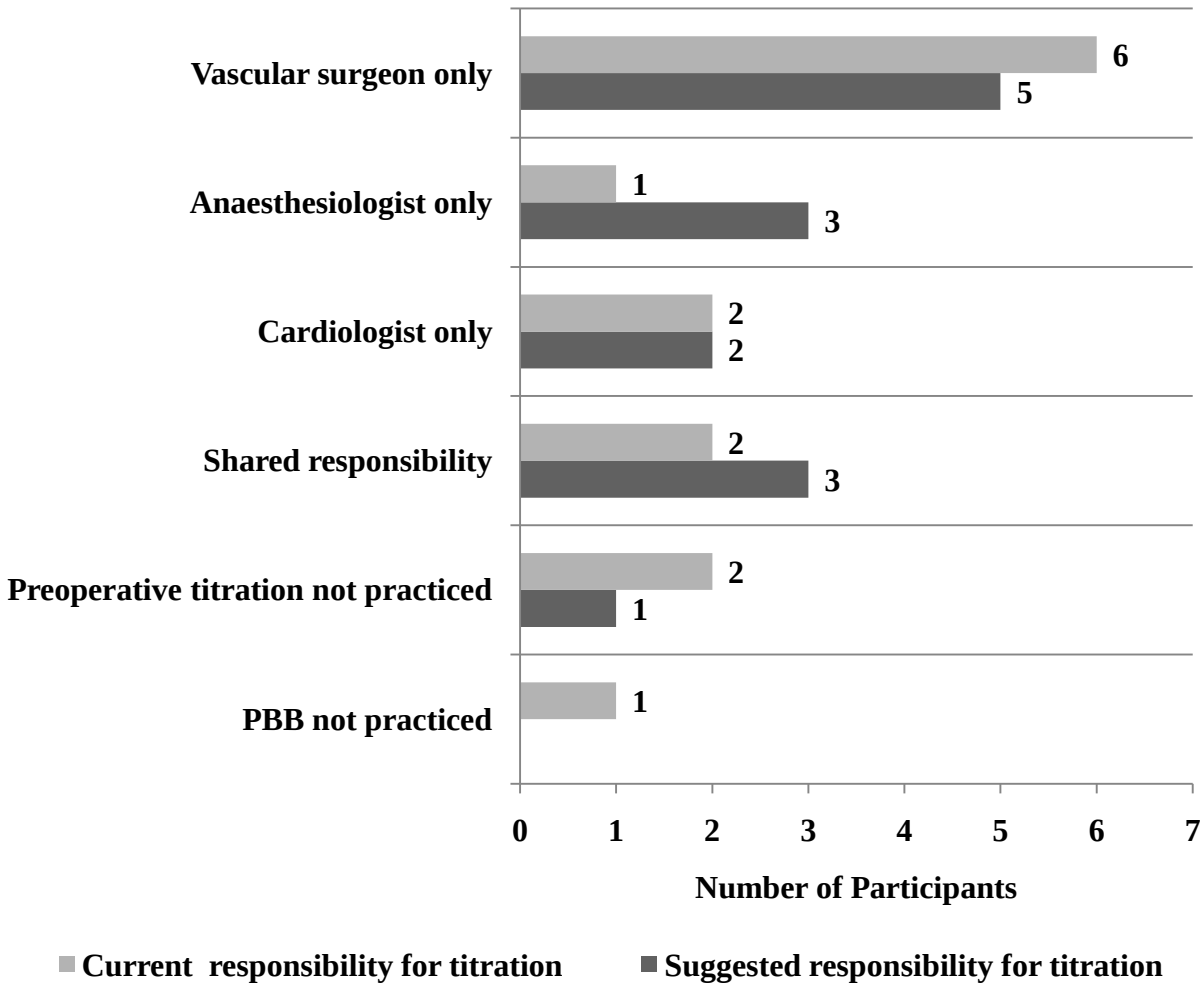

Figure 4.24 Horizontal bar graph illustrating current and suggested clinician responsibility for the titration of beta blockers before major vascular surgery

Half of the participants believed that vascular surgeons should be involved in the titration of beta blockers preoperatively, but only five participants thought that vascular surgeons should have sole control over this aspect of practice. One participant recommended a change of practice in favour of the vascular surgeons taking future responsibility for preoperative beta blocker titration.

Five of the vascular surgeons suggested that they should be directly responsible in future. In contrast, only two of the anaesthesiologists thought that vascular surgeons should be responsible for titration, and even then, not without support.

Three participants indicated that anaesthesiologists should be responsible for the titration of beta blockers before major vascular surgery. Two of these participants were anaesthesiologists, and one specifically indicated that vascular surgeons should not continue to control this aspect of practice.

Three participants indicated that cardiologists should control beta blocker titration. The experience and training of cardiologists was thought to make them the ideal clinicians to control this process. Two of these participants believed that the cardiologist could be effective as the sole clinician responsible for titration. The other participant suggested that including specialist physicians in the process of titration, once the decision to commence beta blockers was made, could limit the increase in work load for cardiologists.

4.4.4 Suggested future roles in beta blocker withdrawal

Withdrawal of beta blocker medication after surgery, when used as a risk reduction strategy, was an aspect of PBB that was poorly managed. **Figure 4.25** illustrates the suggested changes in clinician responsibility for beta blocker withdrawal after major vascular surgery.

All 14 participants indicated that beta blocker medication, administered only around the time of surgery, was a valid strategy for reducing the risk of adverse cardiac events, and that this should ideally be practiced at their hospital in future.

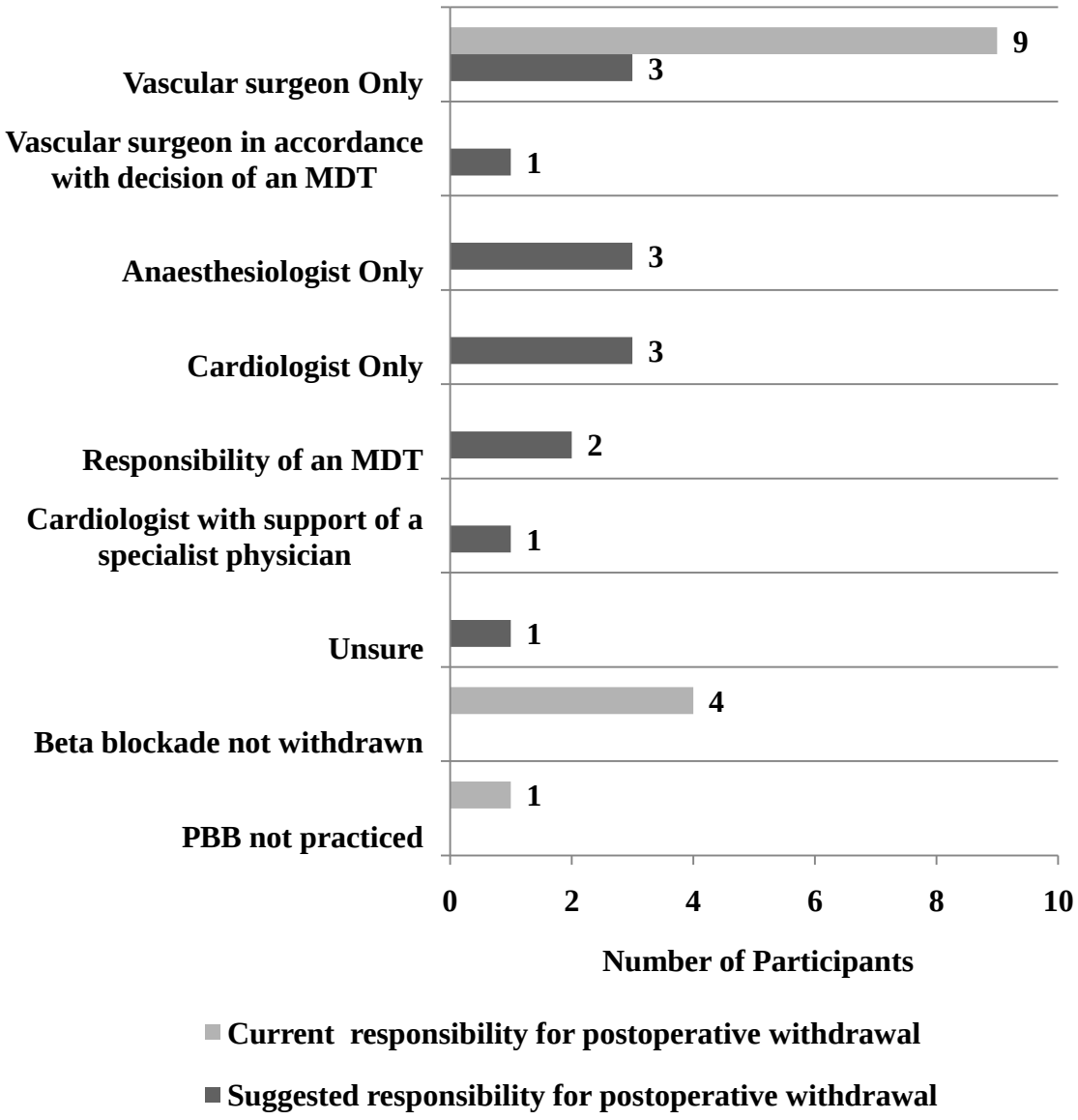

Figure 4.25 Horizontal bar graph illustrating suggested change in the responsibility for beta blocker withdrawal after major vascular surgery when used as a perioperative risk reduction strategy

Ten participants recommended a change in the control over beta blocker withdrawal. This was second only to the recommendation for changes in the development of policy. There was widespread recommendation to shift away from vascular surgeon responsibility for this aspect of practice, with just four participants indicating that they thought vascular surgeons should continue to take responsibility. However, one of these four participants suggested that a combined MDT decision, or a protocol defining an appropriate approach, would be ideal. Only one of the anaesthesiologists indicated that withdrawal should be the responsibility of vascular surgeons.

Three participants indicated that anaesthesiologists should be responsible for withdrawal of beta blocker medication. One of these participants believed that the responsibility for management of the overall process should remain with the anaesthesiologist who initiated the intervention.

Four participants indicated that cardiologists should take responsibility for decisions related to withdrawal of beta blockade. Patient presentation for surgery was identified as a point of care opportunity for intervention by one of these participants. Another of these participants suggested that the management of the patient's ongoing risk was beyond that which could realistically be expected of the anaesthesiologist, and therefore, deferred responsibility for withdrawal decisions to the cardiologists.

Two of the vascular surgeons were not comfortable with their current role, which included responsibility for the withdrawal of beta blockers. Both of these participants recommended an MDT determined approach in the future.

4.5 Barriers to the implementation of perioperative beta blockade as a strategy

Problems related to the evidence for perioperative beta blockade (10 participants), staffing insufficiencies (11 participants), and hospital related problems (11 participants), were commonly identified as barriers. (**Figure 4.26 – Figure 4.28**) These barriers were identified by at least one participant from each hospital. Interdepartmental differences in opinion, and the lack of clarity in distinction of responsibilities, were not commonly identified as problems. (**Figure 4.29**)

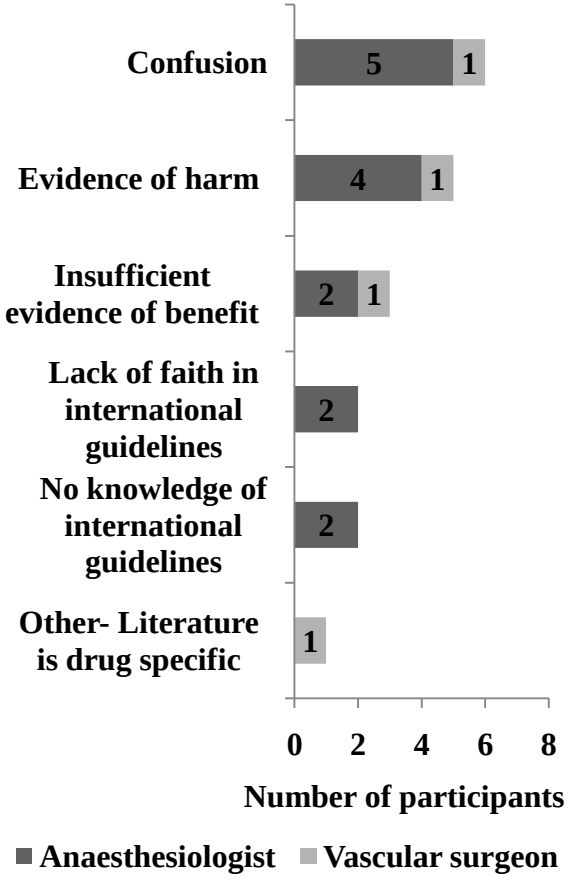

Figure 4.26 Horizontal bar graph showing barriers to the implementation of perioperative beta blockade related to problems with evidence available in the literature

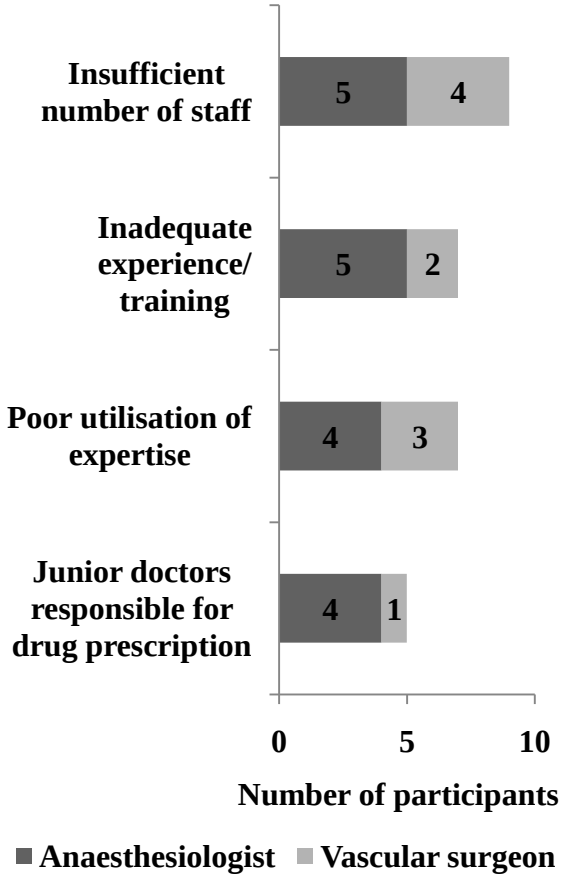

Figure 4.27 Horizontal bar graph highlighting the staffing insufficiencies that may have an impact on the practice of perioperative beta blockade

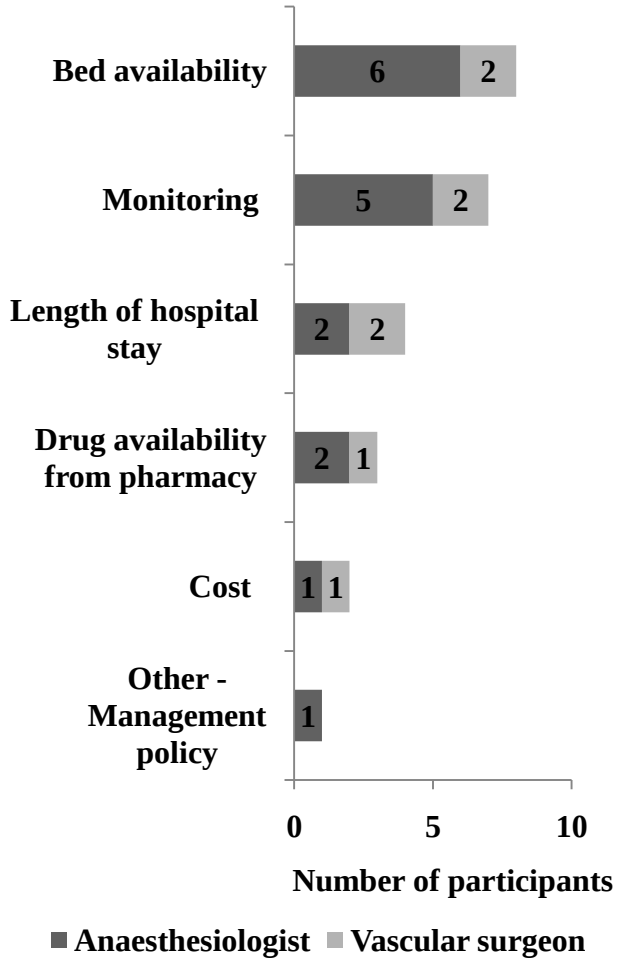

Figure 4.28 Horizontal bar graph showing hospital related barriers to the implementation of perioperative beta blockade

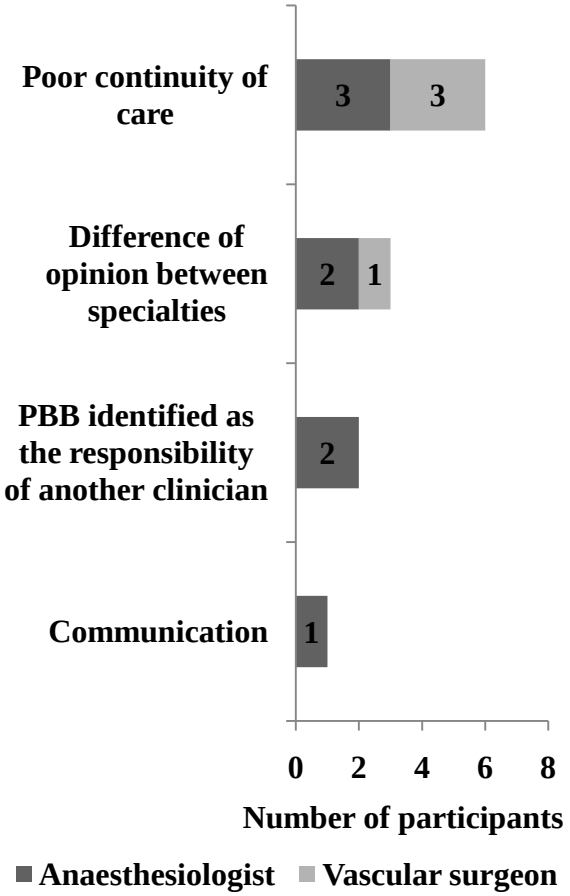

Figure 4.29 Horizontal bar graph highlighting the communication and inter-departmental dynamics that may have an impact on the practice of perioperative beta blockade

A total of 20 potentially important barriers to the practice of perioperative beta blockade (PBB) were identified. Participants' opinions on the presence of 17 potential barriers were addressed in the semi-structured questionnaire. (**Question 38, Appendix 1**) Three further potential barriers were identified by the participants. (**Question 38E, Appendix 1**)

One of the participants expressed concern that the evidence should be interpreted in the knowledge that it is drug and implementation method specific. Another participant highlighted an inability to effect a change in hospital management policy, with respect to the introduction of a preoperative anaesthetic assessment clinic for vascular surgery patients, as an important barrier. Finally, deficiencies in communication were identified as an important barrier to the capability of a facility to safely and effectively introduce PBB.

All of the participants identified at least one barrier to the practice of PBB. Across all 14 participants, a total of 84 indications for the presence of a barrier to the practice of PBB were noted (mean of 6 barriers per participant). The majority of barriers were noted by the anaesthesiologists (69.05%). Only one of the vascular surgeons noted more than six potential barriers. None of the anaesthesiologists noted less than six potential barriers.

4.5.1 Problems with the evidence

Barriers identified that related to the evidence for PBB as a strategy, contributed more than one quarter (25.9%) of all anaesthesiologist concerns. The vascular surgeons were considerably less concerned with problems related to the evidence, in terms of both number and proportion (15.4%) of total vascular surgeon indications of concern. Four of the vascular surgeons did not indicate that any aspect of the evidence was a barrier to the implementation of practice. One of the vascular surgeons specified that the availability of the American Heart Association guidelines had eliminated interpretation of the evidence as a barrier to implementation of PBB. However, the lack of a recent update of intended practice implies that the most recent guidelines were not being followed at that hospital.

A lack of faith in guidelines (2 participants), poor knowledge of the guidelines (2 participants), and confusion (6 participants) were all identified as significant barriers to the implementation of PBB. One of the participants indicated that the evidence should be interpreted in the knowledge that it is drug specific. Only five participants listed evidence of harm as a barrier to the practice of PBB.

4.5.2 Staffing insufficiencies

Staffing factors were a major concern at all of the hospitals. This group of barriers accounted for one third of all barriers noted, and made the largest contribution of all of the groups. The vascular surgeons were considerably more concerned with staff insufficiencies than any other group of barriers. All but three participants indicated that staffing had an impact on how practice was implemented. These three participants represented three different hospitals.

The barriers related to insufficient number of staff, or insufficient training, or poor management of staff as a resource.

A shortage of staff was the single most commonly identified barrier to practice (9 participants). The shortages related to both specialists (anaesthesiologists and cardiologists) and nursing staff. Four participants highlighted an insufficient number of anaesthesiologists as a cause for the limited involvement of anaesthesiologists in the practice of PBB. One of these participants indicated that the number of appointed anaesthesiologists had been reduced, making it impossible to provide a service that required extra responsibilities to be shared between too few anaesthesiologists. Another participant indicated that there had been a 40% reduction in theatre time as a result of not appointing new anaesthesia trainees. Four of the participants indicated that a shortage of cardiologists had a bearing on practice. Two participants identified the insufficient

number and experience of nursing staff, as a major concern. Their concern was largely related to the feasibility of monitoring patients effectively. A shortage of vascular surgeons was not identified as a barrier by any of the participants.

