PREOPERATIVE TESTING AND MEDICAL THERAPY INTERVENTION TO IMPROVE PERIOPERATIVE OUTCOMES IN NONCARDIAC SURGICAL PATIENTS

by

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As the candidate's supervisor, I agree to the submission of this dissertation.
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Co-supervisor: Professor R.N. Rodseth

Declaration

I, Christella Sinthuja Alphonsus, declare that:

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1. The role of cardiac rehabilitation using exercise to decrease natriuretic peptide levels in non-surgical patients: a systematic review. **CS Alphonsus**, P Govender, RN Rodseth, BM Biccard. *Perioperative Medicine* 2019;8(14). doi: 10.1186/s13741-019-0124-0
2. Natriuretic peptide-directed medical therapy: a systematic review. **CS Alphonsus**, P Govender, RN Rodseth, BM Biccard. *Perioperative Medicine* 2020;9(5). doi: 10.1186/s13741-019-0134-y
3. A prospective observational study of preoperative natriuretic peptide testing in adult non-cardiac surgical patients in Western Cape hospitals. **CS Alphonsus** et al. *S Afr Med J* 2021;111(4):338–342.
4. Towards the quantification of perioperative cardiovascular risk in the African context: a sub-analysis of the SASOS and ASOS studies. **CS Alphonsus** et al. *S Afr Med J* 2021;111(11):1065–1069.
5. South African cardiovascular risk stratification guideline for non-cardiac surgery. **CS Alphonsus** et al. S Afr Med J. 2021;111(10b):1019–1025.

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Dedication

This work is dedicated to my loving parents and my lovely sister in deep gratitude for their support and encouragement.

Contents

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Abstract

Introduction: Cardiovascular disease is the leading cause of death worldwide and a growing concern in low and middle-income countries, including those in Africa. Patients with cardiovascular disease often have poorly managed chronic conditions in the African setting, which impacts their outcomes when they present for noncardiac surgery. This cohort has an increased risk of perioperative cardiovascular complications. This series of studies explored evidence-based perioperative cardiovascular management strategies in patients with high-risk cardiac comorbidities presenting for noncardiac surgery.

Methods: This was achieved through five objectives which formed five separate but interconnected research studies. The first objective was to study the approach of natriuretic peptide-directed medical therapy in non-surgical patients to inform development of a preoperative protocol in surgical patients through a systematic review. The second objective was to conduct a systematic review on exercise therapy in non-surgical patients to inform development of a preoperative protocol in surgical patients. The third objective was to define the population which would need optimisation before surgery in the Western Cape, South Africa through a prospective observational study of risk stratification. The fourth objective was to explore the broader applicability of perioperative cardiovascular management of high-risk patients by examining cardiovascular outcomes after surgery on the African continent (a sub-study of a larger African cohort study). The fifth objective was to produce national guidelines on cardiovascular risk stratification in a South African and African surgical population.

Main results: The systematic reviews showed potential utility for exercise therapy in the optimisation of cardiac patients for noncardiac surgery. Medical therapy optimisation guided by natriuretic peptide testing did not demonstrate a consistent reduction in natriuretic peptides, but did support a potential mortality benefit in non-surgical patients. The cohort of cardiac patients presenting for noncardiac surgery in the Western Cape carries significant cardiac risk and needs perioperative cardiovascular management. This was confirmed by the rate of adverse cardiovascular outcomes reported on the African continent. These data supported the development of context-specific national cardiovascular risk stratification guidelines.

Conclusion: The cardiovascular burden and risk for perioperative cardiovascular complications presents a challenge in low- and middle-income countries like South Africa, and more broadly, in Africa. This is a growing phenomenon which needs the collaborative effort of perioperative physicians and the implementation of evidence-based strategies in perioperative cardiovascular management.

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Abbreviations

ACC	American College of Cardiology
ACEI	angiotensin converting enzyme inhibitor
AHA	American Heart Association
AHF	acute heart failure
AMSTAR	assessment of multiple systematic reviews
ARA	aldosterone receptor antagonist
ARB	angiotensin II receptor blocker
ASA	acetylsalicylic acid
ASOS	African Surgical Outcomes Study
AT	anaerobic threshold
AUC	area under the curve
B-blocker	beta blocker
BNP	B-type natriuretic peptide(s)
CAD	coronary artery disease
CCF	congestive cardiac failure
CCS	Canadian Cardiovascular Society
CHF	chronic heart failure
CI	confidence interval
CRT	cardiac resynchronisation therapy
CVD	cardiovascular disease
COVID-19	coronavirus disease 2019
ECG	electrocardiogram
EF	ejection fraction
ESA	European Society of Anaesthesiology
ESC	European Society of Cardiology
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
GSH	Groote Schuur Hospital
HF	heart failure
HfrEF	heart failure with reduced ejection fraction
HIC	high-income country or countries
HREC	Human Research Ethics Committee (Faculty of Health sciences, University of Cape Town)
hsTnT	high sensitivity troponin T
ICD	implantable converter defibrillator
IPAQ	International Physical Activity Questionnaire
IQR	interquartile range
LBBB	left-bundle branch block
LMIC	low- and middle-income country or countries
LVEF	left ventricular ejection fraction
MACE	major adverse cardiac events

MANAGE	management of myocardial injury after noncardiac surgery
MC	multidisciplinary care
MI	myocardial infarction
MINS	myocardial injury after noncardiac surgery
MRC	Medical Research Council
N	total population
n	number of patients affected
NCD	non-communicable disease
NP	natriuretic peptide(s)
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
PAD	peripheral arterial disease
POISE-3	Perioperative Ischemic Evaluation-3
PRIMA	Can pro-brain-natriuretic peptide guided therapy of chronic heart failure improve heart failure morbidity and mortality? (Trial)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PROSPERO	International Prospective Register of Systematic Reviews
PVD	peripheral vascular disease
RCRI	Revised Cardiac Risk Index
ROC	receiver operating characteristic
RR	relative risk
SA	South Africa or South African
SASOS	South African Surgical Outcomes Study
SD	standard deviation
SMD	standardised mean difference
SPSS	Statistical Package for the Social Sciences
SSA	sub-Saharan Africa
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TIA	transient ischaemic attack
UN	United Nations
VISION	Vascular Events in Noncardiac Surgery Patients Cohort Evaluation
VO2	maximum oxygen consumption
VT	ventilatory threshold

1 Introduction

1.1 Background

1.1.1 Perioperative cardiovascular complications after noncardiac surgery

The occurrence of a pathological phenomenon very similar to myocardial infarction (MI) in surgical patients in the postoperative period was first noted by clinicians in a 1930s case series, produced by Master and colleagues, of 35 patients at Mount Sinai Hospital in New York. In these patients, myocardial infarction had been diagnosed on electrocardiogram (ECG) or on post-mortem. In 52% of patients, MI was diagnosed within three days of surgery, with a 66% mortality rate. The majority of patients with MI did not have chest pain. Additionally, there were 13 patients in whom the diagnosis was suspected but who did not fulfil the diagnostic criteria. In the 19 patients who were autopsied, all were noted to have coronary artery disease.[1]

The next case series, published in 1952 by Wroblewski and LaDue, described 15 cases that were again characterised by a high mortality rate (40%), with a minority of patients having had typical chest pain. The authors commented on sinus tachycardia as a potential trigger for myocardial ischaemia due to the shortening of diastole.[2]

This scenario, comprising of surgical patients with pre-existing coronary artery disease who have postoperative silent myocardial ischaemia which is not consistently seen on ECG and without typical chest pain, has continued to concern perioperative physicians due to the high mortality rate of these patients. Over the subsequent decades, with the advent of more precise diagnostic tests using cardiac biomarkers, these patients have been shown to have myocardial injury and troponin leak.[3] However, identifying the pathological cause of the myocardial ischaemia has continued to be a challenge.