Poor use of expertise was specifically related to the lack of anaesthesiologist support in this study. In addition, five of the participants were uncomfortable with the junior doctor responsibility for prescribing medication.

4.5.3 Hospital related barriers

At approximately 30% of the total, hospital related problems were the second largest contributing group of identified barriers.

Bed availability and inadequate monitoring appeared to be interdependent. Half of the participants specifically identified inadequate monitoring as a barrier to PBB. Eight participants identified availability of beds as a limitation. Five of the participants selected both bed availability and monitoring as barriers. Three participants did not specifically select monitoring as a barrier in conjunction with their concern about bed availability. However, their concern surrounding bed availability, in all but one instance, related to a perceived need for an appropriate level of care and monitoring during beta blocker titration. Therefore, it is likely that nine of the participants had important concerns about the potential adverse effects of beta blockers.

The vascular surgeons at four of the hospitals did not think that monitoring or bed availability created any barrier to the introduction of beta blockers in the perioperative period. Incidentally, a proactive approach to PBB was practiced at both of the hospitals represented by the only two

vascular surgeons who believed that monitoring was a barrier. This implies that the introduction of beta blockade was not viewed as a cause for significant restriction in practice. In contrast, five of the anaesthesiologists specifically identified monitoring as a barrier to PBB. If concern about appropriate bed availability, at the time of beta blocker titration, was a reflection of a requirement for monitoring at a higher level than that which was standard, then all of the anaesthesiologists can be considered to have identified monitoring as a potential barrier to the practice.

As a further consequence of limited bed availability, one of the participants indicated that the extended length of stay that would be necessary for appropriate titration of beta blocker medication before surgery, had an impact on the feasibility of following ideal practice guidelines.

Three of the participants indicated that problems with the availability of certain medications complicated the implementation of PBB at their hospital, and that this was a major barrier to the implementation of PBB.

4.5.4 Communication and inter-departmental dynamics

Barriers related to communication and inter-departmental dynamics contributed least to the overall number of barriers that were reported.

Poor continuity of care was identified as a barrier by six of the participants. Continuity of care has been presented in this group of problems, as it was apparent that the poor continuity was more closely related to communication problems, and differences in opinion, than to staffing insufficiencies.

Differences in opinion between anaesthesiologist and vascular surgeon were only identified as a significant barrier to practice by three participants. One of these participants cited a difference in focus as the reason for the vascular surgeons' reluctance to participate in proposed practice. The other two participants were from the same hospital. The vascular surgeon at this hospital indicated that there had been essentially no senior anaesthesiologist involvement in the management of vascular surgery patients for a number of years. The anaesthesiologist at this hospital identified a lack of political will as the major barrier to a collective approach, but believed that this could be addressed with simple dialogue.

One of the participants specifically noted that deficiencies in communication were a significant barrier to the capability of a facility to safely and effectively introduce PBB.

CHAPTER FIVE - DISCUSSION

Chapter Five initially discusses the limitations of the study. Thereafter, matters pertaining to the primary and secondary objectives are discussed.

5.1 Limitations of the study

5.1.1 Reproducibility of the results

5.1.1.1 Sample limitations

Although, the sample size was small, it was deemed to be fully inclusive of a defined group of participants.

The study method attempted to facilitate inclusion of the most appropriate clinicians. It is possible that the most appropriate clinicians were not included in the study, as there was more than one specialist from each discipline involved in practice at many of the institutions. (**Table 4.1**)

The intended practice of the included participants may not be a reflection of the intended practice of other clinicians practicing at the same hospital. However, the majority of participants indicated that they thought the current practice of the other clinicians, involved in perioperative management of vascular surgery patients, was essentially the same. (**Table 4.2**)

The relative inexperience of the anaesthesiologists included in the study, also raises concern about whether the most appropriate clinicians were invited to participate. However, interest in vascular anaesthesia was very limited at the facilities where anaesthesiologists were included

with very few years of involvement in the management of vascular surgery patients. (**Figure 4.1** and **Table 4.1**)

Similarly, the recent arrival of the vascular surgeon at Hospital R creates concern about the participant's awareness of current practice, but the participant was the only specialist vascular surgeon employed at that hospital, and there was agreement that initiation of beta blockers was based on cardiologist opinion.

The role played by the cardiologists was under-estimated, and future studies should include the cardiologists, as the approach of the cardiologist may have a significant impact on practice.

There was marked inconsistency in paired participant responses, and it is possible that results may be subject to a sampling error. However, the overall impression is that the inconsistencies relate more to poorly defined practice within hospitals, and across the country.

5.1.1.2 Timing of the study

The results of the study reflect opinion on current practice at the time of the interview only. There is concern surrounding the reproducibility of the data as a result of the time sensitive nature of the study. (**Section 1.9.2**)

However, the timing of the study is also important. The aim of the study was to understand how specialist training facilities in South Africa have chosen to implement perioperative beta blockade (PBB) as a risk reduction strategy, and to assess the potential need for reassessment of these strategies, in light of ongoing controversy and recent shifts in guideline recommendations.

The safety of PBB was called into question after publication of the POISE trial.[3] Changes to international consensus guidelines were inevitable, despite criticisms leveled at the intervention

strategy.[110,111] The updated ACCF/AHA guideline[5] was published four months before the conduct of this study, and the ESC published their first guideline concurrently.[4] The POISE trial[3] was published in May 2008, 21 months before the study commenced.

The updated guidelines had been eagerly anticipated, as the POISE results had sparked widespread debate.[113,114,117] It was, therefore, expected that recent assessment, and perhaps even updates in strategy, would have occurred at training facilities across South Africa. One concern was that the study would reveal a fluid situation, with changes at many of the facilities, but that these changes would still be in the process of implementation. This may have created confusion amongst participants. Although two of the participants reported that practice was recurrently updated, with no standard approach (**Table 4.3**), there does not appear to have been marked shifts in practice at, or around, the time of the study, and this is unlikely to be the cause for inconsistent responses between paired participants.

More than half of the participants (8 participants) indicated that developments in international literature motivated change in management strategy. (**Section 4.1.3.2**) However, few (four participants) specified that there had been changes since the POISE study, and only two of the participants indicated that the POISE data had been directly responsible for the change. It is apparent that at least three of the seven hospitals had seen no update since some ill-defined point in time before the 2007 ACC/AHA guideline[201] was published in October 2007. The participants included in the study were well selected, and it is unlikely that they would have been unaware of the recent literature. It is not clear whether the more recent literature simply had no impact on local practice at these hospitals, or whether changes to practice were specifically deemed unnecessary.

5.1.2 Validity of the data

5.1.2.1 Research assumptions and contextuality

The following assumptions were made: (**Section 1.4**)

- It was assumed that the invited participants would be aware of current intended practice at their hospital.
- It was assumed that the specialist training facilities in the state sector are more likely to have a structured approach, to optimal perioperative care of major vascular surgery patients, than non specialist hospitals in the state sector.

The results of this study call into question the validity of both of these assumptions. There were numerous aspects of practice that the participants were unable to comment on, or had a different opinion to their paired participant. There was little evidence of a structured approach at many of the facilities, and none of the facilities had a documented protocol. (**Section 4.1.3.1**)

Limitation due to contextuality was discussed in **Section 1.9.3**. An example of the potential for practice to be different in the private healthcare sector is evident from six participants' intention to use a different beta blocker if presented with the opportunity to choose specific medication. (**Section 4.2.3.2**)

5.1.2.2 Quality of the data

There were no problems with processing of data, and there were no device failures during the interviews.

The quality of the data remains a function of the design of the research tool. The tool was not previously validated, but piloting of the semi-structured questionnaire was helpful in reducing the potential for ambiguity or suggestive interviewing.

Question 40 (**Appendix F**) has not been included in the results. Although not identified as an ambiguous question during the pilot process, it was apparent that the question was subject to variable interpretation.

5.1.2.3 Statistical Analysis

Despite extensive review by a biostatistician, statistical analysis has been avoided. The nature of the study, and the small number of participants, led to major concerns about the validity of any statistical analysis.

5.2 Discussion related to the primary objective of the study

Primary objective:

> To describe current intended practice, with respect to the use of perioperative beta blockade as a tool for risk reduction, in patients undergoing major vascular surgical procedures at South African specialist training facilities for vascular surgery.

Current intended practice is described in **Section 4.2**.

Two important themes emerge from the results of this study. Poor correlation of paired participant responses was common, and practice varied across the country.

5.2.1 Clinician roles

Clinician roles were poorly defined in general. (**Grey shading in Table 4.4**) The poor definition of roles was least problematic at the hospitals where one of the participants had been involved for a very short period of time. This includes the three hospitals that relied almost exclusively on the vascular surgeon's directives (Hospitals V,A and S), and Hospital R, where it was agreed that the cardiologists were responsible for decision making. Reported intended practice was least well defined at the facilities where both participants claimed contributions to aspects of management (Hospitals C, U and L).

Many aspects of perioperative beta blockade (PBB) are still widely debated. It is not unexpected that clinicians would have differing opinions on the intervention. However, poor correlation of responses for clinician roles highlights poor communication between specialists involved in the perioperative management of vascular surgery patients in South Africa. The lack of standardisation of approach appears to be the source of confusion. The lack of protocolised management is not unique to South Africa. Surveys conducted elsewhere in the world have shown that only approximately 10% of clinicians make use of specific department protocols for PBB,[180,182,183] and the introduction of a protocol is not uniformly supported.[185]

Figures 4.2 – 4.8 demonstrate the variation in clinician responsibilities across South African training facilities. The vascular surgery team feature prominently at the majority of hospitals, but the variable role for anaesthesiologists, cardiologists and critical care specialists demonstrates the necessity for good interdepartmental communication and definition of roles. It may also represent different levels of experience and resource availability across the country. Surveys of practice elsewhere in the world show an increased responsibility for the anaesthesiologists when

compared with practice in South Africa. However, the allocation of responsibility also appears to be inconsistent.[180,182,183]

Section 4.2.1.2 groups hospitals on the basis of similarities in dominant clinician responsibilities, in order to facilitate clearer representation of the variability in approach.

The non-specialist responsibility for beta blocker prescription at six of the seven facilities creates concern, especially in light of the reports that the clinician prescribing the medication is not the same clinician responsible for selecting appropriate candidates. (**Figure 4.5**)

5.2.2 Patient Selection

Patient risk factors (type or number), baseline physiological parameters as potential targets for manipulation with beta blocker medication, and also the type of procedure were the components used to select patients as candidates for PBB at South African training facilities. (**Table 4.5**)

Once again there was inconsistency in paired participant responses (**Grey shading in Table 4.5**), and patient selection processes differed from one hospital to the next. (**Figures 4.9 – 4.11**)

Consistent aspects of patient selection for beta blocker medication, and a notable difference in approach promoted by anaesthesiologists and vascular surgeons (**Table 4.6** and **Figure 4.12**), are emphasised in the discussion that follows.

5.2.2.1 Supported indications for beta blocker medication in the perioperative period

The following indications have a strong base of support in the literature, and therefore, in international consensus guidelines.[4,5] These indications were also widely supported by clinicians across South Africa. (**Table 4.6** and **Figure 4.12**)

i. Continuation of appropriate beta blocker medication

At all of the hospitals included in the study, chronic beta blocker medication was continued throughout the perioperative period, provided that the medication was prescribed with an appropriate indication, and that the patient did not develop severe perturbations in haemodynamic status, or any other indication for withholding beta blocker medication. (**Table 4.6** and **Figure 4.12**)

More than half of the patients who died (8/14) in a study designed to identify the factors that predict mortality, when chronic beta blockade was not continued around the time of vascular surgery, had beta blocker medication withdrawn for no apparent reason.[130] Accidental omission of required chronic medication, and in particular beta blockers, is unacceptable given the association with mortality.[111,128,130] The omission of even a single dose may be important.[187]

In a study conducted at Inkosi Albert Luthuli Central Hospital, there was a significant decrease in the number of patients who had chronic beta blocker medication withdrawn in the perioperative period during two periods of evaluation (15.5% vs 5.1%, $p<0.001$),[187] and this may represent an increasing awareness for adverse outcomes associated with withdrawal of beta blockers, at a South African training facility. It was apparent that this awareness was present across the country.

ii. Initiation of beta blocker medication in patients with evidence of inducible myocardial ischaemia or known ischaemic heart disease (IHD)

Although not necessarily routine, treatment options for medical patients with evidence of inducible myocardial ischaemia include the introduction of beta blocker medication.[123,156] Consensus guidelines support the introduction of beta blockers in patients with known IHD or

inducible myocardial ischaemia before vascular surgery, albeit with slightly different degrees of confidence.[4,5] Support for the use of beta blockers in such patients is outlined in **Section 2.6.1.2**.

Introduction of beta blocker medication in patients with inducible myocardial ischaemia was generally supported across South Africa (**Table 4.6** and **Figure 4.12**), despite this being a controversial area requiring further investigation.[5]

The vascular surgeons in control of practice at three of the hospitals did not indicate that evidence of inducible myocardial ischaemia, on preoperative testing, was a specific factor taken into consideration during patient selection for PBB. (**Table 4.6**) The reason for not including the presence of inducible myocardial ischaemia as part of their risk assessment is unclear, because all of the participants in this study shared a personal opinion that this should be an independent indication for beta blockade. [Individual participant opinions on how PBB should be implemented were obtained, but have not been included in the results of this report to prevent confusion between intended practice at each hospital and the participants' own opinions. Individual opinions on a number of aspects of PBB were addressed during the interviews. (**Question 41, Appendix F**) The participant's responses to these questions are shown in **Table G**. (**Appendix G**)]

Not all patients with a positive test result have significant coronary artery disease (CAD). If all patients with a positive test result were commenced on beta blockers, a number of patients would be at risk for adverse effects related to beta blocker use in the perioperative period, without necessarily gaining benefit. Alongside inevitable delays attributable to preoperative testing, this could be a reason for not relying on the results of preoperative tests at these facilities. The use of preoperative tests was not assessed in this study, because of the additional complexity that would

have been caused. The assessment of preoperative testing would be a valuable addition to future studies.

Patients at higher risk are more likely to have CAD in the face of a positive test result, and it is probably reasonable to commence beta blocker medication before surgery in these patients, provided that the test was conducted after appropriate risk assessment.[4,5]

Similarly, the introduction of beta blockers in patients with known IHD was widely supported. (**Table 4.6** and **Figure 4.12**) Two participants indicated that a family history of IHD would affect their decision, but there is no support for the use of family history in the stratification of risk, or for introduction of prophylactic beta blockade.

Four participants did not indicate that known IHD was important in their decision to commence beta blockers. (**Table 4.6** and **Figure 4.12**) However, it is possible that all of these participants would place value on the presence of IHD as an important predictor of risk. The type of procedure was a dominant, the predominant, and the only determinant of patient selection, according to reports of three of these participants. Therefore, patients with IHD undergoing major vascular surgery would automatically have been candidates for beta blockade. No opinion on the introduction of beta blockers in this setting was obtained from the remaining participant.

5.2.2.2 Differences in selection processes recommended by anaesthesiologists and vascular surgeons

International guidelines[4,5] recommend that overall risk on the basis of cumulative risk related to the type of surgery, and the number of patient risk factors, should be determined to identify patients that are more likely to gain benefit from PBB.

In general, patient selection strategies at South African training facilities do not follow these guideline recommendations.

At the time of the study, only the intended practice of three of the anaesthesiologists complied with consensus recommendations. However, two of these three participants were not the only contributors to practice at their hospital (Hospitals C and L), and the intended practice of the anaesthesiologist at the remaining facility (Hospital U) did not follow the recommendations specifically.

Methods of risk stratification reported by the vascular surgeons were variable, and lack the support of recent consensus guidelines.[4,5] The vascular surgeons were more concerned with control of heart rate and the type of procedure. (**Table 4.6**)

i. The role of patient risk factors in selection of candidates for PBB

Only two participants reported that patient risk factors were not considered important in the decision making process. (**Table 4.5**) One of the vascular surgeons reported a proactive approach to introduction of PBB for all patients undergoing major vascular surgical procedures. One of the anaesthesiologists, representing a different hospital, indicated that beta blockers were commenced under the direction of the vascular surgeons, and believed that the introduction of beta blockade was specifically directed at heart rate control.

Despite the suggestion of a lower degree of accuracy when used in the setting of vascular surgery,[11,12,47] the risk index that is most widely accepted and recommended for use in this setting is the Revised Cardiac Risk Index (RCRI).[7] In an attempt to avoid suggestibility, as a research tool limitation, care was taken not to specifically enquire about the use of the RCRI in

patient risk stratification. Therefore, the exact number of risk factors that would determine the need for introduction of beta blocker medication was not assessed.

The anaesthesiologists identified current beta blocker therapy, inducible myocardial ischaemia and components of the RCRI, as important considerations in the decision making process. They specifically indicated that the individual component risk factors assessed in the RCRI would not, on their own, necessarily indicate the need to commence beta blockers, but that the number of risk factors was helpful in stratifying the degree of risk.

The number of risk factors was not an important consideration for the vascular surgeons. (**Table 4.5**) Concern for the total "atherosclerotic load" (V2) and the "physiological reserve of the patient" (U2), may be evidence of acceptance of value in considering overall burden of disease, but do not reflect acceptance of risk stratification practice recommended by international consensus guidelines.[4,5]

These guidelines[4,5] promote the approach of the anaesthesiologists as far as it is outlined above. However, the weight attributed to each component risk factor was not always consistent with the RCRI. Two of the anaesthesiologists specified that the combination of risk factors was more important than the absolute number, and a recent review lends support to attributing variable weights to the risk factors contained in the RCRI.[155] A history of cerebrovascular disease had a variable effect on patient selection. Two of the anaesthesiologists extended assessment to include a history of transient ischaemic attack (TIA). Conversely, the anaesthesiologist in control of practice at Hospital U excluded patients with a previous cerebrovascular accident (CVA) as candidates for PBB. Subanalysis of the POISE data shows that patients with a history of TIA or CVA had the highest population attributable risk for postoperative stroke (PAR 30.5%, CI: 17.1-

48.2).[3] It may, therefore, be prudent that PBB is avoided in such patients, particularly in view of the intention to introduce beta blocker therapy on the morning of surgery at that Hospital.

The recurrent theme amongst anaesthesiologist's recommendations, was that of a gathering of support for the introduction of beta blockade, followed by an assessment of the weight of the supportive information, in an individualised manner.

The vascular surgeon at Hospital R was the only vascular surgeon who attributed value to risk factors contained in the RCRI during patient selection. (**Table 4.6**) Although importance was attached to the number of patient risk factors, (**Table 4.5**) a history of CCF, previous CVA and the type of procedure, were risk factors that were omitted from the proposed assessment of risk. The cardiologists prescribed beta blocker medication at this hospital on the basis of independent medical indications for beta blockade.

ii. Importance attributed to the control of heart rate

Heart rate was the only physiological variable that was identified as a determinant of the potential to gain benefit from PBB. The vascular surgeons showed greater interest in heart rate control than risk factor burden. Their concern for controlling heart rate was shared by all of the anaesthesiologists who claimed a direct role in beta blocker administration. (**Table 4.6**)

The concept of targeting patients with a 'clinically unacceptable heart rate' currently has no firm base in published international guideline recommendations.[4,5] Despite the association of perioperative tachycardia with an increase in the incidence of adverse cardiac events,[21] heart rate control has not been proven to have an association with improved outcome.[167,168] Literature addressing the potential importance of heart rate control is discussed further in **Section 2.6.2.2**.

There was no consistency in terms of what heart rate required intervention, nor the rate to which it should be slowed before surgery. (**Table 4.6**) As a method of risk stratification and potential intervention, that is commonly identified in this study, this concept is worthy of further assessment. However, evaluation and treatment of the cause of the tachycardia should precede the use of beta blocker medication. (**Section 2.4.2**)

iii. Importance of the type of procedure in patient selection for PBB

The lack of benefit shown with the use of metoprolol when administered perioperatively to patients, predominantly on the basis of the patients undergoing major vascular procedures, in two randomised controlled trials (POBBLE[16] and MaVS[17]), is evidence from the literature that specifically does not support this type of procedure as a sole indication for introduction of PBB. In the POBBLE study, patients in the metoprolol group required more inotropic support,[16] and in MaVS there was an increase in bradycardia and hypotension requiring treatment in the metoprolol group.[17] This implies that introducing PBB purely on the basis of the type of procedure has the potential to cause harm.

The type of procedure was reported by the vascular surgeon as a predominant determinant in the decision to commence beta blockers in the perioperative setting at three of the hospitals. (**Table 4.5)** However, it was the sole determinant of the need for PBB according to the intended practice of the vascular surgeon at only one of these hospitals.

The type of procedure is a component of the RCRI,[7] (**Table 2.1**) and was included as an important risk factor in the assessment of overall patient risk by the anaesthesiologists. (**Table 4.6**) However, the importance of the type of procedure did not extend beyond its contribution as a risk factor.

One of the anaesthesiologists reported a difference in approach to risk stratification and intervention in patients undergoing suprainguinal and infrainguinal procedures. The RCRI does not further stratify risk on the basis of the site of major vascular surgery. However, the incidence of perioperatve major adverse cardiac events is different in these two groups of patients, and a number of authors have suggested that this should be accounted for during risk stratification.[11,12,47,48]

The type of procedure was not an important consideration in the decision to commence beta blockers when the decision was the responsibility of a cardiologist.