The myocardial ischaemia could be attributed to the pre-existing coronary artery disease in these patients; however, in many patients, myocardial ischaemia is not typified by intra-arterial thrombosis and infarction.[4] In addition, the troponin leak in some cases is not significant enough to fulfil diagnostic criteria for myocardial

infarction,[5] yet the mortality is similar to events that fulfil the diagnostic criteria for myocardial infarction.[6] The difficulty in identifying a precise pathology has exacerbated the difficulties in clinical definition.

Under the 3rd universal definition of myocardial infarction, perioperative myocardial ischaemia was defined under Type 2 MI due to supply–demand imbalance. Although this indicated a possible pathological cause, this was still a nebulous definition and a seemingly default diagnosis if signs of coronary thrombosis were not found. The causes of supply–demand imbalance are wide-ranging and include arrhythmias, anaemia, respiratory failure, and hypo- or hyper-tension with or without left ventricular hypertrophy.[7] Currently, under the 4th universal definition of myocardial infarction, a separate category of myocardial injury has been created. This requires a troponin value above the 99th percentile upper reference limit (URL). Although this is a progression in incorporating and recognising myocardial injury, there is no commitment made as to the cause of myocardial injury. The supply–demand imbalance terminology has been removed, which still leaves the discussion on causation and subsequent treatment on an uncertain footing.[8]

In addition to the difficulties with the definition and pathological cause of perioperative myocardial injury, there is the clinical reality of correctly identifying, testing, and managing this high-risk group of patients who will face the physiological stress of surgery. Forging ahead with identifying patients at risk of perioperative myocardial injury without a proper foundation of pathological cause is a difficult endeavour. The initial approach has been to consider the information available on clinical assessment. The development of clinical risk indices started with the 1977 Goldman Risk Index, which used prospectively collected data from 1,001 patients and showed nine risk factors to be independently associated with postoperative cardiovascular complications.[9] This index was validated and modified by Detsky in 1986, by adding angina pectoris and congestive cardiac failure to derive a pre-test probability of risk and incorporating type of surgical procedure in predicting postoperative outcome.[10] In 1999, Lee et al. derived the Revised Cardiac Risk Index (RCRI) based on prospective observational data from 4,315 patients, of which 2,893 were the derivation cohort and 1,422 were the validation cohort. The performance of several clinical risk factors were reviewed, from which six independent predictors of major cardiac complications were

identified.[11] However, external validation of the RCRI over many decades has shown that its performance is at best moderate in predicting risk for these complications.[12, 13]

Further strategies to identify high-risk patients have used assessment of functional capacity. This involves assessing the body's capability of dealing with the physiological stress of exercise as a surrogate marker of the ability to withstand the physiological stress of surgery.[14] Many methods have been employed from questionnaires to unstandardised tests (stair-climbing), submaximal tests (six-minute walk test, shuttle-walk test), and the more standardised cardiopulmonary exercise testing.[15] Questionnaires, stair-climbing, and submaximal tests are relatively easy to administer, but the results are limited by subjectivity and patient effort.[15, 16] Cardiopulmonary exercise testing is less biased but requires specific equipment and training to conduct the test and interpret results.[17]

The predictive capability of static echocardiography for postoperative cardiovascular events is also poor, although useful in confirming the presence of intracardiac lesions found during clinical assessment and possibly providing a baseline of cardiac function to tailor the anaesthetic.[18] Similarly, cardiac imaging and non-invasive cardiac testing have been found to have limited capability in predicting postoperative cardiovascular outcomes.[18] The poor performance of these tools in surgical patients, which have been found to be reliable in the diagnosis and management of non-surgical cardiac patients, may be a result of our current lack of understanding of the pathophysiological causes of perioperative cardiac events.

The perioperative period is multidimensional. On the one hand, surgery provides necessary life-saving intervention, but on the other hand, the interplay of patient age, comorbidities, and extent of surgery initiates a cascade of physiological stressors which affect many organ systems in the body.

1.1.2 Surgery and myocardial injury after noncardiac surgery (MINS)

Surgery is sometimes perceived as an isolated and peripheral intervention compared to more widespread healthcare measures related to maternal and child health or chronic comorbidities like diabetes and hypertension. However, surgery intersects

with almost all medical disciplines and there are many diseases that require surgery to halt or ameliorate the pathological process. Surgery is thus an important intervention that is required for a healthy population. Therefore, the overall investment in surgical services and access to surgery not only reduces morbidity but is also a cost-effective intervention.[19]

The Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study provided a window into the cardiovascular disease burden in patients presenting for surgery worldwide and the subsequent cardiac complications. This study was pivotal in identifying the silent postoperative troponin leak is associated with mortality and morbidity in surgical patients. Myocardial injury was documented by postoperative troponin screening for three days. The typical clinical symptoms of myocardial ischaemia were masked, most likely by postoperative analgesia. Silent troponin leak was detected in 8% of patients. The associated 30-day mortality was 9.8%.[6] The morbidity for survivors for up to a year after surgery was also significant.[20] This phenomenon was termed myocardial injury after noncardiac surgery or MINS to identify the troponin leak in the postoperative patient after noncardiac surgery.[6]

The diagnostic definition of MINS with 5th generation high-sensitivity troponin T (hsTnT) is an absolute change of at least 5 ng/L, if the level is between 20 to <65 ng/L, or a hsTnT level of at least 65 ng/L.[21] Although the troponin level used for diagnosis of MINS is low compared to that for diagnosis of myocardial infarction, MINS has a profound impact on mortality within 30 days of surgery and morbidity up to one year after surgery.[21]

1.1.3 Identifying risk of perioperative cardiac complications

Risk assessment is a fundamental aspect of surgery and anaesthesia because surgery fundamentally places a patient in a situation that is intrinsically full of risk. Risk management involves reducing or preventing adverse outcomes. The focus on postoperative cardiac events has prompted a need for preoperative identification of patients at risk of these cardiac events. However, for decades, the tools that have been used for risk assessment, such as non-invasive tests, exercise capacity, and risk indices, have unfortunately failed to reliably identify

all the patients at risk. The use of biomarkers, particularly natriuretic peptides (NP), has been shown to be effective in identifying high-risk patients.[18]

1.1.4 Utility of natriuretic peptide testing in perioperative medicine

Natriuretic peptides are neurohormones synthesized primarily in the heart in response to volume and pressure overload and are responsible for circulatory homeostasis.[22, 23] B-type natriuretic peptides (BNP) have been shown to be produced de-novo in the left ventricle under strain.[24] They are synthesized as a preprohormone which is cleaved to form the active BNP and non-active fragment N-terminal pro-BNP (NT-proBNP). BNP is cleared by endopeptidases and endocytosis after binding to NP receptors. NT-proBNP is cleared through renal excretion.[24]

Due to the relationship between NP and cardiac dysfunction, NP testing is used in diagnosis and management of cardiac failure in non-surgical patients.[25] This application has been extended further in surgical patients.[26] NP have utility in identification, risk stratification, and perioperative planning.[18]

1.1.5 Mitigating the risk of perioperative cardiac complications

In patients with identifiable risk factors, there may be an opportunity in the preoperative period to modify risk factors and reduce myocardial strain. An unexplored further role for NP testing could be to direct preoperative medical therapy optimisation. NP testing has been used in non-surgical patients to direct therapy, but this approach has not been explored in the perioperative patient.[22] Modification of risk factors through optimisation of medical therapy directed by NP testing could provide a strategy to mitigate perioperative cardiovascular complications.

1.2 Research context

Cardiovascular disease is the leading cause of death worldwide.[27] The population of low- and middle-income countries (LMIC) is five times greater than the population of high-income countries (HIC) and carries a great proportion of this disease burden.[28]

Traditionally, interventions in LMIC have focused on communicable diseases, but there is a growing need for cardiovascular care related to chronic comorbidities. Cardiovascular disease is poorly managed in LMIC, including those in Africa.[29] It is possible that patients with poorly managed cardiovascular disease are also presenting for surgical interventions. In the perioperative space, risk stratification guidelines which have been developed in high-income countries with better infrastructure and resources are unlikely to be transferable to LMIC. A structured approach to the identification and optimisation of patients at risk of cardiac complications before noncardiac surgery could be especially relevant in LMIC.

The use of cardiac biomarkers, as outlined in the Canadian Cardiovascular society guidelines, that have a robust performance in identifying high-risk surgical patients may be a less complex and accessible option in LMIC because an alternative strategy dependent on other diagnostic equipment and specialised staff, which may be lacking, and hence unimplementable, could potentially adversely affect the perioperative course of high-risk patients.

In South Africa, there is still a lack of minimum data sets on the number of high-risk patients presenting for surgery, the burden of cardiovascular disease in surgical patients, postoperative outcomes, and the infrastructure available to manage these patients; and many more gaps in our understanding of this multifactorial problem.

1.3 Aims and objectives

1.3.1 Aim

Aim: The main aim of this PhD was to clinically apply evidence-based perioperative cardiovascular management strategies in patients with high-risk cardiac comorbidities who are presenting for noncardiac surgery. A series of five studies were conducted to achieve this aim.

1.3.2 Objectives

1. To study the approach of BNP-directed medical therapy in non-surgical patients to inform development of a preoperative protocol in surgical patients(systematic review).

2. To study the approach of exercise therapy in non-surgical patients to inform development of a preoperative protocol in surgical patients (*systematic review*).
3. To define the population which would need optimisation before surgery in the Western Cape, South Africa through risk stratification (*prospective observational study*).
4. To explore the larger applicability of perioperative cardiovascular management of high-risk patients by describing the cardiovascular disease burden and outcomes after surgery on the African continent *(sub-study of a prospective, observational study*).
5. To produce national guidelines on cardiovascular risk stratification for a high-risk cardiovascular surgical population in South Africa (*guideline development through a Delphi consensus process*).

These separate objectives collectively outline an approach for perioperative management of cardiac patients for noncardiac surgery through defining the scope of the problem in a local and African context, developing standards of care through guidelines, and investigating potential solutions for optimising patients before surgery.

1.4 Ethical clearance and permission to conduct research

Ethical clearance was provided for each study by the following institutions:

- Study 1: Waiver of ethics approval from the Human Research Ethics Committee (HREC), Faculty of Health Sciences, University of Cape Town because this is a systematic review of already published literature (Appendix 1: Waiver of ethics approval for systematic review).
- Study 2: Waiver of ethics approval from the HREC because this is a systematic review of already published literature (Appendix 1: Waiver of ethics approval for systematic review).
- Study 3: Ethics approval received from the HREC (HREC 463/2019) (Appendix 2), individual hospitals, and the Western Cape Department of Health (WC_201909_006) (Appendix 3).
- Study 4: Ethics approval received from the HREC (HREC 615/2019) (Appendix 4).

- Study 5: Ethics approval received from the HREC (HREC 042/2020) (Appendix 4).

1.5 Reporting structure

This thesis includes publications based on the work conducted towards the PhD. This introduction chapter is followed by two systematic reviews (Chapters 2 and 3) and three chapters (Chapters 4, 5, and 6) that report on the research findings, all five of which include published papers. Each chapter has a synopsis of the study conducted, along with justification for its inclusion in the PhD, prior to presentation of the published paper. The concluding chapter summarises the findings, drawing conclusions and making recommendations for implementation and future research.

2 Natriuretic peptide-directed medical therapy: A systematic review

Publication reference: Alphonsus CS, Govender P, Rodseth RN, Biccard BM. Natriuretic peptide-directed medical therapy: a systematic review. *Perioperative Medicine* 2020;9(5). doi: 10.1186/s13741-019-0134-y

2.1 Declaration from author and co-authors

2.1.1 Declaration from author

The following co-authors contributed to the publication: Dr Pooveshnie Govender (PG), Professor Reitze Rodseth (RR), and Professor Bruce Biccard (BB).

The protocol was developed by CSA, RR, and BB. BB conducted the database searches. Screening, extraction of articles, and data extraction was done by CSA, PG, and BB. CSA prepared the manuscript and PG, RR, and BB provided critical revision for intellectual content and quality. All authors approved the final published version and agreed to be accountable for the accuracy or integrity of the work.

Signature removed

Christella S Alphonsus 16 August 2021

2.1.2 Declaration from co-authors

The undersigned hereby certifies that:

1. This declaration correctly reflects the nature and extent of the candidate's contribution to this work and the nature of the contribution of each of the co-authors.
2. The co-authors meet the criteria for authorship in that they have contributed to the conception, execution, interpretation, drafting, revision, and final approval of the publication.
3. The main author and co-authors take public responsibility for their part of the publication.
4. There is no other author of the publication according to these criteria.
5. Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit.

Location of data: Study-related material are stored on the author's (CSA) password-protected laptop.

Signature removed
Professor Bruce Biccard Date: 16 August 2021

Signature removed
Professor Reitze Rodseth Date: 16 August 2021

Signature removed
Dr Pooveshni Govender Date: 16 August 2021

2.2 Synopsis

2.2.1 Rationale for conducting the study

B-type natriuretic peptide testing

Cardiac biomarkers have emerged as important decision-making tools in the diagnosis and management of cardiovascular diseases in medical specialities outside of the operating theatre. Natriuretic peptides belong to a family of neurohormones, namely atrial natriuretic peptide, brain (or B-type) natriuretic peptide, and C-type natriuretic peptide. Under conditions of cardiac pressure or volume overload, atrial natriuretic peptide and B-type natriuretic peptide are secreted by the atria and ventricles respectively. The release of B-type natriuretic peptide is also related to the pressure loading of myocytes associated with myocardial ischaemia. Furthermore, interaction with inflammatory markers such as interleukin-1β, interleukin-6, and tumour necrosis factor-α can also cause release of B-type natriuretic peptide. While atrial natriuretic peptide is stored and released by the atria, B-type natriuretic peptide is released de-novo by the left ventricle under stress. After release, it is cleaved into active BNP and non-active fragment N-terminal pro-BNP (NT-proBNP). Laboratory tests can detect both BNP and NT-proBNP, but the preference is to test for NT-proBNP due to its longer half-life.

NP testing is still an emerging field in perioperative medicine. Preoperative elevated NP are associated with major adverse cardiac events (MACE). This has made NP testing an important tool for identification of high-risk patients and preoperative risk stratification.

Preoperative optimisation

NP testing is used to monitor and titrate drug therapy in cardiac failure patients, and this could have potential implications for the perioperative management of surgical patients: first, in the identification and risk stratification of high-risk surgical patients, and second, in the implementation of strategies to optimise these patients before surgery. NP testing could be used perioperatively to monitor cardiac health and to

titrate NP-targeted drug therapy, with the goal of improving myocardial strain and thus mitigating postoperative cardiac complications.

Motivation for this study in the PhD

In this chapter, we conducted a systematic review and meta-analysis of NP-directed medical therapy in non-surgical patients. Specific protocols shown to successfully reduce NP are highlighted. These protocols have been identified for their potential use in the preoperative optimisation of surgical patients.

2.2.2 Aim and objectives

Aim

To determine: (a) whether NP-directed medical therapy is an effective method to decrease NP levels in adult medical patients with cardiac failure and (b) whether the decrease in NP levels is associated with increased survival.