5.2.2.3 Other risk factors considered important in patient selection for PBB

Advanced age has been suggested as an important predictor of outcome,[12,48] but was not identified as an important risk factor considered in patient selection in this study. However, the participants did attribute importance to two other risk factors.

i. Hypertension

The five participants who indicated that hypertension was an important consideration were not supported by the reports of their paired participants. (**Table 4.6**) However, they were all directly involved in the administration of beta blockers perioperatively, which suggests that hypertension may be an important consideration at South African training facilities.

Patients with IHD and hypertension are a subgroup of patients that may be expected to derive greater benefit from beta blockade in this setting.[121] One group of investigators has suggested that adjustment of patient risk assessment in the presence of hypertension would improve accuracy.[12] However, there are no randomised controlled trials that assess the effect that the

introduction of beta blockade in hypertensive patients undergoing major vascular surgery has on patient outcome. Although, the use of beta blockade may seem a logical pharmacological choice in this setting, the use of beta blockers in the treatment of hypertension, in the general population, is currently only a fourth line option.[121,122,146] In addition, acute reduction of blood pressure in the perioperative period may be harmful.[202]

ii. Obesity

Obesity was identified as a significant risk factor for myocardial infarction in the general population of sub-Saharan Africa,[197] but has not been independently associated with perioperative mortality.[7,11,45,46,48,53,54]. One of the participants indicated that obesity as a patient risk factor contributed to the decision to commence beta blocker therapy in vascular surgery patients, but there is no evidence that beta blockers have extended indication, or are more effective at reducing risk, or have less potential for harm in obese patients.

5.2.2.4 Contraindications to PBB and situations that demand careful consideration

The major side effects of beta blocker medication, that may be associated with an increase in morbidity and mortality in the perioperative period, affect the cardiovascular and respiratory systems. Bradycardia, hypotension, congestive cardiac failure (CCF) and cerebrovascular accident (CVA) are the major cardiovascular concerns related to the initiation of beta blockers perioperatively. The principal respiratory concern with the administration of beta blockers is the potential to develop bronchospasm. However, a number of other considerations may need to be taken into account. (**Section 2.6.1.1**)

Situations in which beta blockers were avoided, or commenced only after careful consideration, at South African training facilities, are reported in **Section 4.2.2.3**. Generally, the reports of current practice were consistent with considerations highlighted in the literature review.

i. Emergency surgery

There are no trials that directly assess whether it is safe or efficacious to introduce beta blocker medication before emergent major vascular surgery. However, a high mortality associated with emergency vascular surgery has been established.[47] The largest randomised trial aimed at assessing the benefit of PBB included patients undergoing emergency surgery,[3] while other trials did not.[14-19] It is possible that the acute initiation of beta blockade in this setting may have a further negative effect on patient outcome.[3]

Cautious consideration given to the introduction of beta blockers before emergent major surgery currently seems reasonable.[4] The apparent need to balance potential for risk and benefit of beta blocker introduction before emergent major vascular procedures was widely appreciated across South African training facilities. (**Figure 4.13**) Two of the hospitals avoided PBB altogether in this setting.

ii. Bradycardia

Although the overall benefit of tight heart rate control with beta blockade is not universally supported, controlling heart rate remains a central tenet in the practice of PBB. (See **Section 2.6.2.2** for a description of the controversies surrounding the benefit of heart rate control with beta blocker medication) The ESC guideline[4] recommends the titration of beta blockade to achieve a heart rate between 60-70 beats per minute (bpm), and the ACCF/AHA guideline[5]

recommends targeting a heart rate between 60-80 bpm. However, current recommendations are not based on definitive evidence, and require confirmation.

Traditionally, the definition of bradycardia in an adult patient is a heart rate of less than 60 bpm. However, this is based on convenience and mutual agreement rather than science, and support for lowering the threshold for the diagnosis of bradycardia has been reported.[203,204] Avoiding hypoperfusion in the perioperative period is essential. The presence of symptoms related to haemodynamic compromise and decreased organ perfusion, ultimately determine the threshold for acceptable heart rate. The optimal heart rate for achieving balance between myocardial protection and organ compromise has not been determined, and is almost certainly not consistent across heterogenous populations. Titration of beta blocker medication in patients with a heart rate below 60 bpm may increase the risk of the intervention without measurable benefit.

The study protocols of the randomised controlled trials that are assessed in the development of consensus guidelines, called for dose adjustment of beta blockade at a variety of levels, but commonly allowed for continuation of beta blockers at heart rates below 60 bpm. [3,14-19,119] No vascular surgeon specifically advocated the administration of beta blockers below the traditionally accepted definition for the diagnosis of bradycardia (ie 60 bpm). Practice did not allow beta blockade to be commenced in patients with a heart rate less than 60 bpm at the hospitals under vascular surgeon control (Hospitals V,A and S). The anaesthesiologists involved in the initiation of beta blockers, on the other hand, were generally more tolerant of a lower heart rate, and beta blockers were sometimes carefully introduced by anaesthesiologists in patients with a heart rate below 60 bpm (Hospitals C,U and L). At Hospital R, the occasional intraoperative introduction of beta blocker medication was seldom thought to be necessary in the presence of a heart rate less than 80 bpm.

The lack of consensus on this subject is evident in the variable practice reported by the participants in this study. However, there is uniform agreement that slow heart rates are at least a reason for concern. (**Figure 4.14**)

iii. Hypotension

The ESC guidelines recommend that systolic blood pressure should be maintained above 100 mmHg.[4] The ACCF/AHA focused update on perioperative beta blockade recommends titration to a heart rate of 60-80 bpm in the absence of hypotension.[5] Once again, the recommended lower limits of blood pressure that allow continuation of beta blocker medication are not evidence based. However, subgroup analysis of the POISE data, infers an association between hypotension and adverse outcome.[3] Therefore, it is critical that hypotension is avoided in patients receiving beta blocker therapy as a risk reduction strategy.

A uniform, number based assessment of low blood pressure may be inappropriate, since this may increase the potential risk for cerebral ischaemia, in the face of pressure dependant cerebral blood flow, in patients with severe hypertension. It may be prudent to avoid a significant decrease in blood pressure (> 20%) from the patient's baseline, rather than to determine criteria for continuation based on a specific blood pressure in all patients.

The participants included in this study were aware of the need for careful consideration or avoidance of beta blockers in the presence of low blood pressure. (**Figure 4.14**) Only four of the participants gave specific numerical limits in terms of what they considered hypotension to be in this setting. Patient specific limits were suggested by the remaining participants, and this may represent a more rational approach. Three of the anaesthesiologists considered titration of beta

blocker medication even in the face of a low blood pressure. However, this practice was highly selective and the patient response was closely monitored.

iv. Congestive cardiac failure

Careful consideration is prudent before introduction of beta blocker medication in patients with congestive cardiac failure (CCF). The classification and grading of heart failure determine indications for beta blocker administration, and have an impact on methods and timing of initiation.[124] Optimisation of patients with CCF may include the introduction of a beta blocker, but not necessarily as an initial therapy.[124] The significantly greater risk attendant to major surgery in patients with decompensated CCF, favours a delay to allow appropriate investigation and optimisation before elective surgery. [4,5]

The anaesthesiologists recognised the need for careful consideration before the introduction of beta blockers in patients with CCF. Three of the anaesthesiologists indicated that even a history of CCF warranted careful consideration before the introduction of beta blocker medication. Their concern may seem unnecessary. However, a review by Biccard et al advises an individualised approach to perioperative optimisation with beta blockers in patients with heart failure.[138]

Vascular surgeon opinion on the use of beta blockers in the presence of CCF was less clear. Opinion varied from referral to a specialist physician or cardiologist, to absolute contraindication to the use of PBB.

The semi-quantitative questionnaire (**Appendix F**) did not specifically enquire about indications for specialist referral. It is possible that referral was more extensively utilised than reported in the interviews, particularly in the presence of an active cardiac condition.

v. Cerebrovascular disease

Analysis of the POISE data reveals an association between previous cerebrovascular accident (CVA) and adverse outcome.[3] Currently, however, there is no consensus recommendation to avoid, or even caution the use of beta blockers, in patients with a previous CVA. A history of CVA remains a valid component of the RCRI, and its contribution to the process of risk stratification is still recommended by international consensus groups. [4,5]

In the aftermath of the POISE data, two hospitals (Hospitals A and U) avoided the use of beta blockers in patients with a history of CVA undergoing major vascular surgery. One hospital (Hospital L) exercised extra caution before making the decision to introduce beta blockers. However, the presence of cerebrovascular disease was not considered a risk factor that would inherently limit enthusiasm for the introduction of beta blocker medication at the remaining hospitals (Hospitals V,S,C and R).

Four of the anaesthesiologists voiced concerns about the use of beta blockers in the management of patients with cerebrovascular disease. As previously discussed, the anaesthesiologist's interpretation of the RCRI may not be as simple as just calculating the number of risk factors.

There is suggestion from the participants in this study, that it may be reasonable to avoid beta blockers in patients with a previous CVA. The timing of the previous stroke, the underlying pathology (haemorrhagic versus ischaemic CVA), and the response to treatment and risk factor modification, may be important factors that deserve further investigation.

vi. Respiratory disease

Recent literature supports the use of beta blocker therapy in patients with COPD or asthma undergoing major vascular surgery. Caution is recommended in the presence of severe disease or significant reversible airways obstruction.[141]

The potential for deterioration in respiratory function as a result of the administration of beta blockers in patients with asthma and COPD was a consideration at all hospitals. The severity of the disease was an important discriminatory factor for many of the participants.

vii. Sepsis

Sepsis was a chief contributor to the increase in overall mortality in the POISE trial.[3] Beta blockade, in the setting of severe sepsis, may prevent the required increase in cardiac output to meet the massive increase in demand for oxygen delivery. Furthermore, exacerbation of hypotension may lead to a reduction in antibiotic delivery to sites of infection, and an ongoing nidus for infection as a result of ischaemic tissue.

Systemic sepsis caused careful consideration at one of the hospitals. In addition, three of the anaesthesiologists were of the opinion that the potential for significant adverse effect on patient outcome, by the use of beta blockers in the setting of systemic sepsis, created sufficient concern to recommend the avoidance of PBB.

One of the participants was concerned about the introduction of beta blockers in patients with localised sepsis. Delayed presentation means that localised sepsis may be relatively common in patients undergoing interventions related to occlusive atherosclerotic disease in the South

African state sector. Delaying surgery for preoperative titration of beta blocker therapy may not be possible in the setting of localised sepsis.

viii. Impaired glucose tolerance

Only one participant identified the potential adverse effects of beta blockade on glycaemic control, as a cause for additional consideration before selecting patients to receive beta blockers perioperatively. However, the benefits of beta blockers probably outweigh the adverse effect on glycaemic control and lipid profile in well selected patients.

ix. Advanced age

The inclusion of patient age as a predictor of risk has been proposed.[11,12,48] Increasing age was not considered an important risk factor promoting the use of beta blockers at South African training facilities. However, three of the participants indicated that increasing age demanded extra consideration with respect to the safety of beta blockers in the perioperative period. Altered pharmacodynamics and pharmacokinetics make response to therapy less predictable.[137] Thus dose adjustments are often necessary,[148] and therefore, careful consideration is entirely appropriate.

x. Drug interactions

Polypharmacy is not uncommon in patients presenting for major surgery. Care should be taken to avoid concurrent use of medications that are known to be subject to significant adverse effects as a result of drug interaction.

The potential complications associated with concomitant use of beta blockers and calcium channel blockers are described in **Section 2.6.1.1**. The need for careful consideration before

introducing beta blockers in patients already receiving calcium channel blocker medication was appropriately advised by three of the participants. Avoiding concomitant use altogether, as recommended by a further three participants is probably not entirely necessary. However, the class of calcium channel blocker medication is important. Beta blockers should only be administered with extreme caution in patients already receiving benzothiapines (eg diltiazem) and phenylalkylamine derivatives (eg verapamil). Dihydropyridines (eg amlodipine and nifedipine), on the other hand, have no major effect on sinoatrial or atrioventricular node conduction and refractory period.

5.2.3 Specifics of perioperative beta blockade

5.2.3.1 Frequency of PBB at South African training facilities

It is unclear how commonly PBB was used as an intervention strategy. It depends on whether the hospital supported a proactive, selective, or restrictive approach. (**Section 4.2.3.1**) Restrictive approaches may lead to underuse of intervention strategies, and may result in an increase in morbidity and mortality. Recent literature, on the other hand, counts against a recommendation for the use of a proactive approach.

Practice across South Africa varied remarkably. Anaesthesiologists tended to be more selective in approach than some of the vascular surgeons, although there had been a move towards more selective strategies at two of the hospitals under vascular surgeon control (Hospitals V and A). Cardiologists promoted restrictive strategies to patient selection at the two hospitals where they featured prominently in patient selection for beta blockade (Hospitals L and R). Intraoperative

initiation and titration of beta blocker medication provided another option at the four hospitals where the anaesthesiologists had an impact on perioperative decision making.

5.2.3.2 Treatment initiation, titration and withdrawal

It is unclear from the available literature which beta blocker should be used for PBB (**Section 2.6.2.1**); what the initial dose should be, how long before surgery medication should be introduced, whether it should be titrated, and to what specific target end points (**Section 2.6.2.2**); and when and how medication should be withdrawn (**Section 2.6.2.3**). As a result, variation in practice across South African training facilities could have been expected. The extent of inconsistent responses of the paired participants, however, cannot be defended. The degree of inconsistency in paired participant responses (**Grey shading in Tables 4.8 – 4.10**) highlights the need for more effective communication between clinicians involved in the management of patients undergoing major vascular surgery.

i. Choice of beta blocker medication

No study has directly compared the outcomes of patients related to the different agents. The choice of an appropriate agent for use in PBB is reviewed in **Section 2.6.2.1**. Methodological differences make comparisons between studies difficult, if not inappropriate. International guidelines suggest that agents with a higher degree of selectivity, without intrinsic sympathomimetic activity, and a longer duration, may confer an advantage.[4,5] This has not been confirmed in a randomised trial.

Oral atenolol was used at all South African training facilities, largely due to its availability in the state sector, and potentially as a result of favourable cost. (**Table 4.8**) A number of other drugs including intravenous atenolol, carvedilol, labetolol, and esmolol were sometimes used.

The literature may suggest that longer acting agents hold greater potential for benefit.[4,5,164] There is no compelling evidence of benefit with the use of combined alpha and beta receptor antagonists. However, the lack of availability of intravenous atenolol was offered as an explanation for the use of intravenous labetolol at two of the hospitals.

The effects of carvedilol make it an ideal agent for medical patients with congestive cardiac failure or left ventricular dysfunction after myocardial infarction.[205] However, there are no randomised trials favouring the use of carvedilol as a perioperative risk reduction strategy. Cardiologists were generally responsible for the prescription of carvedilol at South African training facilities. Prescription of carvedilol should probably be restricted to patients with independent medical indications for its introduction.

The short duration of action of esmolol makes it ideal for titration to effect. In the setting of PBB, at South African training facilities, the use of esmolol was largely restricted to the intraoperative period. A study by Raby et al, showed benefit with the use of esmolol to control heart rate below a patient specific predetermined ischaemic threshold.[171] However, this study specifically targeted the postoperative period.

Six participants indicated that they would prefer to use another drug, not available to them for use at their hospital. All of these participants were directly responsible for beta blocker initiation, and were not specifically asked whether they would prefer to use a different beta blocker.

ii. Initial prescription, timing of surgery, titration and end point targets

Section 2.6.2.2 describes the uncertainty surrounding best practice in terms of the dose and the need for titration of beta blocker medication. Current literature does not clarify the necessary balance between the potential benefit of tight heart rate control and the risks of hypotension and bradycardia when tight heart rate control is targeted. However, high, fixed doses of beta blocker medication in close proximity to major surgery proved harmful in POISE,[3] and should be avoided.[4,5]

Best practice has not yet been determined, but greater correlation of paired participant responses should be expected.

The use of oral atenolol for PBB was most common. However, there does not appear to be any consistency in the initial beta blocker prescription across South African training facilities. (**Table 4.8**)

The participants did not agree on actual or ideal duration of beta blocker medication before surgery. Titration of beta blocker medication was widely, but not uniformly supported. Delays before surgery allowing time for titration of medication were thought to be fortuitous rather than strategic, and end point targets of titration were diverse. (**Table 4.9**)

The ESC guideline recommends that treatment be initiated at least one week before surgery.[4] The ACCF/AHA focused update recommends the initiation of beta blocker medication days to weeks before surgery.[5] Both guidelines recommend that beta blocker medication should be titrated to heart rate and blood pressure, but the titration targets differ. As discussed in the literature review, these recommendations are based on the small number of trials which have demonstrated benefit. However, the benefit of early introduction is yet to be confirmed. (**Section**

2.6.2.2) These recommendations were widely acknowledged by the participants, but beta blocker medication was commonly administered in close proximity to surgery. The heart rate that was targeted was variable, and none of the participants indicated that blood pressure limits were considered in target end points.

The practice of the two participants who did not indicate an intention to titrate medication before surgery, warrants further discussion. Both of these participants reported that a fixed standard dose of beta blocker medication was prescribed.

The vascular surgeon at Hospital C indicated that a relatively low dose of oral atenolol (25mg) was prescribed. It seems likely that this would be insufficient to control heart rate, to the targeted end point of 60-70 bpm, in many patients. Despite the potential for a reduction in adverse effects as a result of beta blocker medication at a lower dose, the introduction of fixed doses of beta blocker medication, shortly before surgery, no longer enjoys the support of published international guidelines. [4,5]

The moderate fixed standard dose of oral atenolol (50mg), administered on the morning of surgery by the anaesthesiologists at Hospital U, is also not aligned with current international consensus guideline recommendations.[4,5] The intended practice at Hospital U presents an interesting argument that currently remains unresolved. There is evidence that the incidence of perioperative myocardial infarction (PMI) and cardiac death can be reduced with beta blockers commenced on the day of surgery.[3] However, the balance between the risk of beta blocker introduction immediately before the onset of the physiological stresses of major vascular surgery, and initiation of beta blockade in a ward environment that is thought to be inadequately monitored and potentially unsafe, remains central to the argument.

The potential drawbacks of a standard dosing regimen without titration are;

- There is no room for variability in patient response to the medication, and an inherent risk of both under- and overdose
- The intraoperative period may be unpredictable, standard doses of beta blocker therapy administered shortly before surgery, may complicate the intra- and postoperative course
- The postoperative period is characterised by dynamic changes in response to the physiological stress of surgery. A standard dose lacks the required flexibility in this setting, especially in patients receiving oral medication with a long duration of action.

At four of the hospitals intraoperative titration of beta blockers may have compensated for the short preoperative duration of therapy, and improved the efficacy of PBB. Furthermore, there was opportunity to introduce beta blockade over a longer period in an outpatient setting at three of the hospitals. However, the target of therapy in these patients was not restricted to a reduction in perioperative major adverse cardiac events (MACE), and the patients referred for preoperative assessment would commonly continue beta blocker therapy indefinitely after surgery.

There are important potential benefits of preoperative anaesthetic assessment clinics.[206-208] Assessment of high risk patients by senior clinicians at a preoperative assessment clinic is advocated elsewhere in the world.[182,183] However, resource limitations at South African training facilities were highlighted as a barrier to the introduction of preoperative clinics. (**Section 4.5**) Assuming titration targets were well defined, patients would need to be reviewed at least once before surgery, and this would increase the demand on limited resources. Furthermore, the titrated dose of beta blocker medication before surgery may not be the appropriate dose in the

postoperative period. Therefore, safety of the intervention would not necessarily be enhanced. Although the development of preoperative clinics should be encouraged, their development would not eliminate the challenges of effective and safe implementation of PBB.

iii. Withdrawal of beta blockers after surgery

The participant responses to timing and method of withdrawal of beta blockers were also inconsistent. (**Grey shading in Table 4.10**)

The ideal duration of beta blockade in patients receiving beta blockers as part of a perioperative risk reduction strategy, has not been determined. A number of suggestions have been made, and are discussed in **Section 2.6.2.3**.

The immediate postoperative period is a time of high physiological stress,[31] which can often extend for days after surgery.[32] A study by Landesberg et al shows that ischaemic events start to occur immediately after surgery.[23] However, an imbalance in myocardial supply and demand, is probably the dominant mechanism in PMI for at least the first 3-4 days after major surgery.[26] Consequently, not continuing beta blocker medication on return to the general ward after 48-72 hours, as was characteristic of the practice at one of the hospitals in this study, may not adequately protect at risk patients from adverse perioperative cardiac events.

At the opposite end of the spectrum of recommended periods for continuation, one of the participants was of the opinion that if sufficient concern was raised to indicate the need for PBB, then that concern should extend to other events beyond the perioperative period, and beta blocker medication should be continued long term. There is no evidence to support the continuation of beta blocker medication in patients with no independent medical indication for their use. Furthermore, chronic beta blocker medication may have a detrimental effect on metabolic

profile, cardiovascular risk, and may be less protective than other medications.[146] As a result, despite a lack of evidence, unnecessary continuation cannot be recommended.

There is no evidence to favour tapering of beta blockade over abrupt withdrawal. Lack of obvious benefit, and the logistical complications of tapering medications, makes this practice unnecessary.

5.2.3.3 Additions to standard care related to the decision to initiate PBB

All of the participants supported the use of statin medication in vascular surgery patients. (**Figure 4.18**) Practice in South Africa is in keeping with the increased realisation of the beneficial effects of statin medication,[86,87] that have been most impressive in patients undergoing vascular surgery.[209,210] In this study, the uniform acceptance of the role for statins in the routine management of patients undergoing major vascular surgery, provides an interesting contrast to the low level of correlation and differences in intended practice, with respect to PBB. The paucity of reports of adverse effects of statins[211] may be central to the more uniform intended practice.