Objectives

1. To determine whether NP-directed medical therapy can reduce NP levels in patients with cardiac failure at six months after randomisation.
2. To determine whether NP-directed medical therapy can reduce mortality in cardiac failure patients at six months after randomisation.
3. To determine whether this NP-directed medical therapy is safe and effective before it can be tested in a surgical population.
4. To examine the protocols of NP-directed medical therapy in non-surgical patients, to inform the development of preoperative NP-directed medical therapy algorithms.

2.2.3 Main results

Sixty-four full-text articles were reviewed for potential inclusion and 26 trials met the inclusion criteria. Fourteen trials provided data for this review's outcomes.

Study characteristics of included trials:

- All trials included adult patients of 18 years and older.
- The majority of the trials were conducted in outpatient clinics, with follow-up of 15 months or more.
- In 10 of the 18 trials, patients were managed by a specialist cardiologist.
- Most patients were randomised after heart failure was medically stabilised.
- Twelve of the 18 trials enrolled patients with a left ventricular ejection fraction of ≤50%. The remainder of the trials combined patients with preserved and reduced ejection fraction.

Study results:

NP-directed medical therapy showed no significant difference compared to standard care in decreasing NP levels within six months after initiation of NP-directed medical therapy compared to standard care. However, there was a six-month reduction in mortality in the intervention arm.

Below is the content of the published article followed by the references of the paper. *The context and meaning of the published paper are described in detail in the rest of the chapter*.

2.3 Article published in Perioperative Medicine

Natriuretic peptide-directed medical therapy: a systematic review

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Abstract

Natriuretic peptides (NP) are strongly associated with perioperative cardiovascular events. However, in patients with raised NP, it remains unknown whether treatment to reduce NP levels prior to surgery results in better perioperative outcomes. In this systematic review and meta-analysis, we investigate NP-directed medical therapy in non-surgical patients to provide guidance for NP-directed medical therapy in surgical patients. The protocol was registered with PROSPERO (CRD42017051468). The database search included MEDLINE (PubMed), CINAHL (EBSCO host), EMBASE (EBSCO host), ProQuest, Web of Science, and Cochrane database. The primary outcome was to determine whether NP-directed medical therapy is effective in reducing NP levels within 6 months, compared to standard of care. The secondary outcome was to determine whether reducing NP levels is associated with decreased mortality. Full texts of 18 trials were reviewed. NP-directed medical therapy showed no significant difference compared to standard care in decreasing NP levels (standardized mean difference − 0.04 (− 0.16, 0.07)), but was associated with a 6-month (relative risk (RR) 0.82 (95% confidence interval (CI) 0.68–0.99)) reduction in mortality.

Keywords: Cardiac morbidity, Pre-operative evaluation, Myocardial ischaemia

Introduction

Every year, 230 million adults undergo non-cardiac surgery worldwide.[1] In patients who are 45 years or older, 8% will suffer Myocardial Injury after Non-cardiac Surgery (MINS)[2] and 2% will die within 30 days.[3] MINS is typically asymptomatic without the usual features of chest pain and electrocardiogram changes seen with myocardial infarction.[2] MINS has prognostic importance up to a year after surgery.[4]

The biomarker, B-type natriuretic peptide (BNP), has been identified as an important preoperative predictor of perioperative cardiovascular events.[5] Despite this strong association, it remains unknown whether preoperative treatment to normalise or reduce NP (B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide) levels prior to surgery would result in improved perioperative outcomes. This is a novel approach that has not been tested in clinical trials involving surgical patients. Thus, a systematic review of non-surgical trials is necessary to establish whether this approach is safe and effective before it can be tested in a surgical population.

The objective of this systematic review of clinical trials was to determine whether, in adults, medical patients with cardiac failure, NP-directed medical therapy is able to decrease NP levels and whether this is associated with increased survival.

These data could then be used to inform preoperative protocols aimed at decreasing NPs prior to surgery, with the intention of improving perioperative cardiovascular outcomes.

Methods

Protocol and registration

The protocol was registered with PROSPERO (CRD42017051468). The Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guideline were adhered to.[6]

Eligibility criteria

Clinical trials of adult medical patients who were randomised to either NP guided medical therapy or standard care were eligible. We included trials which used NPs to (i) guide medical therapy in non-surgical patients, (ii) up-titrate or modify medical therapy in the response to NP levels, or (iii) included exercise as part of cardiac rehabilitation in non-surgical patients. We required that the trials report the subsequent changes in NP levels. We excluded trials that (i) monitored natriuretic peptides for prognostic or diagnostic purposes, without a strategy to lower natriuretic peptide levels, (ii) reviews of natriuretic peptide or biomarker physiology, and (iii) trials reporting natriuretic peptides in patients with acute myocardial infarction, pulmonary hypertension, cardiac resynchronisation therapy, and left ventricular devices.

Information sources, search, and study selection

Three searches were conducted using search terms ‘brain natriuretic peptide’ AND ‘treatment’, ‘brain natriuretic peptide’ AND ‘heart failure’ and ‘brain natriuretic peptide’ AND ‘exercise’. The following databases were accessed; MEDLINE (PubMed), CINAHL (EBSCO host), EMBASE (EBSCO host), ProQuest, Web of Science, and Cochrane database. No date filter was used. An example of the search is shown in Supplementary appendix 2.1. The initial search was conducted on 22 December 2016 and updated on the 4 March 2018.

Data collection process

Titles were screened for potential inclusion by CA and PG. The abstracts of the potential papers identified through the title search were then screened using inclusion and exclusion criteria by CA and PG. The full texts of potential trials were then extracted for detailed review and analysis. Reference lists were searched for additional papers that could be included in this review. Data extraction was done by one author (CA) and then checked by a co-author. When the required data was not presented in the publication, the authors were contacted for these data.

Data items

We extracted data on the NP reduction within the first six months of randomisation and mortality at 6 months. The data items extracted for this review are shown in Supplementary appendix 2.1: Table S2.1.

Outcomes

The primary outcome for this review was to determine whether a NP-directed medical therapy protocol is effective in reducing NP levels at 6 months after initiation of therapy compared to standard care. The secondary outcome was to determine whether NP-directed medical therapy decreases mortality at 6 months and at the end of the trial. The safety outcomes of changes in medical therapy were evaluated. Specific medical treatment strategies are described.

Risk of bias in individual studies

Assessment of bias in the studies was conducted by CA and verified by BB following discussion. Each randomized trial was assessed using the Cochrane Collaboration risk of bias tool, assessing selection bias, concealment bias, performance bias, detection bias, attrition bias, and other bias. Studies were assessed as having a low, unclear or high risk of bias.

Summary measures and synthesis of results

The statistical analyses were conducted using Review Manager Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Those trials which had data on NP levels within 6 months of therapy initiation were analysed using standardised mean difference (SMD), and these data are presented as a forest plot. Mean and standard deviation (SD) of NP levels were used and those trials which reported NP levels as the median and interquartile range (IQR) were converted to mean and SD, using the formula proposed by Wan et al.[7] Reporting the SMD allowed for the inclusion of all trials, whether BNP or NT-proBNP, was used to monitor the medical therapeutic response. SMD addresses the difference in the effect size for an intervention when the units of measurement differ between trials e.g. use of BNP or NT-proBNP. The SMD is the difference between groups in the mean endpoint divided by the SD of the control group or pooled SD of the treatment and control groups (Hedges' *g*).[8]

A meta-analysis of mortality within 6 months of the initiation of therapy, with subgroup analyses at 4 and 6 months was conducted. The results are reported as relative risk (RR), with 95% confidence intervals (CI), and presented as forest plots. Random

effects models were used where the I^2 statistic >25% (representing significant heterogeneity), otherwise a fixed-effects model was used.

Risk of bias across studies

Risk of bias across studies was assessed with funnel plots for NP reduction and mortality.

Post hoc

After extracting and analysing the data, it was noticed that the methodology used in the exercise trials differed significantly from the medical therapy trials. This difference was so substantial that we deemed it inappropriate to pool the two interventions. We therefore made a post hoc decision to separate the exercise studies from the medical therapy studies. These exercise study data are presented in the accompanying publication (CS Alphonsus et al 2019).

Results

Study selection

Sixty-four full-text articles were reviewed for potential inclusion and 26 trials (presented in 27 publications) met the inclusion criteria. An additional eight trials were added from references (Fig. 2.1). Eighteen trials of medical therapy interventions were identified (reported in 19 publications; 1 trial was reported in 2 separate papers)[9 10] fulfilled the inclusion criteria, although only 14 trials provided data for this review's outcomes. The 16 exercise trials were subsequently removed from this review, following the post-hoc decision to present these trials in a separate paper (CS Alphonsus et al. 2019).

We evaluated previous systematic reviews identified in the search using the AMSTAR format (Supplementary appendix 2.1: Table S2.2).

Study characteristics of included studies

The characteristics of the included clinical trials are shown in Table 2.1. These trials included adult patients of 18 years and older. The majority of the trials examined

outpatient NP-directed medical therapy, with follow-up of 15 months or more. In 10 out of 18 trials, patients were seen by a specialist at a clinic.[11-21] Most patients were randomised once heart failure was medically stabilised and 12 out of 18 trials enrolled patients with EF ≤50%.[12 14-17 19 20 22-26] The remainder of the trials combined patients with preserved and reduced ejection fraction.[9-11 13 18 21 2]

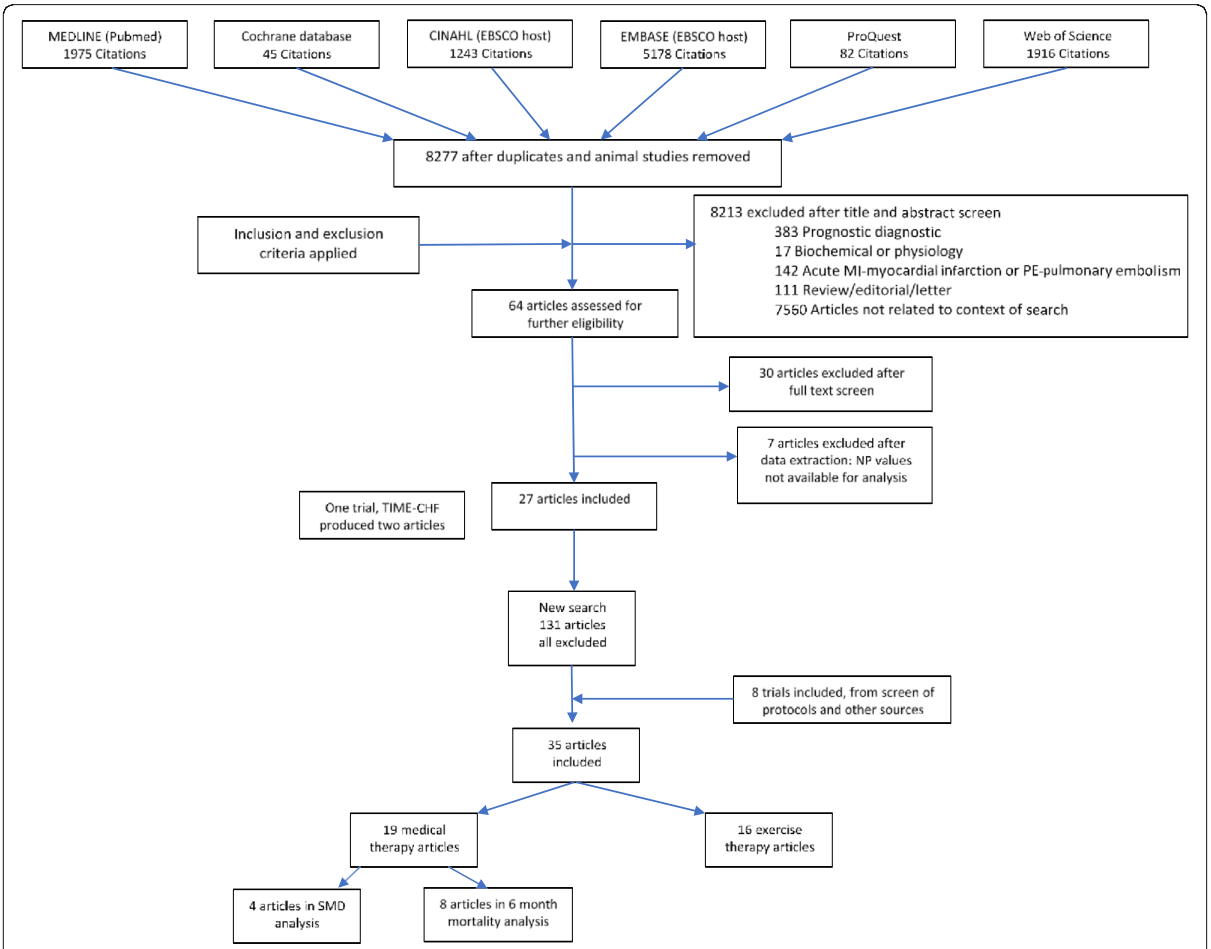

Fig. 2.1 PRISMA flow diagram

Table 2.1 Characteristics of included clinical trials

Clinical trial	Patients	Intervention arm (*n*) vs standard care arm (*n*)†	Follow-up (months)
Murdoch et al. (1999)	Stable CHF, LVEF ≤35%	BNP arm *n* = 10 Standard care *n* = 10	2
Troughton et al. (2000)	Decompensated HF now stabilised, LVEF <40%	BNP arm *n* = 33 Standard care *n* = 36	9.5
Beck-da-Silva et al. (2005)	>18 years, stable CHF but not on β blockers, LVEF ≤40%	BNP arm *n* = 21 Standard care *n* = 20	3
Jourdain et al. (2007)	>18 years, optimised on treatment, LVEF <45%	BNP arm *n* = 110 Standard care *n* = 110	15
Ozkara et al. (2007)	Treated with ACEI/loop diuretic, LVEF ≤ 50%	NT-proBNP arm *n* = 79‡ Standard care *n* = 61	6
Pfisterer et al. (2009)	≥60 years, LVEF ≤45%, 60–74yrs = NT-proBNP ≥400 pg/ml; ≥75 years = NT-proBNP 800 pg/ml	NT-proBNP arm *n* = 251 Standard care *n* = 248	18
Lainchbury et al. (2009)*	>18 years, AHF now stabilised	NT-proBNP arm *n* = 121 Standard care *n* = 122	36
Anguita et al. (2010)	>18 years, AHF	BNP arm *n* = 30 Standard care *n* = 30	18
Persson et al. (2010)	LVEF <50%, males NT-proBNP >800 ng/ml, females >1000 ng/ml	NT-proBNP arm *n* = 125 Standard care *n* = 127	9
Eurlings et al. (2010)	AHF NT-proBNP >1700, randomised at discharge if >10% drop in NT-proBNP	NT-proBNP arm *n* = 174 Standard care *n* = 171	24
Berger et al. (2010)*	AHF now stabilised, LVEF <40%	NT-proBNP + MC arm (only patients with NT-proBNP >2200 pg/ml) *n* = 92 Standard care *n* = 90	Maximum 18; minimum 12
Januzzi Jr et al. (2011)	>21 years, LVEF <40%	NT-proBNP group *n* = 75 Standard care *n* = 76	10
Shah et al. (2011)	Decompensation HF now stabilised, LVEF ≤35%	BNP arm *n* = 68 Standard care *n* = 69	4
Karlstrom (2011)	>18 years BNP >150 ng/L for those aged <75 years, and BNP >300 ng/L for those aged >75 years	BNP arm *n* = 147 Standard care *n* = 132	33