The use of aspirin and other medical interventions were a greater point of focus for the vascular surgeons than the anaesthesiologists. (**Figure 4.18 and Table 4.11**) The anaesthesiologists were more focused on monitoring haemodynamic changes in the immediate perioperative period. These differences in focus are of great interest, as are the differences in interpretation of literature related to the selection of candidates for PBB, discussed above. (**Section 5.2.2.2**) Differences that seem to divide opinion of the participants, on the basis of specialty, may underlie the inconsistent reporting of intended practice within institutions and across the country. These differences in focus and interpretation make effective communication between role

players critically important. However, these differences need not be viewed as a cause of conflict. Institutions should be encouraged to draw on the expertise of all specialist resources to optimise management of patients.

Although the anesthesiologists were concerned with hemodynamic monitoring at the time of surgery, there was no reported difference to standard care and monitoring of patients, before or after surgery, on the basis of their selection as candidates for PBB. There is no literature to support alternative monitoring practices, but risk prediction models[187] and early warning systems[188,189] should be considered. Further research into this aspect of patient management may be the key to improved safety of PBB in future.

5.3 Discussion related to the secondary objectives of the study

There were three secondary objectives in the study. The remainder of the discussion chapter relates to these objectives.

a) To determine whether the anaesthesiologists and vascular surgeons included in the study are satisfied with their institution's current approach to the implementation of perioperative beta blockade, as a risk reduction strategy in the perioperative management of patients undergoing major vascular surgery. (**Section 5.3.1**)
b) To report suggested future modifications to clinician responsibilities in the implementation of perioperative beta blockade. (**Section 5.3.2**)
c) To identify potential barriers to the safe and effective implementation of perioperative beta blockade as an intervention. (**Section 5.3.3**)

5.3.1 Participant satisfaction with current strategy

Participant satisfaction with current practice is reported in **Section 4.3**.

Despite the numerous recommendations for a change in specialist responsibility for specific aspects of perioperative beta blocker therapy (**Figures 4.20- 4.25**), only half of the participants indicated that they were not satisfied with current practice at their hospital.

A number of associations with participant satisfaction are notable, but are useful only in terms of hypothesis generation. These associations may be helpful in developing recommendations for future practice, and have therefore, been included in the discussion.

There appears to be an association between active involvement of the participant in perioperative beta blockade (PBB), and the indication of satisfaction with the hospital's current approach. (**Figure 4.19**)

Two anaesthesiologists had access to vascular surgery patients at a preoperative anaesthetic assessment clinic. Another anaesthesiologist occasionally assessed patients deemed to be at particularly high risk, a few weeks before planned surgery, at the request of the vascular surgeon. The vascular surgeons at all of these facilities indicated that they were satisfied with practice. The involvement of other specialists in the preoperative optimisation of patients possibly increased overall satisfaction. Lack of support from other disciplines and shortages of other specialists were also reported as reasons for dissatisfaction. (**Section 4.3**) This adds weight to the suggestion that multidisciplinary team involvement should be promoted. The move towards multidisciplinary team involvement was widely supported by the participants. (**Figure 4.20**)

Inferences are difficult to make, with any degree of certainty, but it may be noteworthy that the four participants, who reported changes in approach since the POISE publication, were all satisfied with current practice. The participants reporting on practice, at the three hospitals where no changes to policy had been made over a prolonged period, all reported that they were not satisfied with their hospital's current practice.

Finally, it is important to clarify that participant reports of satisfaction did not mean that there were no ongoing concerns about how to implement PBB, nor that the participant was against changes to clinician roles in future. Reassessment of clinician roles was widely supported. (**Section 4.4**)

5.3.2 Suggested changes to clinician roles and responsibilities

The participants suggested numerous changes to the control of perioperative management strategy. Changes to policy development responsibilities were the most common and the most important. Suggested changes to roles in initiation of PBB, titration of medication before surgery, and withdrawal of beta blockade, were also made. The changes are discussed broadly and the feasibility of the suggested changes is considered. The future roles for non-specialists are also discussed.

5.3.2.1 Future roles in perioperative management strategy

Although practice varied markedly across South Africa, practice development has been dominated by the vascular surgeons. (**Figure 4.2**) At institutions where anaesthesiologists have had limited involvement to date, there is impressive support for greater contribution from the anaesthesiologists in future. (**Table 4.12**) A lack of resources, added workload burden and the

possibility of delays are all valid concerns that have an impact on the feasibility of increased involvement. (**Section 5.3.2.3**) Despite these concerns, the anaesthesiologists were willing to accept a more extended role. (**Section 4.4.1**)

i. Policy development

At least one of the participants from each hospital believed that the development of policy should involve multiple disciplines, but there were no hospitals where there was agreement on policy control. All of the vascular surgeons welcomed future involvement of other specialists, and indicated support for multidisciplinary team (MDT) directed decision making in future. It is entirely reasonable that the vascular surgeons consult other specialists with an interest vested in this aspect of care, but it is important that they should remain involved in decisions that affect the overall outcome of their patients. Furthermore, they are more immediately available to introduce interventions aimed at reducing risk. To exclude the vascular surgeons from risk intervention processes would lead to inevitable delays and missed opportunities to intervene.

As our understanding of risk develops, perioperative risk stratification and optimisation is developing into a specialised field. An advantage of an MDT would be the combination of expert opinion related to each aspect of perioperative care.

An MDT approach should probably be encouraged. This would improve communication, understanding of the intended processes, and promote greater support for interventions aimed at risk reduction. Roles will need to be clarified. The allocated roles will likely continue to be site specific. At each hospital the most suitable clinician to lead the process should be identified, and special interest in the field should be taken into consideration. The specialties included in the

MDT should be chosen on the basis of current practices, available staff, and motivation to be involved.

The vascular surgeons and anaesthesiologists should be included in policy development at all hospitals. There is probably a role for the cardiologist at most facilities, although the limited availability of cardiologists, as a result of reports of an insufficient number of specialists, may restrict their involvement significantly at some of the hospitals. Future studies of practice in South Africa should include the cardiologists. Success may also rely on intensivist and specialist physician acceptance of proposed practice. Their involvement may improve continuity of care, which was a commonly recognised barrier to PBB. (**Figure 4.29**)

Involvement of multiple specialists should also be cautioned. It may increase confusion, increase the chance of error by omission, and lead to unnecessary delays. Irrespective of the approach that is adopted, success of the approach will depend on accurate delineation and acceptance of roles. Communication will remain a key component of the process.

ii. Initiation

Suggested changes to clinician responsibilities for beta blocker initiation were less common. (**Section 4.4.2**) Feasibility and the perceived benefit of early introduction of beta blockade were the source of motivation in favouring vascular surgeon responsibility for the initiation of PBB. However, endorsement of the vascular surgeons as the clinicians responsible for initiation of PBB must be interpreted in the context of future policy development being under the control of an MDT or the anaesthesiologists.

There was a desire to move away from the reliance on the cardiologists for beta blocker initiation in the perioperative setting. This was due to the cardiologists' reported reluctance to introduce

beta blocker therapy as a risk reduction strategy in the absence of independent medical indications for beta blocker medication, and also the shortage of cardiologists, which limits the number of patients that could be referred for assessment.

In essence, the process of PBB initiation is dependent on identification of appropriate candidates for PBB, followed by initiation of the medication. The decision to commence PBB is the area that warrants greatest attention. Identification of the patients who are likely to benefit from PBB remains a significant challenge. Approaches at each hospital will probably continue to differ, as has been shown in this study. If consensus can be reached on how the practice should be implemented, and the indications for commencing PBB simplified, then the potential benefits of point of care introduction by the vascular surgeons may be realised. If the identification of patients remains complex and relies on individualised patient assessment, for all but the most straightforward cases, then the anaesthesiologists and cardiologists possibly provide expertise beyond that which is available within the Vascular Surgery Department. Practice should ultimately balance the benefit of perceived expertise of the anaesthesiologists and other specialists, against the greater convenience of vascular surgeon control over initiation.

iii. Titration of beta blocker medication

In general the vascular surgeons are well placed, from a practical point of view, to be responsible for the titration of PBB before major vascular surgery. In addition, the vascular surgeons were confident that they were capable of fulfilling this role. In contrast, the anaesthesiologists were less confident in the ability of the vascular surgeons to effectively control this aspect of practice. One anaesthesiologist even recommended omitting preoperative titration altogether, as a consequence of concern over the safety of such a practice.

Differences in opinion within hospitals were common. There was partial agreement about who should lead the process of beta blocker titration at two of the hospitals. The vascular surgeons were to fulfill the role at Hospital V, and the cardiologists at Hospital R. However, the anaesthesiologist at both of these hospitals recommended a degree of support in the process. Areas of agreement between the anaesthesiologist and vascular surgeon at these two hospitals were more prevalent than at any of the other hospitals included in the study. However, recommendations for future practice at these two hospitals were very different. This highlights the difficulty with making recommendations across all hospitals.

Titration practice in future will need to be determined by the clinicians that develop policy at each of the hospitals.

iv. Withdrawal of beta blockers

As a poorly defined aspect of PBB, many of the participants recommended a change to clinician responsibilities. At the time of the study, all nine of the participants who claimed that PBB was practiced, indicated that the vascular surgeons were responsible for the withdrawal of beta blockers in patients that did not have an ongoing indication to continue use. (**Table 4.4**) Recommendations for future practice were very different. (**Figure 4.25**)

The withdrawal of beta blockade requires two separate considerations; the decision to withdraw, and also the responsibility for ensuring the safe withdrawal of the medication. Logistic limitations mean that it may not be feasible for both aspects to be carried out by the same specialty.

Vascular surgeons are ordinarily responsible for patient management once patients return to the ward, they are commonly responsible for the discharge of the patient from hospital, and they generally review patients at an outpatient clinic after discharge from hospital. Despite the convenience of multiple points of patient contact in the postoperative period, favouring their involvement in the withdrawal process, there was widespread recommendation to shift away from vascular surgeon responsibility for this aspect of practice. The lack of specific training pertaining to this aspect of patient management, especially when it extends beyond the perioperative period, and the potential benefit to be gained from wider consultation, were offered as reasons for transferring responsibility for the decision to other specialists, or teams of specialists.

Taking overall responsibility for PBB as an intervention was cited as a reason for anaesthesiologist involvement in beta blocker withdrawal. Greater awareness of the sequelae of altered physiology in high risk patients undergoing major vascular surgery favoured anaesthesiologist responsibility for withdrawal of medication, where the cardiologists were unavailable. However, the ongoing management of patients is beyond what could realistically be expected of an anaesthesiologist. One participant suggested that it would be reasonable to hand over the process of beta blocker continuation or withdrawal to another clinician, provided that the plan for withdrawal was clearly communicated.

The point of care opportunity, familiarity with indications for ongoing beta blockade, and the potential need for further intervention, are all reasons for favouring the involvement of cardiologists in decisions related to ongoing therapy.

It seems reasonable that the decision to withdraw beta blockade should be made by the team or clinician that is responsible for initiating the process. Additionally, the physical withdrawal of the medication could take advantage of the favourable logistics of regular vascular surgeon contact with the patient in the postoperative period. There should be a low threshold for referral to another specialist in challenging cases. All patients identified as requiring ongoing beta blockade should be referred for ongoing management to either a specialist physician or cardiologist. In the absence of a perioperative cardiac or treatment complication, it is probably reasonable for the clinician responsible for the ongoing management of the patient to review the patient at an outpatient clinic within one month of discharge from hospital.

The lack of agreement in responses makes it difficult to make specific recommendation. Ultimately, the clinician or team that controls policy development will need to clarify this aspect of practice.

5.3.2.2 The role of non-specialists

Junior doctor responsibility for prescribing beta blockers (5 participants) and poor continuity of care (6 participants) were identified as barriers to practice in this study. (**Section 4.5**) Registrars were responsible for titration of beta blockade before surgery at some of the hospitals. (**Figure 4.6**) They were also at least partly responsible for beta blocker prescription at six of the seven hospitals (**Figure 4.5**), but were only responsible for the decision to commence beta blocker medication at one of these hospitals. Although the logistics of such practice may be favourable, lack of continuity could lead to treatment omission, or even failure, and this aspect of practice cannot be supported.

There were only six vascular surgery specialist trainees (clinical fellows) across the country. (**Table 4.1**) The apparent epidemiological changes in cardiovascular risk profile in sub-Saharan Africa,[197] means that the number of new specialists is unlikely to meet the current or future demand for vascular interventions. Sufficient exposure of these trainees to the complexities of policy development should be a priority. One review suggests that clinician performance and patient outcomes, may not improve with increasing clinical experience.[212] It is likely that performance initially improves. However, the results of the review suggest that clinician performance may plateau after some time, and then deteriorate in line with a decrease in knowledge and a lack of adherence to contemporary guideline recommendations. The active involvement of clinical fellows may help to ensure that practice is reviewed and remains up to date.

However, the complex nature of PBB as a risk stratification tool, does not lend itself to appropriate implementation by junior staff. Preoperative outpatient assessment clinics elsewhere in the world have moved towards an increase in senior clinician involvement in decisions regarding patient management.[182] A further study in the United States reported that more than half of the residents (equivalent to registrar in South Africa) at 24 major academic centres were unable to provide appropriate recommendations for the management of five different hypothetical patients.[213] In a survey conducted in the United States, Ellis et al showed that the decision to commence beta blockade was related to the level of training of the anaesthesiologist, and not only the practice setting.[186]

Unless a well defined policy is in place, and until there is evidence that junior staff are capable of introducing interventions appropriately, specialists must remain responsible for development and control over PBB.

5.2.3.3 Feasibility of recommended practice

Recommended changes to clinician roles need to take into account the associated potential logistical implications.

In order for clinician involvement to be feasible, there needs to be enough clinicians within the specialty to cover the role. This should not interfere with the other responsibilities of the clinician. The clinician allocated this responsibility should have sufficient experience, and must be appropriately trained for the role. In addition, success of the practice will be dependent on the motivation of the clinician to be involved, and involvement of a specialist should not cause undue delay in management of the patient.

There are logistical considerations related to an increase in anaesthesiologist or cardiologist involvement, and what is considered ideal practice may not be feasible at South African training facilities:

i. Availability of staff

- Number: Anaesthesiologist (5 participants) and cardiologist (4 participants) shortages were specifically identified as a potential problem.
- Other responsibilities: Practical limitations of anaesthesiologists having to see patients at a time that they would not usually do so, was a further potential problem that was identified (3 participants).

ii. Appropriate training for the role

- Concern was raised that the current training of South African anaesthesiologists in the role of ‘perioperative physician’ may be inadequate.

iii. Motivation

- Anaesthesiologists may be reluctant to take on extra responsibilities (2 participants).
- Cardiologists were reluctant to be involved in the perioperative management of vascular surgery patients (3 participants).

iv. Delays in management

- Involvement of more specialists may lead to delays in patient management (1 participant).

Any future changes to practice must take the above into account, and must not concentrate on routine involvement of specialists that have marked limitations in terms of availability, situation specific training, or lack of motivation to be involved.

5.3.3 Barriers to the implementation of perioperative beta blockade as a strategy

The reasons for not following clinical practice guidelines differ from one aspect of medicine to the next. Knowledge of guidelines affected by a lack of awareness or lack of familiarity; clinician attitudes affected by the level of agreement, self-efficacy, outcome expectancy, and the inertia of previous practice; and also external factors such as lack of time or staffing deficiencies, all have an effect on clinician compliance with guideline recommendations.[214]

This study assessed the affect of four components believed to be essential for safe and effective implementation of a perioperative strategy:

i. There must be a base of evidence that favours the intervention, and there must be a need for the intervention. (Barriers related to problems with the evidence for PBB)
ii. Skilled personnel are needed to understand the nuances that surround effective implementation of the intervention, and there must be a sufficient number of appropriately trained staff to safely manage the process. (Staffing insufficiencies)
iii. There must be an environment that facilitates the appropriate level of support for such a strategy. (Hospital related barriers)
iv. Effective communication and interaction at all levels is an essential component. (Barriers related to communication and interdepartmental dynamics)

The need for an intervention that reduces perioperative risk in patients undergoing major vascular surgery is clearly evident. (**Section 2.1 and 2.2**) Appropriate allocation of resources relies on the identification of the barriers that limit development and implementation of perioperative risk reduction strategies. All four of the components listed above pose challenges to the implementation of PBB as a strategy at South African training facilities for vascular surgery.

Literature that addresses barriers to the implementation of PBB is limited. The findings from elsewhere in the world are presented in **Section 2.7**.

5.3.3.1 Inconsistent evidence

Interpretation of the literature is complex. The heterogeneity within, and between, trials is a source of uncertainty, and the methodological limitations of many of the studies have been exposed. (**Table 2.2**) Even consensus guidelines differ in their recommendations, and have required recurrent updates.[4,5] As a result, it is no surprise that a lack of faith in guidelines (2 participants), poor knowledge of the guidelines (2 participants) and confusion (6 participants) were all identified as important barriers to the implementation of PBB. (**Figure 4.26** and **Section 4.5.1**) It is important to note that the ideal methods of patient selection and the optimal treatment regimen are not known.

A Canadian study highlighted a need for further education of anaesthesiologists on guideline recommendations.[181] Knowledge of recent guidelines was not assessed in this study, but was identified as a potential barrier. All of the vascular surgeons included in the study had a role in development of policy for perioperative patient management, yet none of them reported risk stratification practices in accordance with published guideline recommendations.

Publication of the POISE study[3] highlighted the potential for harm with perioperative beta blockade. The evidence for harm in the POISE study was a direct cause for the modification of approach at two of the hospitals, but was only listed as an important barrier by five of the participants. The POISE data may have lead to restrictions being applied to the practice, but it had not led to termination of the strategy.

Similarities in approach were limited in this study, as is characteristic of an intervention that remains ill-defined.

5.3.3.2 Staffing

The barriers were related to insufficient number of staff, insufficient training, or poor management of staff as a resource. (**Figure 4.27** and **Section 4.5.2**)

POISE highlights the potential for increased mortality if the intervention is inappropriately instituted. It is clear that the complexities of the practice demand attention from the most experienced clinicians (Inadequate experience/training – 7 participants), and the most appropriate specialist (Poor utilisation of expertise – 7 Participants).[182]

Poor utilisation of expertise was specifically related to the lack of anaesthesiologist support in this study. Fortunately, a willingness to accept greater anaesthesiologist involvement in the future was widely expressed by the participants. (**Table 4.12**) Greater involvement of anaesthesiologists and multiple specialists would bring practice more in line with the rest of the world.[180,182,183]

There is an increasing awareness of the need for anaesthesiologist involvement in patient management at preoperative assessment clinics.[182] These clinics may facilitate an increase in appropriate introduction of beta blockers in the perioperative period,[206] they allow for improved coordination of care between different specialties,[207] and they result in more appropriate referral of patients for cardiac assessment.[208] Two of the hospitals had functional preoperative assessment clinics. The anaesthesiologist at a third hospital reviewed complex cases, weeks before surgery, on an individualised basis. The introduction of assessment clinics should be promoted at all South African training facilities.

A shortage of specialist and nursing staff was a prominent problem. Staff shortages are likely to cause restrictions on practice that extend beyond those specifically related to PBB.

5.3.3.3 Monitoring

Effective monitoring has become one of the most critical limitations in the safety of PBB. Adverse outcomes in the practice of PBB are thought to be related to bradycardia and hypotension.[154] If bradycardia and hypotension are avoided, or immediately treated and reversed, safety of the intervention may be markedly improved. However, there has been little focus on whether safe implementation of PBB can be improved with appropriate titration, and whether the titration of beta blocker medication requires appropriate monitoring. Currently, it is not known how often to monitor. Even the targets of therapy are not well established. Moreover, any potential for benefit from more regular monitoring, and more invasive monitoring, has not been assessed.

The potential barrier to practice presented by the need for effective monitoring was commonly recognised. (**Section 4.5.3**) Titration of beta blocker medication was avoided and medication commenced on the day of surgery, at one of the hospitals, due to a perceived inability to monitor patients effectively. Surprisingly, the potential limitation of practice presented by the problem of ineffective monitoring, and the logical need for timeous intervention in patients with bradycardia and hypotension, had not led to any change in the way that patients were monitored for common adverse effects at any of the hospitals. (**Figure 4.17**)

More regular assessment and documentation of the simple measurements of non-invasive blood pressure and heart rate may be sufficient to aid with the early identification and treatment of adverse effects. If this could be achieved with more regular checks by a nurse or nursing assistant in a dedicated area of the general vascular surgery ward, perhaps then the risks of PBB could be reduced without a major increased requirement for staff and specialised resources.

However, improved detection of these adverse effects would need to be paired with appropriate intervention.

Given current resource limitations at the majority of the state sector hospitals, requirement for a higher level of care in terms of the need to be nursed in a high care environment, and by personnel with a higher level of training or qualification, would markedly restrict the feasibility of the practice.

Introducing measures that increase the safety of PBB as a strategy are likely to represent an ongoing challenge.

5.3.3.4 Cost

Although a study by Biccard et al suggests that PBB would be a cost effective strategy in South Africa,[191] cost as a barrier to the practice of PBB may be under-estimated.

Cost may increase with longer hospital stays related to a perceived need for preoperative titration. Improved monitoring and regular follow up of patients would have their own cost implications. The use of more expensive drugs was desired by many of the participants. Although not yet proven to be more effective, the use of these agents may be important determinants of both efficacy and safety. Preoperative anaesthetic assessment clinics provide another great opportunity for introduction of beta blockers days to weeks before planned surgery. However, benefit in the South African environment will need to be shown to justify the cost of such a set up. The potential for benefit with titration over weeks will need to be balanced with the risk of harm caused by delaying surgical intervention.

5.3.3.5 Communication problems and inter-departmental dynamics

Poor communication was abundant at South Africa's training facilities, and is likely to pose the greatest challenge to any future attempt to introduce perioperative management strategies.

Poor communication was a recurrent theme across all areas of practice assessed in this study. Inconsistent responses with respect to current intended practice were widespread. (**Grey shading in Tables 4.2, 4.4, 4.5, 4.7, 4.8, 4.9 and 4.10**) The poor correlation of paired participant responses cannot be explained by inconsistencies in the literature alone. The poor understanding of an intervention that targets a reduction in adverse events in a patient group at high risk is unacceptable.

Differences in opinion on practice were particularly noticeable at those facilities where both the anaesthesiologists and the vascular surgeons had a role to play in the control or implementation of practice. The apparent lack of awareness of the differences in opinion, and how the differences in opinion had an impact on intended practice, is a reflection of major deficiencies with respect to communication.

Three participants identified differences in opinion between anaesthesiologists and vascular surgeons as a significant barrier to practice. (**Figure 4.29**) However, these differences in opinion need not be a barrier. Anaesthesiologists and vascular surgeons have different areas of expertise and focus. (**Table 4.11** and **Section 5.2.3.3**) A multidisciplinary team derived approach, should aim to include favourable aspects of alternative suggestions to produce a strategy supported by all role players. Effective communication will be the key to the success of such teams.

CHAPTER SIX - CONCLUSION

This study describes the intended approach to perioperative beta blockade, at each of the specialist training facilities for vascular surgery in South Africa, and identifies the need for review of a number of aspects of perioperative management.

This is a descriptive study, facilitated by the conduct of a partially selective survey. One anaesthesiologist and one vascular surgeon, from each of the seven recognised training facilities for vascular surgery in South Africa, agreed to participate in the study. Each of the participants was identified as a potential role player by the training facility, or by the Vascular Society of Southern Africa (VASSA). A semi-structured questionnaire was used to assess intended practice of each of the participants, and their answers were recorded during a face-to-face interview.

There are inevitable limitations to survey-type research. However, this research method generated a large amount of detailed information, at a relatively low cost, and with an efficient use of time. Extensive statistical analysis of the data was avoided, since the validity of such analysis in this study is questionable. As a result, the data are discussed individually to produce an accurate description of current intended practice.

Recent developments had not prompted a change in approach at most facilities. There was inconsistency in methods of risk stratification, treatment implementation, titration practices, and the timing of withdrawal of medication. The marked variety in reports of intended practice within each facility, and across the country, highlights the uncertainty surrounding perioperative beta blockade as an intervention. Recommendations were fairly consistent for aspects of the practice that benefit from the highest level of support in the literature and published guidelines.

However, beyond the few areas of widespread consensus, opinions on current and future practice were diverse.

Describing participant satisfaction with current strategy, reporting suggested modifications to clinician responsibilities in the future, and identifying potential barriers to the intervention were secondary objectives. Not only is this the first study that describes current practice in South Africa, but addressing each of these secondary objectives improved understanding of the limitations of current practice, and allows recommendations for future practice to be made.

There was widespread dissatisfaction with current practice. The participants supported a major role for anaesthesiologists in the future, and a move towards multidisciplinary involvement in policy development and patient management. Such a shift would align responsibility for this aspect of patient management with practice reported elsewhere in the world. The need for appropriate monitoring was identified as one of many important barriers. Problems with communication were clearly evident, and will need to be addressed.

More research is necessary before any firm recommendations can be made. South African training facilities are well placed to make a significant contribution to both local and international literature. However, studies must be carefully designed to avoid adding to a body of inconclusive evidence. The response rate to this study suggests that a collaborative approach, across multiple facilities, would be supported.

The variable practice across the country; the poor correlation of participant responses; widespread dissatisfaction with current strategy; suggested changes to clinician responsibilities; and the identification of multiple barriers to the implementation of strategy, highlight the need for review at all facilities.

CHAPTER SEVEN – RECOMMENDATIONS FOR FUTURE PRACTICE

This chapter synthesises the results and discussion chapters of the research report, and in conjunction with the review of the literature, attempts to make a number of recommendations for future development of the practice of perioperative beta blockade (PBB) at South African training facilities.

7.1 Clinician responsibilities

The decision to commence PBB, in any patient for whom indications for introduction of the strategy are unclear, should be made at the most senior level, or escalated to involve multiple disciplines in the decision.

Although registrar involvement should be encouraged, registrar led decisions on implementation of PBB should probably be restricted to straightforward indications for beta blocker therapy, and continuation of established therapy, until the practice is more accurately defined.

The clinician that decides to introduce beta blocker therapy should remain responsible for the prescription of the medication, and attention should be paid to dose strategy and proposed titration targets. It seems reasonable to delegate the responsibility for titration of beta blockade to another clinician, provided that appropriate monitoring standards are developed, adhered to, and that the goals of titration are clearly defined.

The clinicians responsible for each component of PBB should be clearly defined, and in identifying the appropriate clinician, consideration should be given to experience, training,

motivation, and the feasibility of their involvement. The clinicians involved should be chosen in a hospital specific manner, and will depend on the resources and staff that are available.

All specialties with a role to play should be consulted to assess opinion on how practice should be implemented.

7.2 Changes to practice

It is evident that there were multiple approaches to PBB. It is clear that future proposed practice will probably also be site specific, and this reflects the lack of proven benefit for many aspects of PBB. Individual components are difficult to study, as the overall benefit and potential hazards of PBB are still so widely debated. The challenge for clinicians involved in PBB, will be to optimise the practice in terms of aspects that have some evidence that they are beneficial. The problem should be approached in a logical manner in order to avoid unnecessary risk. In the absence of new evidence emerging in the field, and recently published literature concentrating on reviews of the same body of evidence, clinicians will need to critically assess how practice can be best implemented within their own environment.

7.2.1 Specific recommendations

1. This study supports introduction/continuation of beta blockers in patients with widely accepted indications for beta blocker therapy in the perioperative period. Support for these indications can also be drawn from published trials and expert opinion.

- Beta blockers should be continued in patients receiving appropriate long term medication.
- Introduction of beta blockers is supported in patients with evidence of inducible myocardial ischaemia on preoperative testing.

2. An individualised approach to all other patients undergoing major vascular surgery may be required. Currently, it is recommended that a selective approach should be used. Current guidelines support the use of risk indices to determine the degree of patient risk. The use of a risk index derived in South African patients may improve the stratification process. There is also encouraging data emerging from strategies that promote the preoperative measurement of B-type Natriuretic Peptide (BNP) and cardiopulmonary exercise testing (CPET).
3. Some situations may imply the need for a lower threshold for beta blocker introduction. There was support for PBB in the situations listed below. However, PBB implementation in these situations is not necessarily supported by evidence from well conducted randomised trials.

- Clinically unacceptable heart rate

  There are many potential causes for an increased heart rate in the perioperative period, and treatment should be directed at the underlying cause before considering the introduction of beta blocker therapy.

- Multiple clinical risk factors (RCRI)

  In this study specific combinations implied either a reduced (presence of IHD) or increased threshold (CVA or current CCF) for beta blocker introduction. Current understanding of risk remains inadequate and further development of stratification processes is necessary.

4. Beta blockers are to be avoided in patients with an absolute contraindication to their use.
5. There should be careful consideration before cautious introduction of beta blockers in patients with a medical condition that is associated with an increased risk of a significant adverse effect.
6. Beta blockers should be started well in advance of the procedure, medication should be titrated against heart rate and blood pressure whenever time allows, and PBB should only be initiated if the process can be safely implemented. The limits for safety, and targets for efficacy, are not known.
7. Clinicians must remain vigilant for derangements in heart rate and blood pressure throughout the perioperative period, and should attend to any derangements as soon as they are identified, particularly if the patient has signs or symptoms of decreased organ perfusion. A higher level of care, or at least more regular monitoring of patient heart rate and blood pressure, is recommended. However, there is no evidence to support the use of this strategy.
8. Beta blocker medication should not be stopped in the immediate postoperative period. In the absence of a compelling indication for ongoing use, the recommended duration of therapy remains unclear. There is no specific evidence in favour of tapering beta blocker medication.

9. PBB is not the only important perioperative risk intervention. Many other interventions have strong and clear evidence of benefit. PBB should be viewed as just one aspect of an overall risk reduction strategy. Such a strategy should include general measures (eg. lifestyle modification) and specific interventions (eg. thromboprophylaxis, antiplatelet agents, glucose control, statin medication, and ACE inhibitors).

7.3 Breaking down the barriers

i. Future research

Research in the field, and particularly within the South African environment, is an essential component for future development of perioperative strategies. Further studies must be actively supported and encouraged. It is hoped that this study may promote a collaborative approach to further research, as the patient numbers required for studies in this field to reach statistical significance are extremely large. The high burden of cardiovascular disease in South Africa makes this country an ideal setting for research in this field. The potential contribution has already been recognised, with a number of hospitals in South Africa involved in the enrolment of patients into the PeriOperative Ischemic Evaluation – 2 trial.

Improved research, and the results of studies conducted within South Africa, can be expected to generate greater leverage when it comes to negotiations over the allocation of resources. Limited resource underlies many of the barriers that were identified in this study.

ii. Staffing

Appropriate training of staff, and sufficient number of staff, remain significant barriers at all hospitals. Review of current practices, and the development of a team of clinicians with a strong interest in the field, may revitalise the practice. Restructuring of the current system, and the consolidation of interested parties, may allow an improvement to be realised. However, greater numbers of staff will require the cooperation of hospital management. Further research in the field may be required before sufficient support for an increased allocation of resource is considered.

iii. Monitoring

Monitoring of patients receiving beta blocker medication was one of the major barriers to practice identified in this study. In the current environment of uncertainty about the potential for harm with PBB, any clinician that commences beta blocker therapy must take responsibility for the safety of the intervention. At the very least, close attention should be afforded to the effects of beta blocker therapy on heart rate and blood pressure. There are no current guidelines on the degree of monitoring required. Monitoring simple measures of blood pressure and heart rate, at more regular intervals than would ordinarily be taken as a standard, may be one way of reducing significant adverse effects of the medication. A dedicated observation sheet specifically for patients commenced on PBB, with patient specific limits identified on the sheet, may be a relatively simple intervention that would raise awareness of the need to be vigilant. This could form part of an early warning scoring system.

iv. Communication

There was poor correlation of responses across the entire group with respect to current intended practice. The areas of disagreement need to be reassessed and intended practice clarified. Effective communication between role players in the perioperative management of vascular surgery is likely to be an important determinant of the success of PBB as an intervention.

LIST OF APPENDICES

Appendix A Ethics approval certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R 14/49 Dr Richard lawson

CLEARANCE CERTIFICATE	**M091105**
PROJECT	Perioperative Beta Blockade for Major Vascular Surgery: A Descriptive Study of Current Intended Practice Across South African Specialist Training Facilities
INVESTIGATORS	Dr Richard lawson.
DEPARTMENT	Department of Anaesthesia
DATE CONSIDERED	2009/11/27
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 2009/12/20 **CHAIRPERSON** .....
(Professor PR Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof AC Lundgren

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

Appendix B Post-Graduate Committee approval

Faculty of Health Sciences
Medical School, 7 York Road, Parktown, 2193
Fax: (011) 717 2119
Tel: (011) 717-2745

Reference: Ms Tania Van Leeve
E-mail: tania.vanleeve@wits.ac.za
21 December 2009
Person No: 9601140X
PAG

Dr RB Lawson
104 Forest Road
Athol
Sandton
2196
South Africa

Dear Dr Lawson

Master of Medicine (In the specialty Anaesthesia): Approval of Title

We have pleasure in advising that your proposal entitled "*Perioperative Beta Blockade for major vascular surgery: A descriptive study of current intended practice across South African specialist training facilities.*" has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix C Participant information sheet

Good morning, my name is Richard Lawson. I am a Registrar in the Department of Anaesthesia at The University of the Witwatersrand. I have a keen interest in the use of beta blocker medication as an intervention to reduce perioperative risk in patients undergoing major vascular surgery.

I am conducting a survey and I would be most grateful if you would consider participating. I will be inviting appropriate participants from all other hospitals that provide specialist vascular surgical training in South Africa. I will be interviewing one vascular surgeon and one anaesthetist (with a special interest in anaesthesia for major vascular surgery) from each of these recognised training facilities. After combining all participants' answers, we can expect to learn more about current opinion and practice with respect to perioperative beta blocker therapy in patients undergoing major vascular surgery. This may help to identify aspects of common practice and aspects of practice that lack consistency across the country. This will hopefully assist with the identification of targets for future research.

If you accept the invitation to participate, I will travel to meet with you at a time and place of your convenience. The research method involves a face-to-face interview. I will be asking you questions about the current practice at your hospital and asking some of your own thoughts regarding perioperative beta blocker therapy for patients undergoing major vascular surgery. This is a controversial topic in the literature. The interview will last about 20-30 minutes.

Your written informed consent is required for participation in the study. I will also be asking for separate written informed consent for the voice recording of the interview. The recording device will not be concealed during the interview. Recordings will be kept safely locked away for a

period of 2 years and then they will be destroyed in accordance with Health Professions Council of South Africa regulations.

A code sheet will be used to assist with the identification of the source of information. Only I will have access to the code. This code sheet will be secured and will be kept separate from all other data collected during the study. Nobody will be able to link you to the answers that you give. The information will remain confidential and there will be no "come-backs" from the answers that you give. Furthermore, there will be no direct reference to individual hospitals with the aim being to assess practice across all included training facilities. Please understand that you are not being forced to take part in this study and the choice whether to participate or not is yours alone. If you choose not to take part in answering these questions, you will not be affected in any way. If you agree to participate, you may stop me at any time and tell me that you don't wish to continue with the interview. If you do this there will also be NO penalties and you will NOT be prejudiced in ANY way. If you need to change any of the answers given during the interview or have any concerns whatsoever, you are encouraged to contact me via electronic mail or telephonically. The contact details are listed below. Please feel free to contact me at any time.

Thank you for considering participation.

Dr Richard Lawson (MBBCh, DASA)

Email: drrlawson@yahoo.co.uk

24hr contact: 0826860198

Fax: 0118841589

Appendix D Consent form for participation in study

I hereby agree to participate in Dr Lawson's study regarding the use of perioperative beta blocker therapy in patients undergoing major vascular surgery.

I understand that I am participating freely and without being forced in any way to do so. I also understand that I can stop this interview at any point should I not want to continue and that this decision will not in any way affect me. I understand that this is a research project and its purpose is not necessarily to benefit me personally.

I have received the telephone number of Dr Lawson should I need to speak about any issues which may arise from this interview.

I understand that the interview will remain confidential.

I have had an opportunity to ask Dr Lawson questions about the interview process and I am happy to proceed.

……

Signature of participant

Full Name:……. **Date**:……..

……

Signature of Witness

Full Name:…….. **Date**:……..

Appendix E Consent form for voice recording

I hereby agree to the voice recording of the face-to-face interview in Dr Lawson's study regarding the use of perioperative beta blocker therapy in patients undergoing major vascular surgery. I understand that I am consenting to the voice recording freely and without being forced in any way to do so. I also understand that I can stop the recording of this interview at any point should I not want to continue, and that this decision will not in any way affect me. I understand that the interview will remain confidential. I understand that the voice recording will be kept safely locked away for a period of 2 years and that it will then be destroyed in accordance with Health Professions Council of South Africa regulations. I have received the telephone number of Dr Lawson should I need to speak about any issues which may arise from this interview. I have had an opportunity to ask Dr Lawson questions about the interview process and voice recording and I am happy to proceed.

……

Signature of participant

Full Name:……. **Date**:……..

……

Signature of Witness

Full Name:…….. **Date**:……..

Appendix F Semi-structured Interview

Participant Demographics

Study Identification Number:

Rationale for identification as an appropriate participant:

- Anaesthetist/
- Vascular Surgeon

No. of years involved in perioperative management of vascular patients

- <1
- 1-5
- >5

No. of years involved in current hospital/department

- <1
- 1-5
- >5

Study Identification Number:

PREAMBLE:

For the purposes of this research project major vascular surgery includes surgical procedures on the aorta and peripheral vasculature. It excludes surgery to the carotid arteries and limb amputations.

Reassurance is given that information will remain confidential.

Explanation is given that the clinician may not be able to answer all questions. This is largely to be expected due to the wide range of questions, some of which may fall beyond the participant's field of expertise. To be unsure of an answer is entirely acceptable, and may of itself be important information during data interpretation and the generating of hypothesis.

SECTION A: PROTOCOL/PRACTICE DEVELOPMENT

1) At this hospital how frequent is it that patients undergoing major vascular surgery are prescribed beta blockers?

- i. Never
- ii. Occasionally
- iii. Regularly
- iv. Almost always, in the absence of a contraindication
- v. Unsure

2) Is there a standardized approach at this hospital for the identification of patients who should receive beta blocker therapy before undergoing major vascular surgery?

- i. Yes. Specify_____.
- ii. No
- iii. Unsure

3) What do the role players in perioperative management of major vascular surgery patients at this hospital utilise to aid in the decision as to whether beta blockers should be commenced?

- i. Not practiced
- ii. Department Protocol
- iii. Defined guidelines from the literature. Specify_____.
- iv. Discretion of Multidisciplinary Team
- v. Discretion of surgeon
- vi. Discretion of anaesthetist
- vii. Discretion of other medical specialty. Specify_____.
- viii. Other. Specify_____.
- ix. Unsure

4) Do the other vascular surgeons and/or anaesthetists within this hospital make use of the same approach?

- i. Not at all
- ii. Some overlap
- iii. Essentially the same
- iv. Unsure

5) When was the current approach to the perioperative management of major vascular surgery patients at this hospital last modified?

- i. No standardised approach
- ii. After November 2009
- iii. May 2008- November 2009
- iv. October 2007- May 2008
- v. Before October 2007
- vi. Unsure

6) What promoted the most recent change?

- i. No previous protocol
- ii. No recent change
- iii. International literature. Specify_____.
- iv. Personal experience
- v. Hospital experience
- vi. Inability to institute previous protocol
- vii. Other. Specify_____.
- viii. Unsure

7) Who is currently responsible for the development and maintenance of hospital policy when it comes to risk stratification and perioperative patient optimization in patients for major vascular surgery?

- i. No policy
- ii. Vascular surgeons only
- iii. Anaesthetists only
- iv. Cardiologists only
- v. National/Provincial Committees
- vi. Multidisciplinary team within the hospital
- vii. Other. Specify_____.
- viii. Unsure

8) How many surgeons with a special interest in vascular surgery (At the level of Fellow or above) do you currently have working in this hospital on a regular basis?

- i. 1
- ii. 2
- iii. 3
- iv. 4
- v. 5 or more
- vi. Unsure

9) How many of these surgeons are directly involved in the development of policy for the perioperative initiation of beta blockers in patients undergoing major vascular surgery?

- i. None
- ii. 1
- iii. 2
- iv. 3
- v. 4
- vi. 5
- vii. All
- viii. Unsure

10) How many anaesthetists at this hospital are known to have a special interest in Vascular Anaesthesia?

- i. None
- ii. 1
- iii. 2
- iv. 3
- v. 4
- vi. 5 or more
- vii. Unsure

11) How many anaesthetists cover an anaesthetic slate for major vascular surgical patients at least once a week?

- i. None
- ii. 1
- iii. 2
- iv. 3
- v. 4
- vi. 5 or more
- vii. Unsure

12) Are anaesthetists involved in the development of a protocol for perioperative beta blocker administration to major vascular surgical patients at this hospital?

- i. Yes
- ii. No
- iii. Unsure

13) Further comments on protocol or practice development?

_____.

_____.

_____.

SECTION B: PATIENT SELECTION

14) Whose responsibility is it to identify the major vascular surgery patients that should receive beta blocker therapy perioperatively?

- i. Not practiced
- ii. Junior doctors
- iii. Vascular surgery Registrar or equivalent
- iv. Specialist Vascular Surgeon or equivalent
- v. Anaesthetic registrar or equivalent
- vi. Specialist Anaesthetist or equivalent
- vii. Specialist Cardiologist or equivalent
- viii. Multidisciplinary team
- ix. Other. Specify____.
- x. Unsure

15) What is the predominant determinant for selection of patients to receive beta blockers perioperatively at this hospital?

- i. Not practiced
- ii. Type of procedure
- iii. Specific patient risk factors
- iv. Number of specific patient risk factors
- v. Baseline physiological values which can be manipulated by beta blocker therapy
- vi. Other. Specify_____.
- vii. Unsure

16) Does the type of vascular procedure itself determine which patients receive perioperative beta blockers at your hospital?

- i. Yes
- ii. No
- iii. Unsure

17) Do patient specific factors affect your decision on perioperative beta blocker therapy?

- i. Yes
- ii. No
- iii. Unsure

18) Which patient specific risk factors, if any, are important in your decision to administer beta blockers in patients undergoing major vascular surgery?

- i. Beta blockade not practiced
- ii. Patient risk factors don't affect decision
- iii. Evidence of inducible myocardial ischaemia
- iv. Current beta blocker therapy
- v. Heart rate. Specify_____.
- vi. History of ischaemic heart disease or previous myocardial infarction
- vii. Diabetes Mellitus/Insulin requirement preoperatively
- viii. Renal dysfunction. Specify_____.
- ix. History of cerebrovascular accident
- x. History of transient ischaemic attack
- xi. Sex of patient. Specify_____.
- xii. Hypertension
- xiii. Hypercholesterolaemia
- xiv. Family history of ischaemic heart disease
- xv. Obesity
- xvi. Sedentary lifestyle
- xvii. Cigarette smoking
- xviii. Age. Specify_____.
- xix. Sex of patient. Specify_____.
- xx. Other. Specify_____.
- xxi. Unsure

19) Which types of patient are specifically not commenced on beta blocker therapy in the perioperative period?