Maeder et al. (2013)	≥60 years, LVEF >45%, 60–74yrs = NT-proBNP ≥400 pg/ml; ≥75 years = NT-proBNP 800 pg/ml	NT-proBNP arm *n* = 59 Standard care *n* = 64	18
Schou et al. (2013)	>18 years, Optimised on treatment and implantable ICD/CRT, LVEF <45%, NT-proBNP >1000	NT-proBNP arm *n* = 199 Standard care *n* = 208	Median 30
Carubelli et al. (2016)	Randomised after clinical stabilisation of AHF	NT-proBNP arm *n* = 137 Standard care *n* = 134	Mean 18
Stienen et al. (2018)	Decompensated HF, NT-proBNP levels >1700 ng/ml within 24 h of hospital admission. In hospital intervention	NT-proBNP arm *n* = 201 Standard care *n* = 203	6
Felker et al. (20170	LVEF ≤ 40%, NT-proBNP >2000 pg/mL/BNP >400 pg/mL	NT-proBNP arm *n* = 446 Standard care *n* = 448	12

CHF chronic heart failure, *AHF* acute heart failure, *NT-proBNP* N-terminal pro b-type natriuretic peptide, *LVEF* left ventricular ejection fraction, *ARB* angiotensin II receptor blocker, *ACEI* angiotensin converting enzyme inhibitor, *ARA* aldosterone receptor antagonist, *B-blocker* beta blocker, *ICD/CRT* implantable converter defibrillator/cardiac resynchronisation therapy, *BNP* B-type natriuretic peptide, *MC* multidisciplinary care, *NYHA* New York Heart Association, *HF* heart failure
†Check Additional file 1
*Randomised to three-arm but only 2 meet the inclusion criteria for this review, NP-directed arm and control arm most reflecting usual patient care
‡ Only patients in the intervention arm received spironolactone

The conduct of the trial intervention arms is shown in Table 2.2. All trials randomised patients into NP-directed medical therapy or clinical/usual care. Two trials were three-arm trials, but for this analysis, only the interventional and usual care arms were included.[11 21] In the majority of trials, the NP threshold for inclusion was consistent across age and gender, with the exception of three trials, where the threshold was either age- or gender-specific.[9 10 20 22] Nine trials set population NP targets,[11 15-19 21 26 27] eight trials set individualised NP targets,[9 10 12-14 20 22 23 25] and one trial had no set NP target, but directed medical therapy to reduce the NP level.[24] The management of the standard care arms is shown in Supplementary appendix 2.1

Two trials were stopped early,[15 26] Felker et al. for the benefit, and Januzzi et al. for futility.

Table 2.2 The conduct of the natriuretic-peptide (NP)-directed clinical trials

Clinical Trial	Level of care in interventional group	Frequency of visits	NP target
Murdoch	Specialist HF clinic	Every 2 weeks	Single target BNP <50 pg/ml
Troughton	Specialist HF clinic	Every 3 months	Single target N-BNP <200 pmol/L
Beck-da- Silva	Nurse-led HF clinic	Every 3 months	Individualised according to symptoms in relation to BNP levels.
Jourdain	Specialist care at the clinic	1 month (for 3 months) then 3 months	Single target BNP <100 pg/ml
Ozkara	Physician clinic visits	Treatment not adjusted throughout study	No BNP target set
Lainchbury*	Research clinic (with possible specialist input)	Every 3 months	Single target NT-proBNP <150 pmol/L
Maeder; Pfisterer	Outpatient visits	1, 3 ,6, 12, 18 months	NT-proBNP <400 pg/mL in <75 years and <800 pg/mL in ≥75 years
Eurlings	Specialist care at the clinic	2 weeks, 1 month, then 3 months	Individualised NT-proBNP <10% of randomisation level
Berger*	HF specialist clinic	Every 2 weeks till NT-proBNP target met. Then as required.	Single target NT-proBNP <2200 pg/ml
Persson	Primary care centres	10 days, 1, 3, 6, 9 months	Individualised NT-proBNP <50% from baseline level
Anguita	Cardiology clinic	1, 2, 3, 6, 24, 18 months	Single target BNP <100 pg/ml
Shah	HF clinic with specialist input	1 week, 1, 2, 3, 4 months after discharge	Individualised BNP <2 times discharge level
Januzzi	HF clinic	Every 3 months	Single target NT-proBNP ≤1000 pg/ml
Karlstrom	Outpatient visits	2, 6, 10, 16, 2, 36, 48 weeks, then every 6 months	<75 years (BNP <150 ng/L) and ≥75 years (BNP <300 ng/L)

Schou	Specialist heart failure clinic	Every 1–3 months	Individualised NT-proBNP <30% of randomisation level
Carubelli	Single centre, initially in hospital management and then outpatient visits	Frequent visits if NT-proBNP still raised after discharge. Then telephonic follow up at 1, 3, and 6 months	Single target NT-proBNP ≤3000 pg/ml
Felker	Outpatient visits	2 and 6 weeks, then every 3 months	Single target NT-proBNP <1000 pg/mL
Stienen	Intervention carried out in the hospital	1 week and at 1, 3, and 6 months	Individualised to reduce NT-proBNP by at least 30% by discharge

NP natriuretic peptide, *NT-proBNP* N-terminal pro B-type natriuretic peptide, *LVEF* left ventricular ejection fraction, *ARB* angiotensin II receptor blocker, *ACEI* angiotensin-converting enzyme inhibitor, *BNP* B-type natriuretic peptide, *NYHA* New York Heart Association, *HF* heart failure
*Lainchbury and Berger: three-arm trial but only NT-proBNP guided management group and usual care group compared

Risk of bias within studies and across studies

The risk of bias of the included trials is shown in Supplementary appendix 2.1: Figs. S2.1 and S2.2. The random sequence generation was unclear in half the trials, and blinding of patients and investigators was low. Many trials did not clearly document if outcome assessors were blinded. The funnel plots for SMD (Supplementary appendix 2.1: Fig. S2.3), and 6-month mortality (Supplementary appendix 2.1: Fig. S2.4) did not suggest publication bias.

Results of individual studies and synthesis of results

The efficacy of NP-directed medical therapy in reducing NP levels within 6 months compared to standard care

Fourteen out of 18 medical therapy trials presented data on change in NP levels during the trial,[9-20 22 25-27] of which 7 out of 14 trials presented data on NP levels within the first 6 months of the trial.[9 10 14 18 25-27] Three trials Shah, Carubelli, and Stienen were excluded as the data was reported at differing time points before 6 months: Stienen (mean 12 ± 10 days),[25] Carubelli (mean 11 ± 9 days)[27] and Shah (4 months).[14] The overall point estimate of the four remaining trials was non-significant at 6 months of

NP-directed medical therapy with low heterogeneity in the included trials (Fig. 2.2), (SMD − 0.04, 95% CI − 0.16, 0.07).

Reduction in NP levels and its association with mortality

Seventeen out of 18 studies reported mortality at trial completion.[9-18 20-27] After extracting the end of trial mortality data, it was deemed inappropriate to conduct a meta-analysis, as the duration of the trial follow up periods differed between the trials. It was therefore impossible to conduct a meta-analysis at a fixed long-term time point.

Eight of the 18 trials[9-11 13 14 18 25 26] reported mortality within the first 6 months of the intervention. Two trials reported mortality at 4 months, and 6 trials reported mortality at 6 months. NP-directed medical therapy was associated with a reduction in mortality within the first 6 months of the intervention (RR 0.82, 95% CI 0.68–0.99). Subgroup analysis suggested little heterogeneity between the 4-month and 6-month outcomes (Fig. 2.3).