- i. All patients
- ii. Emergency surgery required
- iii. History of cerebrovascular disease
- iv. Elderly. Specify_____.
- v. Bradycardia. Specify _____.
- vi. Clinically acceptable heart rate. Specify_____.
- vii. Patient already receiving a calcium channel blocker
- viii. Hypotension. Specify_____.
- ix. Clinically acceptable blood pressure. Specify_____.
- x. Asthma
- xi. COPD with reversible airway obstruction
- xii. COPD without reversible component
- xiii. Cigarette smokers
- xiv. Systemic sepsis
- xv. Localised sepsis
- xvi. Peripheral vascular disease
- xvii. Aneurysmal disease
- xviii. Inflammatory arteritis
- xix. HIV related arteriopathy
- xx. Diabetes Mellitus
- xxi. Other. Specify_____.
- xxii. Unsure
- xxiii. None of the above

20) Which of these types of patient demand extra consideration before introduction of beta blockers in the perioperative setting?

- i. No specific extra consideration required on basis of patient type
- ii. Emergency surgery required
- iii. History of cerebrovascular disease
- iv. Current congestive cardiac failure
- v. History of congestive cardiac failure
- vi. Elderly. Specify_____.
- vii. Bradycardia. Specify _____.
- viii. Clinically acceptable heart rate. Specify_____.
- ix. Patient already receiving a calcium channel blocker
- x. Hypotension. Specify_____.
- xi. Clinically acceptable blood pressure. Specify_____.
- xii. Asthma
- xiii. COPD with reversible airway obstruction
- xiv. Cigarette smokers
- xv. Systemic sepsis
- xvi. Localised sepsis
- xvii. Peripheral vascular disease
- xviii. Aneurysmal disease
- xix. Inflammatory arteritis
- xx. HIV related arteriopathy
- xxi. Diabetes Mellitus
- xxii. Other. Specify_____.
- xxiii. Unsure

21) Further comments on patient selection:

_____.

_____.

_____.

_____.

SECTION C: TREATMENT INITIATION, MONITORING AND WITHDRAWAL

22) Who is responsible for the prescribing of beta blocker therapy in major vascular surgical patients?

- i. Not practiced
- ii. Junior doctors
- iii. Vascular surgery Registrar or equivalent
- iv. Specialist Vascular Surgeon or equivalent
- v. Anaesthetic registrar or equivalent
- vi. Specialist Anaesthetist or equivalent
- vii. Specialist Cardiologist or equivalent
- viii. Multidisciplinary team
- ix. Other. Specify____.
- x. Unsure

23) In relation to the surgery, when is beta blocker medication ideally initiated?

- i. Not practiced
- ii. In theatre
- iii. The day of surgery
- iv. The day before surgery
- v. 1 week before surgery
- vi. 1-2 weeks before surgery
- vii. 2-4 weeks before surgery
- viii. >4 weeks before surgery
- ix. No recommendation
- x. Patient dependant. Specify_____.
- xi. Other. Specify_____.
- xii. Unsure

24) In reality, how long before surgery are beta blockers commenced in the majority of these patients?

- i. Not practiced
- ii. In theatre
- iii. The day of surgery
- iv. The day before surgery
- v. 1 week before surgery
- vi. 1-2 weeks before surgery
- vii. 2-4 weeks before surgery
- viii. >4 weeks before surgery
- ix. No recommendation
- x. Patient dependant. Specify_____.
- xii. Other. Specify_____.
- xiii. Unsure

25) Which beta blockers, if any, are used?

- i. Not practiced
- ii. Atenolol po
- iii. Atenolol iv
- iv. Metoprolol po
- v. Metoprolol iv
- vi. Bisoprolol
- vii. Labetalol po
- viii. Labetalol iv
- ix. Esmolol iv
- x. Other. Specify_____.
- xi. Unsure

26) What is the reason for your choice of a specific beta blocker in this setting?

- i. Not practiced
- ii. Availability
- iii. Cost
- iv. Favourable pharmacokinetics
- v. Favourable pharmacodynamics
- vi. Ease of titration
- vii. Familiarity with drug effects
- viii. Personal preference
- ix. Evidence of benefit from the literature
- x. Evidence of safety from the literature
- xi. In accordance with protocol/policy
- xii. Other. Specify_____.
- xiii. Unsure

27) How is beta blocker therapy prescribed in these patients?

- o i. Not practiced
- o ii. Standard dose for all patients. Specify .
- o iii. Standard dose for all patients, followed by titration
- o iv. Patient specific adjusted dose
- o v. Patient specific adjusted dose, followed by titration
- o vi. Low initiation dose and then titrate
- o vii. Other. Specify_____.
- o viii. Unsure

28) Is beta blocker therapy titrated? Who is responsible for titration of beta blocker treatment before surgery?

- o i. Not practiced
- o ii. Not titrated
- o iii. Registered Nurse
- o iv. Junior doctors
- o v. Vascular surgery registrar or equivalent
- o vi. Specialist Vascular Surgeon or equivalent
- o vii. Anaesthetic registrar or equivalent
- o viii. Specialist Anaesthetist or equivalent
- o ix. Specialist Cardiologist or equivalent
- o x. Multidisciplinary team
- o xi. Other. Specify____.
- o xii. Unsure

29) If medication is titrated, what endpoints are targeted?

- i. Not practiced
- ii. Not targeted
- iii. Absolute heart rate. Specify_____.
- iv. Drop in heart rate
- v. Limited HR response to exercise
- vi. No HR response to exercise
- vii. Blood Pressure
- viii. Duration of treatment
- ix. Other. Specify____.
- x. Unsure

30) In what way, if any, is the routine management of patients commenced on perioperative beta blocker therapy any different to the management of those patients not commenced on beta blocker therapy?

- i. Not practiced
- ii. No difference to standard care
- iii. BP and/or HR assessed and charted more regularly during drug initiation and titration
- iv. Nursed at a higher level of dependency preoperatively
- v. Nursed at a higher level of dependency postoperatively
- vi. Lower threshold for invasive monitoring
- vii. Change in anaesthetic technique
- viii. Hospitalised for longer period preoperatively
- ix. Hospitalised for longer period postoperatively
- x. Earlier follow up after discharge
- xi. Other. Specify____.
- xii. Unsure

31) Are beta blockers administered during surgery?

- i. Never
- ii. Very rarely (<1%)
- iii. Sometimes (<5%)
- iv. Regularly (5-30%)
- v. Often (30-50%)
- vi. Very often (>50%)
- vii. Unsure

32) For how long after surgery are beta blockers usually continued?

- i. Not practiced
- ii. Not specifically continued
- iii. No recommendation
- iv. <72 hrs
- v. 3-5 days
- vi. Stopped on discharge from hospital
- vii. Up to 2 weeks
- viii. 2-6 weeks
- ix. Continued indefinitely
- x. Decision deferred to other medical doctor
- xi. Other. Specify_____.
- xii. Unsure

33) How are beta blockers withdrawn after surgery?

- i. Not practiced
- ii. Tapered
- iii. Abrupt withdrawal
- iv. Not withdrawn
- v. Unsure

34) Are there any other interventions aimed at modifying patient risk in major vascular surgical patients that are considered at this hospital?

- i. None
- ii. Pharmacological heart rate control other than beta blocker
- iii. Statins
- iv. Aspirin
- v. Thromboprophylaxis
- vi. Other. Specify____.
- vii. Unsure

35) In which circumstances are Statins prescribed at this hospital for patients undergoing major vascular surgery?

- i. Never
- ii. Not often
- iii. Irregularly as costs are prohibitive
- iv. In patients already taking a statin
- v. Only in patients with Hypercholesterolaemia or other specific indication
- vi. Almost always in the absence of a contraindication
- vii. Other. Specify_____.
- viii. Unsure

36) Further comments on treatment initiation, titration or withdrawal:

_____.

_____.

_____.

_____.

SECTION D: OBSTACLES TO TREATMENT WITH BETA BLOCKERS PERIOPERATIVELY

37) Have you had difficulties with the development of a protocol for the perioperative use of beta blockers in major vascular surgical patients?

- i. Yes
- ii. No
- iii. Never attempted
- iv. Previous failed protocol, but new protocol now developed
- v. Unsure

38) What are the barriers to perioperative beta blocker therapy in general?

A) Hospital related:

- i. Bed issues
- ii. Length of stay
- iii. Pharmacy
- iv. Monitoring
- v. Cost
- vi. Other

B) Staffing:

- i. Insufficient number
- ii. Inadequate experience/training
- iii. Junior doctors responsible for prescribing
- iv. Poor continuity/ too many role players
- v. Poor utilization of expertise
- vi. Other

C) Evidence:

- i. Insufficient evidence of benefit
- ii. Evidence of harm
- iii. Lack of faith in guidelines
- iv. Confusion
- v. No knowledge of guidelines
- vi. Other

D) Interdepartmental:

- i. Difference of opinion between involved disciplines
- ii. Responsibility of another department
- iii. Other

E) Other:

- i. Specify_____.
- ii. Unsure

39) Further comments on obstacles to perioperative beta blocker therapy:

_____.

_____.

_____.

SECTION E: MISCELLANEOUS

40) Do you think that beta blockade has overall benefit when used in the perioperative management of major vascular surgical patients?

- i. Yes
- ii. No
- iii. Unsure

41) With consideration for the potential adverse effects of beta blockers in this setting which of the following statements reflect your current thoughts on perioperative beta blocker initiation in patients undergoing major vascular surgery?

- i. Patients undergoing major vascular surgery should commence beta blockers unless there is an absolute contraindication
- ii. Still believe there is a likely overall benefit in well chosen individuals
- iii. Concerns should limit use to distinct patient groups until more evidence is obtained
- iv. Patients already taking beta blockers before the perioperative period should continue to take beta blockers throughout the perioperative period
- v. Patients with evidence of inducible myocardial ischaemia on preoperative testing should receive beta blockers in the perioperative period
- vi. Only patients with an indication for beta blocker therapy irrespective of planned surgery, should commence beta blockers before surgery
- vii. The number of patient risk factors is still an important consideration when deciding who should receive beta blockers
- viii. For many patients undergoing major vascular surgery, commencing beta blockers in the perioperative period is not currently defensible
- ix. Beta blockers should not be initiated in the perioperative period in patients undergoing major vascular surgery
- x. Increased vigilance for side effects and proactive early treatment of derangements in BP and HR is prudent
- xi. When beta blockers are commenced this should be done well in advance of the procedure and titrated carefully

Further comments:

_____.

_____.

_____.

_____.

42) In your opinion, which specialty should take the lead role in protocol/policy development for methods of risk reduction in patients undergoing major vascular surgery?

- o i. Vascular surgery
- o ii. Anaesthesia
- o iii. Cardiology
- o iv. Critical care
- o v. General Medicine
- o vi. Multidisciplinary team
- o vii. Other. Specify_____.
- o viii. No opinion

43) In your opinion which specialty should be responsible for the initiation of beta blockers?

- o i. Perioperative initiation of beta blockers not recommended
- o ii. Vascular surgery
- o iii. Anaesthesia
- o iv. Cardiology
- o v. Critical care
- o vi. General Medicine
- o vii. Multidisciplinary. Specify_____.
- o viii. Other. Specify_____.
- o ix. No opinion

44) In your opinion, which specialty should be responsible for the titration of beta blocker therapy?

- i. Perioperative beta blockers not recommended
- ii. Titration not necessary
- iii. Vascular surgery
- iv. Anaesthesia
- v. Cardiology
- vi. Critical care
- vii. General Medicine
- viii. Multidisciplinary. Specify_____.
- ix. Other. Specify_____.
- x. No opinion

45) In your opinion, which specialty should be responsible for withdrawal of beta blocker therapy?

- i. Perioperative beta blockers not recommended
- ii. Once commenced should not be withdrawn routinely
- iii. Vascular surgery
- iv. Anaesthesia
- v. Cardiology
- vi. Critical care
- vii. General Medicine
- viii. Multidisciplinary. Specify_____.
- ix. Other. Specify_____.
- x. No opinion

46) Are you satisfied with your institutions current practice with regards to perioperative beta blocker administration in major vascular surgery patients?

- i. Yes
- ii. No
- iii. No opinion

47) Further comments about perioperative beta blocker therapy or risk stratification and modification in general:

_____.

_____.

_____.

_____.

Appendix G Additional results that do not contribute to the objectives of the study

The participants' individual opinions on aspects of perioperative beta blockade (PBB) were assessed in **Question 41** of the semi-structured interview. (**Appendix F**) These opinions may be of interest to the reader, but do not contribute to the primary and secondary objectives. These results appear in the appendix to avoid confusion between intended practice at South African training facilities and the participants' individual opinions on PBB as an intervention. Individual opinions are shown below in **Table G**. Grey shading highlights participant agreement with the statement that is considered.

All of the participants supported continuation of chronic beta blocker medication and introduction of beta blockers in patients with inducible myocardial ischaemia. Increased vigilance for haemodynamic derangement and early introduction of medication followed by titration were widely, but not uniformly, supported.

These opinions are consistent with recommendations made for future practice. (**Chapter 7**)

Table G. Table showing individual opinions on aspects of perioperative beta blockade

(Grey shading highlights agreement with the statement considered)

Absolute indications			PBB not indicated		Important caveats to introduction			
Patients already taking beta blockers before the perioperative period should continue to take beta blockers throughout the perioperative period	**Patients with evidence of inducible myocardial ischaemia on preoperative testing should receive beta blockers in the perioperative period**		**Beta blockers should not be initiated in the perioperative period in patients undergoing major vascular surgery**		**Increased vigilance for side effects and proactive early treatment of derangements in BP and HR is prudent**		**When beta blockers are commenced this should be done well in advance of the procedure and titrated carefully**	
Anaes	**VS**	**Anaes**	**VS**	**Anaes**	**VS**	**Anaes**	**VS**	**Anaes**	**VS**
V1	V2	V1	V2	V1	V2	V1	V2	V1	V2
A1	A2	A1	A2	A1	A2	A1	A2	A1	A2
S1	S2	S1	S2	S1	S2	S1	S2	S1	S2
C1	C2	C1	C2	C1	C2	C1	C2	C1	C2
U1	U2	U1	U2	U1	U2	U1	U2	U1	U2
L1	L2	L1	L2	L1	L2	L1	L2	L1	L2
R1	R2	R1	R2	R1	R2	R1	R2	R1	R2
7	**7**	**7**	**7**	**0**	**0**	**7**	**6**	**6**	**5**
14		**14**		**0**		**13**		**11**	

Proactive approach		Selective approach						Restrictive approach			
Patients undergoing major vascular surgery should commence beta blockers unless there is an absolute contraindication		Still believe there is a likely overall benefit in well chosen individuals		The number of patient risk factors is still an important consideration when deciding who should receive beta blockers		Concerns should limit use to distinct patient groups until more evidence is obtained		Only patients with an indication for beta blocker therapy irrespective of planned surgery, should commence beta blockers before surgery		For many patients undergoing major vascular surgery, commencing beta blockers in the perioperative period is not currently defensible	
Anaes	**VS**	**Anaes**	**VS**	**Anaes**	**VS**	**Anaes**	**VS**	**Anaes**	**VS**	**Anaes**	**VS**
V1	V2	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2
A1	A2	A1	A2	A1	A2	A1	A2	A1	A2	A1	A2
S1	S2	S1	S2	S1	S2	S1	S2	S1	S2	S1	S2
C1	C2	C1	C2	C1	C2	C1	C2	C1	C2	C1	C2
U1	U2	U1	U2	U1	U2	U1	U2	U1	U2	U1	U2
L1	L2	L1	L2	L1	L2	L1	L2	L1	L2	L1	L2
R1	R2	R1	R2	R1	R2	R1	R2	R1	R2	R1	R2
0	**5**	**7**	**6**	**7**	**3**	**4**	**4**	**1**	**0**	**2**	**2**
5		**13**		**10**		**8**		**1**		**4**	

REFERENCES

(1) HPCSA Available at: http://www.hpcsa.co.za/conduct_generic_ethical_rules.php. Accessed 10/19/2010, 2010.

(2) World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. 2008; Available at: http://www.wma.net/en/30publications/10policies/b3/17c.pdf. Accessed October 23, 2012.

(3) POISE Study Group, Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 2008 May 31;371(9627):1839-1847.

(4) Poldermans D, Bax JJ, Boersma E, De Hert S, Eeckhout E, Fowkes G, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: the Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). Eur.Heart J. 2009 Nov;30(22):2769-2812.

(5) American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, et al. 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. J.Am.Coll.Cardiol. 2009 Nov 24;54(22):e13-e118.

(6) Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet 2008 Jul 12;372(9633):139-144.

(7) Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999 Sep 7;100(10):1043-1049.

(8) Vernick W, Fleisher LA. Risk stratification. Best Pract.Res.Clin.Anaesthesiol. 2008 Mar;22(1):1-21.

(9) Devereaux PJ, Goldman L, Cook DJ, Gilbert K, Leslie K, Guyatt GH. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. CMAJ: Canadian Medical Association Journal 2005 09/13;173(6):627-634.

(10) Sukhija R, Yalamanchili K, Aronow WS. Prevalence of left main coronary artery disease, of three- or four-vessel coronary artery disease, and of obstructive coronary artery disease in

patients with and without peripheral arterial disease undergoing coronary angiography for suspected coronary artery disease. Am.J.Cardiol. 2003 Aug 1;92(3):304-305.

(11) Kertai MD, Boersma E, Klein J, van Sambeek M, Schouten O, van Urk H, et al. Optimizing the prediction of perioperative mortality in vascular surgery by using a customized probability model. Arch.Intern.Med. 2005 Apr 25;165(8):898-904.

(12) Welten GM, Schouten O, van Domburg RT, Feringa HH, Hoeks SE, Dunkelgrun M, et al. The influence of aging on the prognostic value of the revised cardiac risk index for postoperative cardiac complications in vascular surgery patients. Eur.J.Vasc.Endovasc.Surg. 2007 Dec;34(6):632-638.

(13) Biccard BM. Anaesthesia for vascular procedures : how do South African patients differ? : SASA refresher text. Southern African Journal of Anaesthesia and Analgesia 2008 Jan / Feb;14(1):109-115.

(14) Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. N.Engl.J.Med. 1996 Dec 5;335(23):1713-1720.

(15) Poldermans D, Boersma E, Bax JJ, Thomson IR, van de Ven LL, Blankensteijn JD, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. N.Engl.J.Med. 1999 Dec 9;341(24):1789-1794.

(16) Brady AR, Gibbs JS, Greenhalgh RM, Powell JT, Sydes MR, POBBLE trial investigators. Perioperative beta-blockade (POBBLE) for patients undergoing infrarenal vascular surgery: results of a randomized double-blind controlled trial. J.Vasc.Surg. 2005 Apr;41(4):602-609.

(17) Yang H, Raymer K, Butler R, Parlow J, Roberts R. The effects of perioperative beta-blockade: results of the Metoprolol after Vascular Surgery (MaVS) study, a randomized controlled trial. Am.Heart J. 2006 Nov;152(5):983-990.

(18) Juul AB, Wetterslev J, Gluud C, Kofoed-Enevoldsen A, Jensen G, Callesen T, et al. Effect of perioperative beta blockade in patients with diabetes undergoing major non-cardiac surgery: randomised placebo controlled, blinded multicentre trial. BMJ 2006 Jun 24;332(7556):1482.

(19) Zaugg M, Bestmann L, Wacker J, Lucchinetti E, Boltres A, Schulz C, et al. Adrenergic receptor genotype but not perioperative bisoprolol therapy may determine cardiovascular outcome in at-risk patients undergoing surgery with spinal block: the Swiss Beta Blocker in Spinal Anesthesia (BBSA) study: a double-blinded, placebo-controlled, multicenter trial with 1-year follow-up. Anesthesiology 2007 Jul;107(1):33-44.

(20) Mangano DT, Browner WS, Hollenberg M, Li J, Tateo IM. Long-term cardiac prognosis following noncardiac surgery. The Study of Perioperative Ischemia Research Group. JAMA 1992 Jul 8;268(2):233-239.

(21) Landesberg G. Monitoring for myocardial ischemia. Best Pract.Res.Clin.Anaesthesiol. 2005 Mar;19(1):77-95.

(22) Devereaux PJ. Can attenuation of the perioperative stress response prevent intermediate or long-term cardiovascular outcomes among patients undergoing noncardiac surgery? Anesthesiology 2009 Aug;111(2):223-226.

(23) Landesberg G, Mosseri M, Zahger D, Wolf Y, Perouansky M, Anner H, et al. Myocardial infarction after vascular surgery: the role of prolonged stress-induced, ST depression-type ischemia. J.Am.Coll.Cardiol. 2001 Jun 1;37(7):1839-1845.

(24) Fleischmann KE, Goldman L, Young B, Lee TH. Association between cardiac and noncardiac complications in patients undergoing noncardiac surgery: outcomes and effects on length of stay. Am.J.Med. 2003 Nov;115(7):515-520.

(25) Landesberg G, Beattie WS, Mosseri M, Jaffe AS, Alpert JS. Perioperative myocardial infarction. Circulation 2009 Jun 9;119(22):2936-2944.

(26) Biccard BM, Rodseth RN. The pathophysiology of peri-operative myocardial infarction. Anaesthesia 2010 Jul;65(7):733-741.

(27) Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. Circulation 2003 Oct 7;108(14):1664-1672.

(28) Priebe HJ. Perioperative myocardial infarction--aetiology and prevention. Br.J.Anaesth. 2005 Jul;95(1):3-19.

(29) Gandhi R, Petruccelli D, Devereaux PJ, Adili A, Hubmann M, de Beer J. Incidence and timing of myocardial infarction after total joint arthroplasty. J.Arthroplasty 2006 Sep;21(6):874-877.

(30) Le Manach Y, Perel A, Coriat P, Godet G, Bertrand M, Riou B. Early and delayed myocardial infarction after abdominal aortic surgery. Anesthesiology 2005 May;102(5):885-891.

(31) Breslow MJ, Parker SD, Frank SM, Norris EJ, Yates H, Raff H, et al. Determinants of catecholamine and cortisol responses to lower extremity revascularization. The PIRAT Study Group. Anesthesiology 1993 Dec;79(6):1202-1209.

(32) Sametz W, Metzler H, Gries M, Porta S, Sadjak A, Supanz S, et al. Perioperative catecholamine changes in cardiac risk patients. Eur.J.Clin.Invest. 1999 Jul;29(7):582-587.

(33) Longhitano S, Coriat P, Agro F. Postoperative myocardial infarction: pathophysiology, new diagnostic criteria, prevention. Minerva Anestesiol. 2006 Dec;72(12):965-983.

(34) Cruickshank JM, Prichard BNC. Beta-adrenoceptors. In: Cruickshank JM, Prichard BNC, editors. Beta-blockers in clinical practice London: Churchill Livingstone; 1996. p. 9-86.

(35) Cruickshank JM. Are we misunderstanding beta-blockers. Int.J.Cardiol. 2007 Aug 9;120(1):10-27.

(36) London MJ, Zaugg M, Schaub MC, Spahn DR. Perioperative beta-adrenergic receptor blockade: physiologic foundations and clinical controversies. Anesthesiology 2004 Jan;100(1):170-175.

(37) Priebe HJ. Triggers of perioperative myocardial ischaemia and infarction. Br.J.Anaesth. 2004 Jul;93(1):9-20.

(38) Heidland UE, Strauer BE. Left ventricular muscle mass and elevated heart rate are associated with coronary plaque disruption. Circulation 2001 Sep 25;104(13):1477-1482.

(39) Lowes BD, Gilbert EM, Abraham WT, Minobe WA, Larrabee P, Ferguson D, et al. Myocardial gene expression in dilated cardiomyopathy treated with beta-blocking agents. N.Engl.J.Med. 2002 May 2;346(18):1357-1365.

(40) Yasumura Y, Takemura K, Sakamoto A, Kitakaze M, Miyatake K. Changes in myocardial gene expression associated with beta-blocker therapy in patients with chronic heart failure. J.Card.Fail. 2003 Dec;9(6):469-474.

(41) Yeager MP, Fillinger MP, Hettleman BD, Hartman GS. Perioperative beta-blockade and late cardiac outcomes: a complementary hypothesis. J.Cardiothorac.Vasc.Anesth. 2005 Apr;19(2):237-241.

(42) Padayachee L, Rodseth RN, Biccard BM. A meta-analysis of the utility of C-reactive protein in predicting early, intermediate-term and long term mortality and major adverse cardiac events in vascular surgical patients. Anaesthesia 2009 Apr;64(4):416-424.

(43) Jenkins NP, Keevil BG, Hutchinson IV, Brooks NH. Beta-blockers are associated with lower C-reactive protein concentrations in patients with coronary artery disease. Am.J.Med. 2002 Mar;112(4):269-274.

(44) Anzai T, Yoshikawa T, Takahashi T, Maekawa Y, Okabe T, Asakura Y, et al. Early use of beta-blockers is associated with attenuation of serum C-reactive protein elevation and favorable short-term prognosis after acute myocardial infarction. Cardiology 2003;99(1):47-53.

(45) Goldman L, Caldera DL, Nussbaum SR, Southwick FS, Krogstad D, Murray B, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. N.Engl.J.Med. 1977 Oct 20;297(16):845-850.

(46) Detsky AS, Abrams HB, Forbath N, Scott JG, Hilliard JR. Cardiac assessment for patients undergoing noncardiac surgery. A multifactorial clinical risk index. Arch.Intern.Med. 1986 Nov;146(11):2131-2134.

(47) Boersma E, Kertai MD, Schouten O, Bax JJ, Noordzij P, Steyerberg EW, et al. Perioperative cardiovascular mortality in noncardiac surgery: validation of the Lee cardiac risk index. Am.J.Med. 2005 Oct;118(10):1134-1141.

(48) Bertges DJ, Goodney PP, Zhao Y, Schanzer A, Nolan BW, Likosky DS, et al. The Vascular Study Group of New England Cardiac Risk Index (VSG-CRI) predicts cardiac complications more accurately than the Revised Cardiac Risk Index in vascular surgery patients. J.Vasc.Surg. 2010 Sep;52(3):674-83, 683.e1-683.e3.

(49) Ford MK, Beattie WS, Wijeysundera DN. Systematic review: prediction of perioperative cardiac complications and mortality by the revised cardiac risk index. Ann.Intern.Med. 2010 Jan 5;152(1):26-35.

(50) Samy AK, Murray G, MacBain G. Glasgow aneurysm score. Cardiovasc.Surg. 1994 Feb;2(1):41-44.

(51) Steyerberg EW, Kievit J, de Mol Van Otterloo JC, van Bockel JH, Eijkemans MJ, Habbema JD. Perioperative mortality of elective abdominal aortic aneurysm surgery. A clinical prediction rule based on literature and individual patient data. Arch.Intern.Med. 1995 Oct 9;155(18):1998-2004.

(52) L'Italien GJ, Paul SD, Hendel RC, Leppo JA, Cohen MC, Fleisher LA, et al. Development and validation of a Bayesian model for perioperative cardiac risk assessment in a cohort of 1,081 vascular surgical candidates. J.Am.Coll.Cardiol. 1996 Mar 15;27(4):779-786.

(53) Biccard BM, Bandu R. Clinical risk predictors associated with cardiac mortality following vascular surgery in South African patients. Cardiovasc.J.Afr. 2007 Jul-Aug;18(4):216-220.

(54) Kaafarani HM, Itani KM, Thornby J, Berger DH. Thirty-day and one-year predictors of death in noncardiac major surgical procedures. Am.J.Surg. 2004 Nov;188(5):495-499.

(55) Eagle KA, Rihal CS, Mickel MC, Holmes DR, Foster ED, Gersh BJ. Cardiac risk of noncardiac surgery: influence of coronary disease and type of surgery in 3368 operations. CASS Investigators and University of Michigan Heart Care Program. Coronary Artery Surgery Study. Circulation 1997 Sep 16;96(6):1882-1887.

(56) Verduzco LA, Lighthall GK. The evolving role of preoperative testing in vascular surgery patients: can a little knowledge be dangerous? Semin.Cardiothorac.Vasc.Anesth. 2011 Sep;15(3):75-84.

(57) Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery--

-executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Circulation 2002 Mar 12;105(10):1257-1267.

(58) Fox K, Garcia MA, Ardissino D, Buszman P, Camici PG, Crea F, et al. Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur.Heart J. 2006 Jun;27(11):1341-1381.

(59) Kertai MD, Boersma E, Bax JJ, Heijenbrok-Kal MH, Hunink MG, L'talien GJ, et al. A meta-analysis comparing the prognostic accuracy of six diagnostic tests for predicting perioperative cardiac risk in patients undergoing major vascular surgery. Heart 2003 Nov;89(11):1327-1334.

(60) Mondillo S, Ballo P, Agricola E, Guerrini F, Barbati R, Ammaturo T, et al. Noninvasive tests for risk stratification in major vascular surgery. Vasa 2002 Aug;31(3):195-201.

(61) Rodseth RN, Lurati Buse GA, Bolliger D, Burkhart CS, Cuthbertson BH, Gibson SC, et al. The predictive ability of pre-operative B-type natriuretic peptide in vascular patients for major adverse cardiac events: an individual patient data meta-analysis. J.Am.Coll.Cardiol. 2011 Jul 26;58(5):522-529.

(62) Biccard BM, Lurati Buse GA, Burkhart C, Cuthbertson BH, Filipovic M, Gibson SC, et al. The influence of clinical risk factors on pre-operative B-type natriuretic peptide risk stratification of vascular surgical patients. Anaesthesia 2012 Jan;67(1):55-59.

(63) Feringa HH, Schouten O, Dunkelgrun M, Bax JJ, Boersma E, Elhendy A, et al. Plasma N-terminal pro-B-type natriuretic peptide as long-term prognostic marker after major vascular surgery. Heart 2007 Feb;93(2):226-231.

(64) Mahla E, Baumann A, Rehak P, Watzinger N, Vicenzi MN, Maier R, et al. N-terminal pro-brain natriuretic peptide identifies patients at high risk for adverse cardiac outcome after vascular surgery. Anesthesiology 2007 Jun;106(6):1088-1095.

(65) Redfern G, Rodseth RN, Biccard BM. Outcomes in vascular surgical patients with isolated postoperative troponin leak: a meta-analysis. Anaesthesia 2011 Jul;66(7):604-610.

(66) Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators, Devereaux PJ, Chan MT, Alonso-Coello P, Walsh M, Berwanger O, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. JAMA 2012 Jun 6;307(21):2295-2304.

(67) Smith TB, Stonell C, Purkayastha S, Paraskevas P. Cardiopulmonary exercise testing as a risk assessment method in non cardio-pulmonary surgery: a systematic review. Anaesthesia 2009 Aug;64(8):883-893.

(68) Hennis PJ, Meale PM, Grocott MP. Cardiopulmonary exercise testing for the evaluation of perioperative risk in non-cardiopulmonary surgery. Postgrad.Med.J. 2011 Aug;87(1030):550-557.

(69) Struthers R, Erasmus P, Holmes K, Warman P, Collingwood A, Sneyd JR. Assessing fitness for surgery: a comparison of questionnaire, incremental shuttle walk, and cardiopulmonary exercise testing in general surgical patients. Br.J.Anaesth. 2008 Dec;101(6):774-780.

(70) Stringer W, Casaburi R, Older P. Cardiopulmonary exercise testing: does it improve perioperative care and outcome? Curr.Opin.Anaesthesiol. 2012 Apr;25(2):178-184.

(71) McFalls EO, Ward HB, Moritz TE, Goldman S, Krupski WC, Littooy F, et al. Coronary-artery revascularization before elective major vascular surgery. N.Engl.J.Med. 2004 Dec 30;351(27):2795-2804.

(72) Poldermans D, Schouten O, Vidakovic R, Bax JJ, Thomson IR, Hoeks SE, et al. A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery: the DECREASE-V Pilot Study. J.Am.Coll.Cardiol. 2007 May 1;49(17):1763-1769.

(73) Boersma E, Poldermans D, Bax JJ, Steyerberg EW, Thomson IR, Banga JD, et al. Predictors of cardiac events after major vascular surgery: Role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. JAMA 2001 Apr 11;285(14):1865-1873.

(74) Biccard BM, Rodseth RN. A meta-analysis of the prospective randomised trials of coronary revascularisation before noncardiac vascular surgery with attention to the type of coronary revascularisation performed. Anaesthesia 2009 Oct;64(10):1105-1113.

(75) Nuttall GA, Brown MJ, Stombaugh JW, Michon PB, Hathaway MF, Lindeen KC, et al. Time and cardiac risk of surgery after bare-metal stent percutaneous coronary intervention. Anesthesiology 2008 Oct;109(4):588-595.

(76) Rabbitts JA, Nuttall GA, Brown MJ, Hanson AC, Oliver WC, Holmes DR, et al. Cardiac risk of noncardiac surgery after percutaneous coronary intervention with drug-eluting stents. Anesthesiology 2008 Oct;109(4):596-604.

(77) Monaco M, Stassano P, Di Tommaso L, Pepino P, Giordano A, Pinna GB, et al. Systematic Strategy of Prophylactic Coronary Angiography Improves Long-Term Outcome After Major Vascular Surgery in Medium- to High-Risk Patients: A Prospective, Randomized Study. J.Am.Coll.Cardiol. 2009 September 8;54(11):989-996.

(78) Kertai MD. Preoperative Coronary Revascularization in High-Risk Patients Undergoing Vascular Surgery: A Core Review. Anesthesia & Analgesia March 2008 March 2008;106(3):751-758.

(79) Landesberg G, Mosseri M. PRO: Preoperative Coronary Revascularization in High-Risk Patients Undergoing Vascular Surgery. Anesthesia & Analgesia March 2008 March 2008;106(3):759-763.

(80) Garcia S, McFalls EO. CON: Preoperative Coronary Revascularization in High-Risk Patients Undergoing Vascular Surgery. Anesthesia & Analgesia March 2008 March 2008;106(3):764-766.

(81) Schouten O, Dunkelgrun M, Feringa HHH, Kok NFM, Vidakovic R, Bax JJ, et al. Myocardial Damage in High-risk Patients Undergoing Elective Endovascular or Open Infrarenal Abdominal Aortic Aneurysm Repair. European Journal of Vascular and Endovascular Surgery 2007 5;33(5):544-549.

(82) Blankensteijn JD, de Jong SE, Prinssen M, van der Ham AC, Buth J, van Sterkenburg SM, et al. Two-year outcomes after conventional or endovascular repair of abdominal aortic aneurysms. N.Engl.J.Med. 2005 Jun 9;352(23):2398-2405.

(83) Schouten O, van Waning VH, Kertai MD, Feringa HH, Bax JJ, Boersma E, et al. Perioperative and long-term cardiovascular outcomes in patients undergoing endovascular treatment compared with open vascular surgery for abdominal aortic aneurysm or iliaco-femoro-popliteal bypass. Am.J.Cardiol. 2005 Sep 15;96(6):861-866.

(84) De Bruin JL, Baas AF, Buth J, Prinssen M, Verhoeven EL, Cuypers PW, et al. Long-term outcome of open or endovascular repair of abdominal aortic aneurysm. N.Engl.J.Med. 2010 May 20;362(20):1881-1889.

(85) Poldermans D, Bax JJ, Schouten O, Neskovic AN, Paelinck B, Rocci G, et al. Should major vascular surgery be delayed because of preoperative cardiac testing in intermediate-risk patients receiving beta-blocker therapy with tight heart rate control? J.Am.Coll.Cardiol. 2006 Sep 5;48(5):964-969.

(86) Davignon J. Beneficial cardiovascular pleiotropic effects of statins. Circulation 2004 Jun 15;109(23 Suppl 1):III39-43.

(87) Schouten O, Boersma E, Hoeks SE, Benner R, van Urk H, van Sambeek MR, et al. Fluvastatin and perioperative events in patients undergoing vascular surgery. N.Engl.J.Med. 2009 Sep 3;361(10):980-989.

(88) Wijeysundera DN, Naik JS, Beattie WS. Alpha-2 adrenergic agonists to prevent perioperative cardiovascular complications: a meta-analysis. Am.J.Med. 2003 Jun 15;114(9):742-752.

(89) Nelson AH, Fleisher LA, Rosenbaum SH. Relationship between postoperative anemia and cardiac morbidity in high-risk vascular patients in the intensive care unit. Crit.Care Med. 1993 Jun;21(6):860-866.

(90) Carson JL, Duff A, Poses RM, Berlin JA, Spence RK, Trout R, et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. Lancet 1996 Oct 19;348(9034):1055-1060.

(91) Kuriyan M, Carson JL. Anemia and clinical outcomes. Anesthesiol.Clin.North America 2005 Jun;23(2):315-25, vii.

(92) Frank SM, Beattie C, Christopherson R, Norris EJ, Perler BA, Williams GM, et al. Unintentional hypothermia is associated with postoperative myocardial ischemia. The Perioperative Ischemia Randomized Anesthesia Trial Study Group. Anesthesiology 1993 Mar;78(3):468-476.

(93) Frank SM, Fleisher LA, Breslow MJ, Higgins MS, Olson KF, Kelly S, et al. Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events. A randomized clinical trial. JAMA 1997 Apr 9;277(14):1127-1134.

(94) Ragoonanan TE, Beattie WS, Mazer CD, Tsui AK, Leong-Poi H, Wilson DF, et al. Metoprolol reduces cerebral tissue oxygen tension after acute hemodilution in rats. Anesthesiology 2009 Nov;111(5):988-1000.

(95) Beattie WS, Wijeysundera DN, Karkouti K, McCluskey S, Tait G, Mitsakakis N, et al. Acute surgical anemia influences the cardioprotective effects of beta-blockade: a single-center, propensity-matched cohort study. Anesthesiology 2010 Jan;112(1):25-33.

(96) Foex P, Sear JW. Challenges of beta-blockade in surgical patients. Anesthesiology 2010 Oct;113(4):767-771.

(97) Viljoen JF, Estafanous FG, Kellner GA. Propranolol and cardiac surgery. J.Thorac.Cardiovasc.Surg. 1972 Nov;64(5):826-830.

(98) Prys-Roberts C, Foex P, Biro GP, Roberts JG. Studies of anaesthesia in relation to hypertension. V. Adrenergic beta-receptor blockade. Br.J.Anaesth. 1973 Jul;45(7):671-681.

(99) Pasternack PF, Imparato AM, Baumann FG, Laub G, Riles TS, Lamparello PJ, et al. The hemodynamics of beta-blockade in patients undergoing abdominal aortic aneurysm repair. Circulation 1987 Sep;76(3 Pt 2):III1-7.

(100) Stone JG, Foex P, Sear JW, Johnson LL, Khambatta HJ, Triner L. Myocardial ischemia in untreated hypertensive patients: effect of a single small oral dose of a beta-adrenergic blocking agent. Anesthesiology 1988 Apr;68(4):495-500.

(101) Pasternack PF, Grossi EA, Baumann FG, Riles TS, Lamparello PJ, Giangola G, et al. Beta blockade to decrease silent myocardial ischemia during peripheral vascular surgery. Am.J.Surg. 1989 Aug;158(2):113-116.

(102) London MJ. Quo vadis, perioperative beta blockade? Are you "POISE'd" on the brink? Anesth.Analg. 2008 Apr;106(4):1025-1030.

(103) Shojania KG, Duncan BW, McDonald KM, Wachter RM, Markowitz AJ. Making health care safer: a critical analysis of patient safety practices. Evid Rep.Technol.Assess.(Summ) 2001;(43)(43):i-x, 1-668.

(104) Devereaux PJ, Beattie WS, Choi PT, Badner NH, Guyatt GH, Villar JC, et al. How strong is the evidence for the use of perioperative beta blockers in non-cardiac surgery? Systematic review and meta-analysis of randomised controlled trials. BMJ 2005 Aug 6;331(7512):313-321.

(105) Messerli FH, Bangalore S. When guidelines need guidance.. Am.J.Med. 2008 Sep;121(9):742-743.

(106) Kertai MD, Bax JJ, Klein J, Poldermans D. Is there any reason to withhold beta blockers from high-risk patients with coronary artery disease during surgery? Anesthesiology 2004 Jan;100(1):4-7.

(107) Hoeks SE, Scholte op Reimer WJ, Lenzen MJ, van Urk H, Jorning PJ, Boersma E, et al. Guidelines for cardiac management in noncardiac surgery are poorly implemented in clinical practice: results from a peripheral vascular survey in the Netherlands. Anesthesiology 2007 Oct;107(4):537-544.

(108) Devereaux PJ, Yusuf S, Yang H, Choi PT, Guyatt GH. Are the recommendations to use perioperative beta-blocker therapy in patients undergoing noncardiac surgery based on reliable evidence? CMAJ 2004 Aug 3;171(3):245-247.

(109) Sear JW, Foex P. Recommendations on perioperative beta-blockers: differing guidelines: so what should the clinician do? Br.J.Anaesth. 2010 Mar;104(3):273-275.

(110) Sear JW, Giles JW, Howard-Alpe G, Foex P. Perioperative beta-blockade, 2008: what does POISE tell us, and was our earlier caution justified? Br.J.Anaesth. 2008 Aug;101(2):135-138.

(111) Wallace AW, Au S, Cason BA. Association of the pattern of use of perioperative beta-blockade and postoperative mortality. Anesthesiology 2010 Oct;113(4):794-805.

(112) Sear JW, Foex P. Perioperative beta-blockade in non-cardiac surgical patients. Br.J.Surg. 2008 Sep;95(9):1077-1078.

(113) Chopra V, Plaisance B, Cavusoglu E, Flanders SA, Eagle KA. Perioperative beta-blockers for major noncardiac surgery: Primum Non Nocere. Am.J.Med. 2009 Mar;122(3):222-229.

(114) Flu WJ, van Kuijk JP, Winkel T, Hoeks S, Bax J, Poldermans D. Prevention of acute coronary events in noncardiac surgery: beta-blocker therapy and coronary revascularization. Expert Rev.Cardiovasc.Ther. 2009 May;7(5):521-532.

(115) Bauer SM, Cayne NS, Veith FJ. New developments in the preoperative evaluation and perioperative management of coronary artery disease in patients undergoing vascular surgery. J.Vasc.Surg. 2010 Jan;51(1):242-251.

(116) Brooke BS. Perioperative beta-blockers for vascular surgery patients. J.Vasc.Surg. 2010 Feb;51(2):515-519.

(117) Fleisher LA, Poldermans D. Perioperative beta blockade: where do we go from here? Lancet 2008 May 31;371(9627):1813-1814.