Adverse events in relation to the change in therapy

Seven out of 18 studies recorded adverse effects of medical therapy on electrolytes and the cardiovascular system.[9 10 13-17 19] These were deemed not serious and six of these studies showed no difference in the incidence of adverse effects of therapy between the intervention and control groups.

The specific treatment strategies used in the trials

The treatment strategies and efficacy of these treatments varied between the trials. The two trials that showed the most benefit associated with NP-directed medical therapy,[27] and,[14] showed efficacy for diuretics (the former) and angiotensin-converting enzyme inhibitors and beta-blockers (the latter). The two studies that showed the greatest number of patients reaching target NP levels,[11] and,[22] showed that a combination of therapies was effective, including diuretics, angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers and beta-blockers.

Discussion

The principal findings of this systematic review are that NP-directed medical therapy does not significantly reduce NP levels at 6 months after initiation of NP-directed medical therapy. However, NP-directed medical therapy may be associated with decreased mortality in the short term, and there is little heterogeneity for this finding.

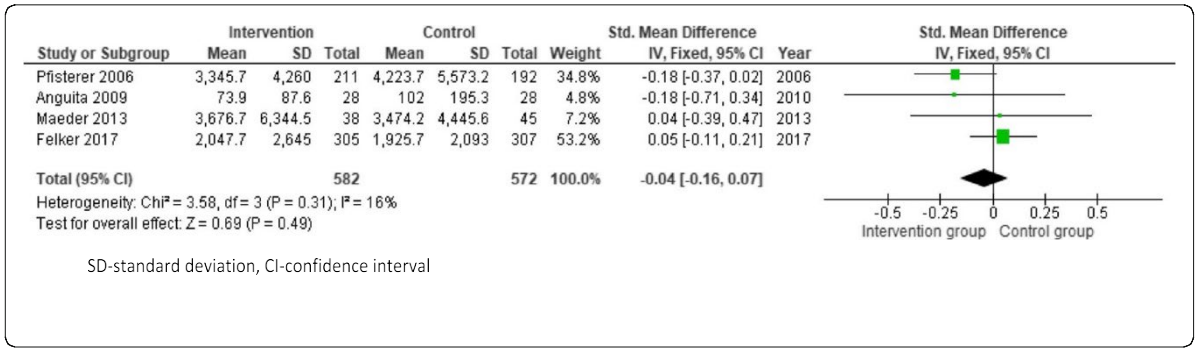

Fig. 2.2 Efficacy of natriuretic peptide-directed medical therapy versus control in reducing BNP-levels within 6 months (standardised mean difference in natriuretic peptide levels in NP-directed medical therapy clinical trials). SD-standard deviation; CI-confidence interval

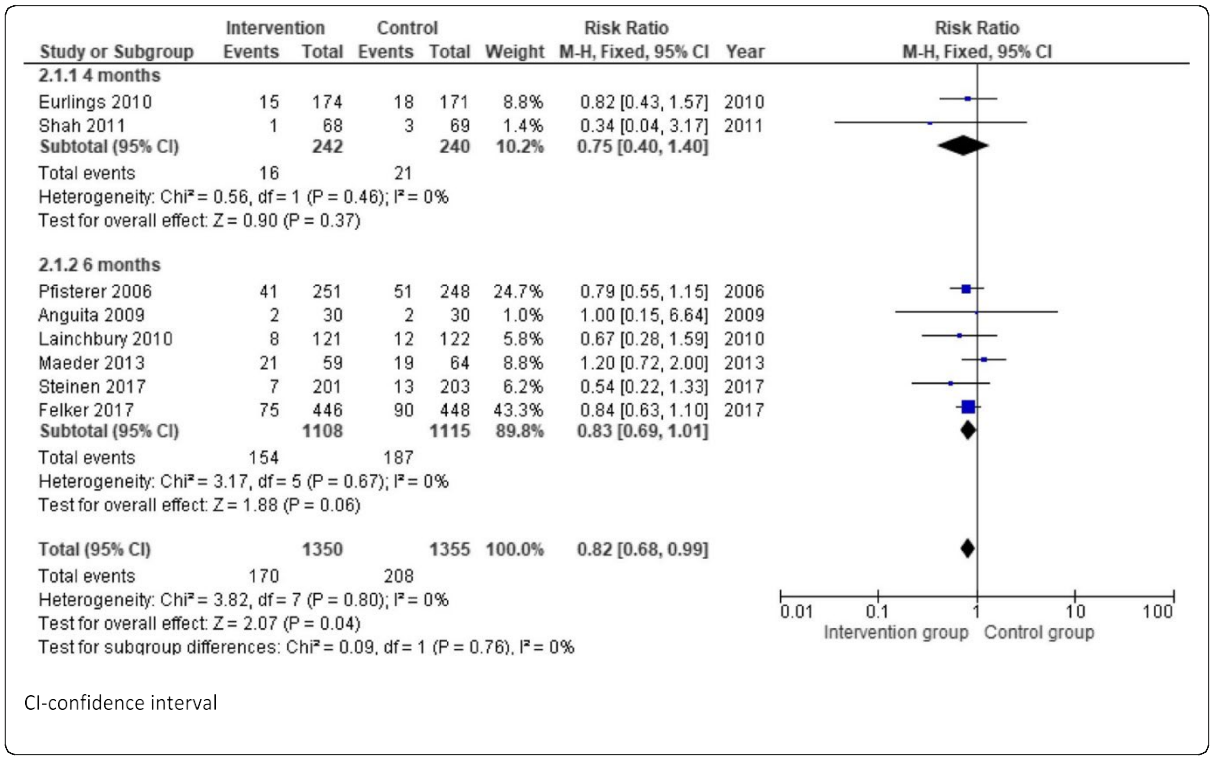

Fig. 2.3 Effect of natriuretic peptide guided medical therapy versus control on mortality after 6 months. CI-confidence interval

Strengths

The strength of this review is that we evaluated the efficacy of NP-directed medical therapy from clinical trials, on the biochemical response of patient NP levels, and the clinically relevant outcome of mortality. The methodology of this systematic review and meta-analysis is robust.

Findings in relation to other studies

There is an important fundamental difference between this meta-analysis, and the other two meta-analyses that were published after the protocol for our meta-analysis was registered.[28 29] The primary outcome of our meta-analysis was to evaluate if it was possible to decrease NP levels with NP-directed therapy, while the primary outcome of the other two meta-analyses was to determine if NP-directed medical therapy was associated with a survival benefit. Evaluation of a potential survival benefit was a secondary outcome in our meta-analysis. Our primary interest was to determine whether perioperative physicians could possibly decrease NP levels prior to elective surgery in patients with high NP levels (and thereby potentially improve the risk profile of poor surgical candidates). Both these meta-analyses also had point estimates favouring survival benefit with NP-directed therapy in the long term. The importance of our meta-analysis is that (i) a reduction in NP levels is not necessarily essential to demonstrate a survival benefit with NP-directed medical therapy, and (ii) that this survival benefit may be seen earlier than what has been previously documented. The utility of NP-directed medical therapy in preoperative surgical patients is unknown, as there are currently no surgical trials in this field. This meta-analysis suggests that there is potential utility in this approach in surgical patients.