(118) Chopra V, Eagle KA. Perioperative beta-blockers for cardiac risk reduction: time for clarity. JAMA 2010 Feb 10;303(6):551-552.

(119) Dunkelgrun M, Boersma E, Schouten O, Koopman-van Gemert AW, van Poorten F, Bax JJ, et al. Bisoprolol and fluvastatin for the reduction of perioperative cardiac mortality and myocardial infarction in intermediate-risk patients undergoing noncardiovascular surgery: a randomized controlled trial (DECREASE-IV). Ann.Surg. 2009 Jun;249(6):921-926.

(120) Lawson R. Perioperative Beta Blockade: A Practice in Need of Optimisation. Southern African Journal of Anaesthesia and Analgesia 2010;16(3).

(121) Seedat YK, Croasdale MA, Milne FJ, Opie LH, Pinkney-Atkinson VJ, Rayner BL, et al. South African hypertension guideline 2006. S.Afr.Med.J. 2006 Apr;96(4 Pt 2):337-362.

(122) Wiysonge CS, Bradley H, Mayosi BM, Maroney R, Mbewu A, Opie LH, et al. Beta-blockers for hypertension. Cochrane Database Syst.Rev. 2007 Jan 24;(1)(1):CD002003.

(123) Fraker TD,Jr, Fihn SD, Gibbons RJ, Abrams J, Chatterjee K, Daley J, et al. 2007 chronic angina focused update of the ACC/AHA 2002 Guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Writing Group to develop the focused update of the 2002 Guidelines for the management of patients with chronic stable angina. Circulation 2007 Dec 4;116(23):2762-2772.

(124) Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009 Apr 14;119(14):e391-479.

(125) Giles JW, Sear JW, Foëx P. Effect of chronic β-blockade on peri-operative outcome in patients undergoing non-cardiac surgery: an analysis of observational and case control studies*. Anaesthesia 2004 06;59(6):574-583.

(126) Shammash JB, Trost JC, Gold JM, Berlin JA, Golden MA, Kimmel SE. Perioperative beta-blocker withdrawal and mortality in vascular surgical patients. Am.Heart J. 2001 Jan;141(1):148-153.

(127) Hoeks SE, Scholte Op Reimer WJ, van Urk H, Jorning PJ, Boersma E, Simoons ML, et al. Increase of 1-year mortality after perioperative beta-blocker withdrawal in endovascular and vascular surgery patients. Eur.J.Vasc.Endovasc.Surg. 2007 Jan;33(1):13-19.

(128) London MJ. Perioperative beta-blockade, discontinuation, and complications: do you really know it when you see it? Anesthesiology 2009 Oct;111(4):690-694.

(129) van Klei WA, Bryson GL, Yang H, Forster AJ. Effect of beta-blocker prescription on the incidence of postoperative myocardial infarction after hip and knee arthroplasty. Anesthesiology 2009 Oct;111(4):717-724.

(130) Biccard BM. Factors associated with mortality when chronic betablocker therapy is withdrawn in the peri-operative period in vascular surgical patients: a matched case-control study. Cardiovasc.J.Afr. 2010 Mar-Apr;21(2):97-102.

(131) Austin PC. Propensity-score matching in the cardiovascular surgery literature from 2004 to 2006: a systematic review and suggestions for improvement. J.Thorac.Cardiovasc.Surg. 2007 Nov;134(5):1128-1135.

(132) Frishman WH. Beta-adrenergic blocker withdrawal. Am.J.Cardiol. 1987 5/15;59(13):F26-F32.

(133) Michel MC, Pingsmann A, Beckeringh JJ, Zerkowski HR, Doetsch N, Brodde OE. Selective regulation of beta 1- and beta 2-adrenoceptors in the human heart by chronic beta-adrenoceptor antagonist treatment. Br.J.Pharmacol. 1988 Jul;94(3):685-692.

(134) Stone PH, Gibson RS, Glasser SP, DeWood MA, Parker JD, Kawanishi DT, et al. Comparison of propranolol, diltiazem, and nifedipine in the treatment of ambulatory ischemia in patients with stable angina. Differential effects on ambulatory ischemia, exercise performance, and anginal symptoms. The ASIS Study Group. Circulation 1990 Dec;82(6):1962-1972.

(135) Tzivoni D, Medina A, David D, Barzilai Y, Brunel P. Effect of metoprolol in reducing myocardial ischemic threshold during exercise and during daily activity. Am.J.Cardiol. 1998 Mar 15;81(6):775-777.

(136) McLenachan JM, Weidinger FF, Barry J, Yeung A, Nabel EG, Rocco MB, et al. Relations between heart rate, ischemia, and drug therapy during daily life in patients with coronary artery disease. Circulation 1991 Apr;83(4):1263-1270.

(137) Lombaard SA, Robbertze R. Perioperative use of beta-blockers in the elderly patient. Anesthesiol.Clin. 2009 Sep;27(3):581-97, table of contents.

(138) Biccard BM. Peri-operative beta-blockade and haemodynamic optimisation in patients with coronary artery disease and decreasing exercise capacity presenting for major noncardiac surgery. Anaesthesia 2004 Jan;59(1):60-68.

(139) Paravastu SC, Mendonca D, Da Silva A. Beta blockers for peripheral arterial disease. Cochrane Database Syst.Rev. 2008 Oct 8;(4)(4):CD005508.

(140) van Lier F, Schouten O, van Domburg RT, van der Geest PJ, Boersma E, Fleisher LA, et al. Effect of chronic beta-blocker use on stroke after noncardiac surgery. Am.J.Cardiol. 2009 Aug 1;104(3):429-433.

(141) Salpeter Shelley R, Ormiston Thomas M, Salpeter Edwin E, Wood-Baker R. Cardioselective beta-blockers for reversible airway disease. 2002(4).

(142) van Gestel YR, Hoeks SE, Sin DD, Welten GM, Schouten O, Witteveen HJ, et al. Impact of cardioselective beta-blockers on mortality in patients with chronic obstructive pulmonary disease and atherosclerosis. Am.J.Respir.Crit.Care Med. 2008 Oct 1;178(7):695-700.

(143) Self T, Soberman JE, Bubla JM, Chafin CC. Cardioselective beta-blockers in patients with asthma and concomitant heart failure or history of myocardial infarction: when do benefits outweigh risks? J.Asthma 2003 Dec;40(8):839-845.

(144) Novotny NM, Lahm T, Markel TA, Crisostomo PR, Wang M, Wang Y, et al. beta-Blockers in sepsis: reexamining the evidence. Shock 2009 Feb;31(2):113-119.

(145) de Montmollin E, Aboab J, Mansart A, Annane D. Bench-to-bedside review: Beta-adrenergic modulation in sepsis. Crit.Care 2009;13(5):230.

(146) De Caterina AR, Leone AM. Why β-Blockers Should Not Be Used as First Choice in Uncomplicated Hypertension. Am.J.Cardiol. 2010 5/15;105(10):1433-1438.

(147) Kasiske BL, Ma JZ, Kalil RS, Louis TA. Effects of antihypertensive therapy on serum lipids. Ann.Intern.Med. 1995 Jan 15;122(2):133-141.

(148) Fu M. Beta-blocker therapy in heart failure in the elderly. Int.J.Cardiol. 2008 Apr 10;125(2):149-153.

(149) Williams BR, Kim J. Cardiovascular drug therapy in the elderly: theoretical and practical considerations. Drugs Aging 2003;20(6):445-463.

(150) Anderson JR, Nawarskas JJ. Cardiovascular drug-drug interactions. Cardiol.Clin. 2001 May;19(2):215-34, v.

(151) Warrington SJ, Holt D, Johnston A, Fitzsimons TJ. Pharmacokinetics and pharmacodynamics of verapamil in combination with atenolol, metoprolol and propranolol. Br.J.Clin.Pharmacol. 1984;17 Suppl 1:37S-44S.

(152) Flockhart DA, Tanus-Santos JE. Implications of cytochrome P450 interactions when prescribing medication for hypertension. Arch.Intern.Med. 2002 Feb 25;162(4):405-412.

(153) Lindenauer PK, Pekow P, Wang K, Mamidi DK, Gutierrez B, Benjamin EM. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. N.Engl.J.Med. 2005 Jul 28;353(4):349-361.

(154) Bangalore S, Wetterslev J, Pranesh S, Sawhney S, Gluud C, Messerli FH. Perioperative beta blockers in patients having non-cardiac surgery: a meta-analysis. Lancet 2008 Dec 6;372(9654):1962-1976.

(155) Leibowitz AB, Porter SB. Perioperative beta-blockade in patients undergoing noncardiac surgery: a review of the major randomized clinical trials. J.Cardiothorac.Vasc.Anesth. 2009 Oct;23(5):684-693.

(156) Smith SC,Jr, Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. Circulation 2006 May 16;113(19):2363-2372.

(157) Pepine CJ, Cohn PF, Deedwania PC, Gibson RS, Handberg E, Hill JA, et al. Effects of treatment on outcome in mildly symptomatic patients with ischemia during daily life. The Atenolol Silent Ischemia Study (ASIST). Circulation 1994 Aug;90(2):762-768.

(158) Biccard BM, Sear JW, Foex P. Acute peri-operative beta blockade in intermediate-risk patients. Anaesthesia 2006 Oct;61(10):924-931.

(159) Poldermans D, Boersma E. Beta-blocker therapy in noncardiac surgery. N.Engl.J.Med. 2005 Jul 28;353(4):412-414.

(160) Beattie WS, Wijeysundera DN, Karkouti K, McCluskey S, Tait G. Does tight heart rate control improve beta-blocker efficacy? An updated analysis of the noncardiac surgical randomized trials. Anesth.Analg. 2008 Apr;106(4):1039-48, table of contents.

(161) Shin J, Johnson JA. Pharmacogenetics of beta-blockers. Pharmacotherapy 2007 Jun;27(6):874-887.

(162) Badgett RG, Lawrence VA, Cohn SL. Variations in pharmacology of beta-blockers may contribute to heterogeneous results in trials of perioperative beta-blockade. Anesthesiology 2010 Sep;113(3):585-592.

(163) Baker JG. The selectivity of beta-adrenoceptor antagonists at the human beta1, beta2 and beta3 adrenoceptors. Br.J.Pharmacol. 2005 Feb;144(3):317-322.

(164) Wallace AW, Au S, Cason BA. Perioperative beta-blockade: atenolol is associated with reduced mortality when compared to metoprolol. Anesthesiology 2011 Apr;114(4):824-836.

(165) Redelmeier D, Scales D, Kopp A. Beta blockers for elective surgery in elderly patients: population based, retrospective cohort study. BMJ 2005 Oct 22;331(7522):932.

(166) Gosgnach M, Aymard G, Huraux C, Fleron MH, Coriat P, Diquet B. Atenolol administration via a nasogastric tube after abdominal surgery: an unreliable route. Anesth.Analg. 2005 Jan;100(1):137-140.

(167) Biccard BM, Sear JW, Foex P. Meta-analysis of the effect of heart rate achieved by perioperative beta-adrenergic blockade on cardiovascular outcomes. Br.J.Anaesth. 2008 Jan;100(1):23-28.

(168) Biccard BM. Heart rate and outcome in patients with cardiovascular disease undergoing major noncardiac surgery. Anaesth.Intensive Care 2008 Jul;36(4):489-501.

(169) Jakobsen CJ, Bille S, Ahlburg P, Rybro L, Pedersen KD, Rasmussen B. Preoperative metoprolol improves cardiovascular stability and reduces oxygen consumption after thoracotomy. Acta Anaesthesiol.Scand. 1997 Nov;41(10):1324-1330.

(170) Wallace A, Layug B, Tateo I, Li J, Hollenberg M, Browner W, et al. Prophylactic atenolol reduces postoperative myocardial ischemia. McSPI Research Group. Anesthesiology 1998 Jan;88(1):7-17.

(171) Raby KE, Brull SJ, Timimi F, Akhtar S, Rosenbaum S, Naimi C, et al. The effect of heart rate control on myocardial ischemia among high-risk patients after vascular surgery. Anesth.Analg. 1999 Mar;88(3):477-482.

(172) Zaugg M, Tagliente T, Lucchinetti E, Jacobs E, Krol M, Bodian C, et al. Beneficial effects from beta-adrenergic blockade in elderly patients undergoing noncardiac surgery. Anesthesiology 1999 Dec;91(6):1674-1686.

(173) Bayliff CD, Massel DR, Inculet RI, Malthaner RA, Quinton SD, Powell FS, et al. Propranolol for the prevention of postoperative arrhythmias in general thoracic surgery. Ann.Thorac.Surg. 1999 Jan;67(1):182-186.

(174) Urban MK, Markowitz SM, Gordon MA, Urquhart BL, Kligfield P. Postoperative prophylactic administration of beta-adrenergic blockers in patients at risk for myocardial ischemia. Anesth.Analg. 2000 Jun;90(6):1257-1261.

(175) Feringa HH, Bax JJ, Boersma E, Kertai MD, Meij SH, Galal W, et al. High-dose beta-blockers and tight heart rate control reduce myocardial ischemia and troponin T release in vascular surgery patients. Circulation 2006 Jul 4;114(1 Suppl):I344-9.

(176) Poldermans D, Schouten O. Chapter 38. Systemic complications: cardiac. In: Cronenwett JL, Johnston KW, editors. Rutherford's Vascular Surgery. 7th ed ed. Philadelphia: Elsevier Health Sciences; 2010.

(177) Poldermans D, Devereaux PJ. The experts debate: perioperative beta-blockade for noncardiac surgery--proven safe or not? Cleve.Clin.J.Med. 2009 Nov;76 Suppl 4:S84-92.

(178) Poldermans D, Schouten O, van Lier F, Hoeks SE, van de Ven L, Stolker RJ, et al. Perioperative strokes and beta-blockade. Anesthesiology 2009 Nov;111(5):940-945.

(179) Lai RC, Xu MX, Huang WQ, Wang XD, Zeng WA, Lin WQ. Beneficial effects of metoprolol on perioperative cardiac function of elderly esophageal cancer patients. Ai Zheng 2006 May;25(5):609-613.

(180) VanDenKerkhof EG, Milne B, Parlow JL. Knowledge and practice regarding prophylactic perioperative beta blockade in patients undergoing noncardiac surgery: a survey of Canadian anesthesiologists. Anesth.Analg. 2003 Jun;96(6):1558-65, table of contents.

(181) Rapchuk I, Rabuka S, Tonelli M. Perioperative use of beta-blockers remains low: experience of a single Canadian tertiary institution. Can.J.Anaesth. 2004 Oct;51(8):761-767.

(182) Price DJ, Kluger MT, Fletcher T. The management of patients with ischaemic heart disease undergoing non-cardiac elective surgery: a survey of Australian and New Zealand clinical practice. Anaesthesia 2004 May;59(5):428-434.

(183) London MJ, Itani KM, Perrino AC,Jr, Guarino PD, Schwartz GG, Cunningham F, et al. Perioperative beta-blockade: a survey of physician attitudes in the department of Veterans Affairs. J.Cardiothorac.Vasc.Anesth. 2004 Feb;18(1):14-24.

(184) Hepner DL. Follow your heart? Adherence to guidelines during preoperative cardiac evaluation. J.Clin.Anesth. 2010 Sep;22(6):399-401.

(185) Fleisher LA. Should my outpatient center have a beta-blocker protocol? Curr.Opin.Anaesthesiol. 2007 Dec;20(6):526-530.

(186) Ellis JE, Tung A, Lee H, Kasza K. Predictors of perioperative beta-blockade use in vascular surgery: a mail survey of United States anesthesiologists. J.Cardiothorac.Vasc.Anesth. 2007 Jun;21(3):330-336.

(187) Biccard BM, Pooran RR. Validation of a model to predict all-cause in-hospital mortality in vascular surgical patients. Cardiovasc.J.Afr. 2008 Nov-Dec;19(6):303-308.

(188) Cuthbertson BH, Boroujerdi M, McKie L, Aucott L, Prescott G. Can physiological variables and early warning scoring systems allow early recognition of the deteriorating surgical patient? Crit.Care Med. 2007 Feb;35(2):402-409.

(189) McGaughey J, Alderdice F, Fowler R, Kapila A, Mayhew A, Moutray M. Outreach and Early Warning Systems (EWS) for the prevention of intensive care admission and death of critically ill adult patients on general hospital wards. Cochrane Database Syst.Rev. 2007 Jul 18;(3)(3):CD005529.

(190) Schmidt M, Lindenauer PK, Fitzgerald JL, Benjamin EM. Forecasting the impact of a clinical practice guideline for perioperative beta-blockers to reduce cardiovascular morbidity and mortality. Arch.Intern.Med. 2002 Jan 14;162(1):63-69.

(191) Biccard BM, Sear JW, Foex P. The pharmaco-economics of peri-operative beta-blocker and statin therapy in South Africa. S.Afr.Med.J. 2006 Nov;96(11):1199-1202.

(192) Lindenauer PK, Fitzgerald J, Hoople N, Benjamin EM. The potential preventability of postoperative myocardial infarction: underuse of perioperative beta-adrenergic blockade. Arch.Intern.Med. 2004 Apr 12;164(7):762-766.

(193) Hepner DL, Correll DJ, Beckman JA, Klickovich RJ, Park KH, Govindarajulu U, et al. Needs analysis for the development of a preoperative clinic protocol for perioperative beta-blocker therapy. J.Clin.Anesth. 2008 Dec;20(8):580-588.

(194) Goodney PP, Eldrup-Jorgensen J, Nolan BW, Bertges DJ, Likosky DS, Cronenwett JL, et al. A regional quality improvement effort to increase beta blocker administration before vascular surgery. J.Vasc.Surg. 2011 May;53(5):1316-1328.e1; discussion 1327-8.

(195) Poon KS, Lee MC, Yang MW, Chang WK, Chen CC, Wu KC, et al. A two-center survey of cardiac events and peri-operative managements of cardiac patients undergoing non-cardiac surgery in Taiwanese population. Acta Anaesthesiol.Sin. 2003 Dec;41(4):173-178.

(196) Weller J, Karim Z. Perioperative beta-blockade: guidelines and practice in New Zealand. Anaesth.Intensive Care 2005 Oct;33(5):645-650.

(197) Steyn K, Sliwa K, Hawken S, Commerford P, Onen C, Damasceno A, et al. Risk factors associated with myocardial infarction in Africa: the INTERHEART Africa study. Circulation 2005 Dec 6;112(23):3554-3561.

(198) Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004 Sep 11-17;364(9438):937-952.

(199) Botes K, Van Marle J. Surgical intervention for HIV related vascular disease. Eur.J.Vasc.Endovasc.Surg. 2007 Oct;34(4):390-396.

(200) Robbs JV, Paruk N. Management of HIV vasculopathy - a South African experience. Eur.J.Vasc.Endovasc.Surg. 2010 Mar;39 Suppl 1:S25-31.

(201) Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof EL, Fleischmann KE, et al. ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Circulation 2007 October 23;116(17):e418-500.

(202) Howell SJ, Sear JW, Foex P. Hypertension, hypertensive heart disease and perioperative cardiac risk. Br.J.Anaesth. 2004 Apr;92(4):570-583.

(203) Spodick DH, Raju P, Bishop RL, Rifkin RD. Operational definition of normal sinus heart rate. Am.J.Cardiol. 1992 May 1;69(14):1245-1246.

(204) Spodick DH. Survey of selected cardiologists for an operational definition of normal sinus heart rate. Am.J.Cardiol. 1993 Aug 15;72(5):487-488.

(205) Keating GM, Jarvis B. Carvedilol: a review of its use in chronic heart failure. Drugs 2003;63(16):1697-1741.

(206) Cantlay KL, Baker S, Parry A, Danjoux G. The impact of a consultant anaesthetist led pre-operative assessment clinic on patients undergoing major vascular surgery. Anaesthesia 2006 Mar;61(3):234-239.

(207) Harnett MJ, Correll DJ, Hurwitz S, Bader AM, Hepner DL. Improving efficiency and patient satisfaction in a tertiary teaching hospital preoperative clinic. Anesthesiology 2010 Jan;112(1):66-72.

(208) Tsen LC, Segal S, Pothier M, Hartley LH, Bader AM. The effect of alterations in a preoperative assessment clinic on reducing the number and improving the yield of cardiology consultations. Anesth.Analg. 2002 Dec;95(6):1563-8, table of contents.

(209) Kapoor AS, Kanji H, Buckingham J, Devereaux PJ, McAlister FA. Strength of evidence for perioperative use of statins to reduce cardiovascular risk: systematic review of controlled studies. BMJ 2006 Dec 2;333(7579):1149.

(210) Hindler K, Shaw AD, Samuels J, Fulton S, Collard CD, Riedel B. Improved postoperative outcomes associated with preoperative statin therapy. Anesthesiology 2006 Dec;105(6):1260-72; quiz 1289-90.

(211) Guyton JR. Benefit versus risk in statin treatment. Am.J.Cardiol. 2006 Apr 17;97(8A):95C-97C.

(212) Choudhry NK, Fletcher RH, Soumerai SB. Systematic review: the relationship between clinical experience and quality of health care. Ann.Intern.Med. 2005 Feb 15;142(4):260-273.

(213) Sweitzer B, Vigoda M, Milokjic N, Boedeker B, Robinson KD, Pilla MA, et al. Residents' Knowledge of ACC/AHA Guidelines for Preoperative Cardiac Evaluation Is Limited. Cleve.Clin.J.Med. 2010 March 1, 2010;77(Electronic Suppl 1):eS11-eS12.

(214) Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA 1999 Oct 20;282(15):1458-1465.