Preoperative risk stratification of high-risk patients is advocated by international guidelines, the most recent being the Canadian Cardiovascular Society (CCS) Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery.[30] Screening for natriuretic peptides is a key component of risk stratification.[30]

Our meta-analysis suggests that there may be a further benefit to the reduction of NP levels prior to surgery. The survival benefit seen with NP-directed medical therapy in this meta-analysis may suggest that an intensification of medical therapy is warranted in patients with marked physiological derangement reflected by a markedly elevated NP level. These high NP levels may reflect some reversibility in volume status and myocyte ischaemia which is responsive to further medical therapy. Indeed, the trials which demonstrated the greatest number of patients reaching a target NP level included a combination of therapies which would have had both volume and ischaemia efficacy.[11 22] The importance of this systematic review is the following. Firstly, these findings suggest that there is potential to improve survival for an elective surgical population through NP-directed medical therapy. Secondly, the perioperative period is a powerful modifier of risk, and decreasing this risk, has the potential to change morbidity and mortality up to a year after surgery.[4]

Limitations

We were unable to obtain data from all the included trials for the SMD, the patients reaching the target NP and the time to NP reduction analysis. This is because most trials did not publish these end-points, nor was this included as part of the trial protocols. It is possible that if we had a larger sample which included data from all trials, then we may have shown an association between NP-directed medical therapy and a reduction in NP levels. However, it appears from this meta-analysis, that it is the intensification of medical therapy, rather than the reduction in NP levels, which may be important for short-term survival.

The non-parametric data for the SMD analysis was transformed to mean and standard deviation to facilitate analysis and caution should be taken when interpreting these results. The range of starting NP level on randomisation in the intervention groups is large and could dramatically influence responsiveness to NP-directed therapy. However, despite these differences in the pre-intervention NP levels, mortality decreased in the NP-directed therapy arm, with little heterogeneity. It could be argued, however, that this early mortality (i.e. at 6 months of therapy initiation) signal is fragile. If a random-effects meta-analysis is conducted, then one cannot demonstrate a survival benefit associated with NP-directed medical therapy (RR 0.88, 95% 0.75–

1.04, *p*= 0.14). Similarly, a sensitivity analysis which excludes all trials with a high risk of bias is not associated with a survival benefit (RR 0.84, 95% CI 0.61–1.15, *p* = 0.27) in a random-effects model. The survival benefit demonstrated in this meta-analysis therefore should be considered 'hypothesis-generating' at best. It was not possible to control for the effect of age or renal function on NP for this analysis.

Finally, the included trials had very different implemented protocols, and thus it is not possible to identify a preferred medical management plan based on these data.

Future research

This systematic review provides support for a clinical trial of preoperative NP-directed medical therapy in high-risk elective surgical patients.

Conclusion

NP-directed medical therapy does not necessarily decrease NP levels, but it may be associated with a survival benefit. There may be a place for preoperative NP-directed medical therapy in high-risk surgical patients.

Supplementary information

Supplementary appendix 2.1: Example of search strategy for the systematic review. Description of the standard care arm. **Table S2.1.** Data extracted for meta-analyses. **Table S2.2.** AMSTAR evaluation of previous systematic reviews. **Fig. S2.1.** Risk of bias summary. **Fig. S2.2.** Risk of bias graph. **Fig. S2.3.** Funnel plot for standard mean difference forest plot. **Fig. S2.4.** Funnel plot for mortality at 4- and 6- months forest plot.

Abbreviations. ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; BB: Beta-blocker; BNP: B-type natriuretic peptide; CI: Confidence interval; IQR: Interquartile range; MINS: Myocardial injury after non-cardiac surgery; NP: Natriuretic peptides; NT-proBNP: N-terminal pro B-type natriuretic peptide; RR: Relative risk; SD: Standard deviation; SMD: Standardized mean difference

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Availability of data and materials. All articles available online and datasets are available from the corresponding author.

Ethics approval and consent to participate. Not applicable.

Consent for publication. Not applicable.

Competing interests. The authors declare that they have no competing interests.

Supplementary appendix 2.1

Example of search strategy for the systematic review. Search strategy: (peptide set AND therapy set) NOT surgery set Natriuretic Peptide, Brain (MeSH) OR Brain Natriuretic Peptide OR Type-B Natriuretic Peptide OR Type B Natriuretic Peptide OR B-type Ventricular Natriuretic Peptide OR B type Ventricular Natriuretic Peptide

AND

Therapeutics (MeSH) Therapeutics OR treatment OR therapy OR rehabilitation

NOT

General Surgery (MeSH) OR Surgical Procedures, Operative (MeSH) OR surgery OR surgical OR operative search strategy: (peptide set AND heart failure set) NOT surgery set

Natriuretic Peptide, Brain (MeSH) OR Brain Natriuretic Peptide OR Type-B Natriuretic Peptide OR Type B Natriuretic Peptide OR B-type Ventricular Natriuretic Peptide OR B type Ventricular Natriuretic Peptide

AND

Heart Failure (MeSH) OR Coronary Artery Disease (MeSH) Heart failure OR cardiac failure OR heart decompensation OR myocardial infarction OR myocardial ischemia OR heart attack OR myocardial infarct

NOT

General Surgery (MeSH) OR Surgical Procedures, Operative (MeSH) OR surgery OR surgical OR operative search strategy: (peptide set AND exercise set) NOT surgery set

Natriuretic Peptide, Brain (MeSH) OR Brain Natriuretic Peptide OR Type-B Natriuretic Peptide OR Type B Natriuretic Peptide OR B-type Ventricular Natriuretic Peptide OR B type Ventricular Natriuretic Peptide

AND

Exercise (MeSH) OR Physical Exertion (MeSH) OR Exercise OR physical exertion OR physical activity OR motor activity OR physical effort

NOT

General Surgery (MeSH) OR Surgical Procedures, Operative (MeSH) OR surgery OR surgical OR operative

Description of the standard care arm

Anguita—Symptom-guided treatment to a clinical Framingham score <2.

Carubelli—No further changes to medical therapy.

Felker—Follow 2013 ACC/AHA guidelines.

Steinen—No further changes to therapy.

Shah—Congestion score (indicative of fluid overload) done at patient discharge and diuretics titrated in these patients.

Pfisterer and Maeder—Symptom guided treatment, reduce symptoms to dyspnoea NYHA class of II or less.

Table S2.1. Data extracted for meta-analyses SMD—standardised mean difference

Author	Year	SMD at 6 months	Mortality at 4 and 6 months
Lainchbury	2010		✓
Eurlings	2010		✓
Shah	2011		✓
Pfisterer	2006	✓	✓
Maeder	2013	✓	✓
Anguita	2009	✓	✓
Felker	2017	✓	✓
Stienen	2017		✓

Table S2.2 AMSTAR evaluation of previous systematic reviews

Author	Journal	Comment	A priori design	Duplicate	Comprehensive review	Publication status	List of studies	Characteristics of studies	Scientific quality assessed	Quality with conclusions	Publication bias discussed
Cardarelli and Lamicao	JABFP 2003	Narrative review	No	No	No	No	Yes	No	No	No	No
Porapakkham	Arch Intern Med 2010	Systematic review and meta-analysis	No	No	No	No	Yes	Yes	No	Yes	Yes
Li	Heart, Lung and Circulation 2013	Meta-analysis	No	Yes	No	No	Yes	Yes	Yes	Yes	No
Savarese	PLOS ONE 2013	Systematic review and individual patient meta-analysis	Yes	Yes	No	No	No	No	No	Yes	Yes
De Vecchis	Journal Cardiovascular Medicine 2014	Systematic review and meta-analysis	No	Yes	Yes	Yes	Yes	Yes	No	No	No
Troughton	European Heart Journal 2014	Systematic review and individual patient meta-analysis	Yes	Yes	No	No	Yes	Yes	No	No	No
Brunner-La Rocca	European Journal of Heart Failure 2015	Systematic review and individual patient meta-analysis	No	Yes	No	No	Yes	Yes	No	No	No
Xin	Heart Fail Rev 2015	Systematic review and meta-analysis	Yes	Yes	No	No	Yes	Yes	No	No	Yes
Pufulete	Systematic Reviews 2017	Systematic review and individual	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

		patient meta-analysis							
Khan	International Journal of Cardiology 2018	Systematic review and meta-analysis	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

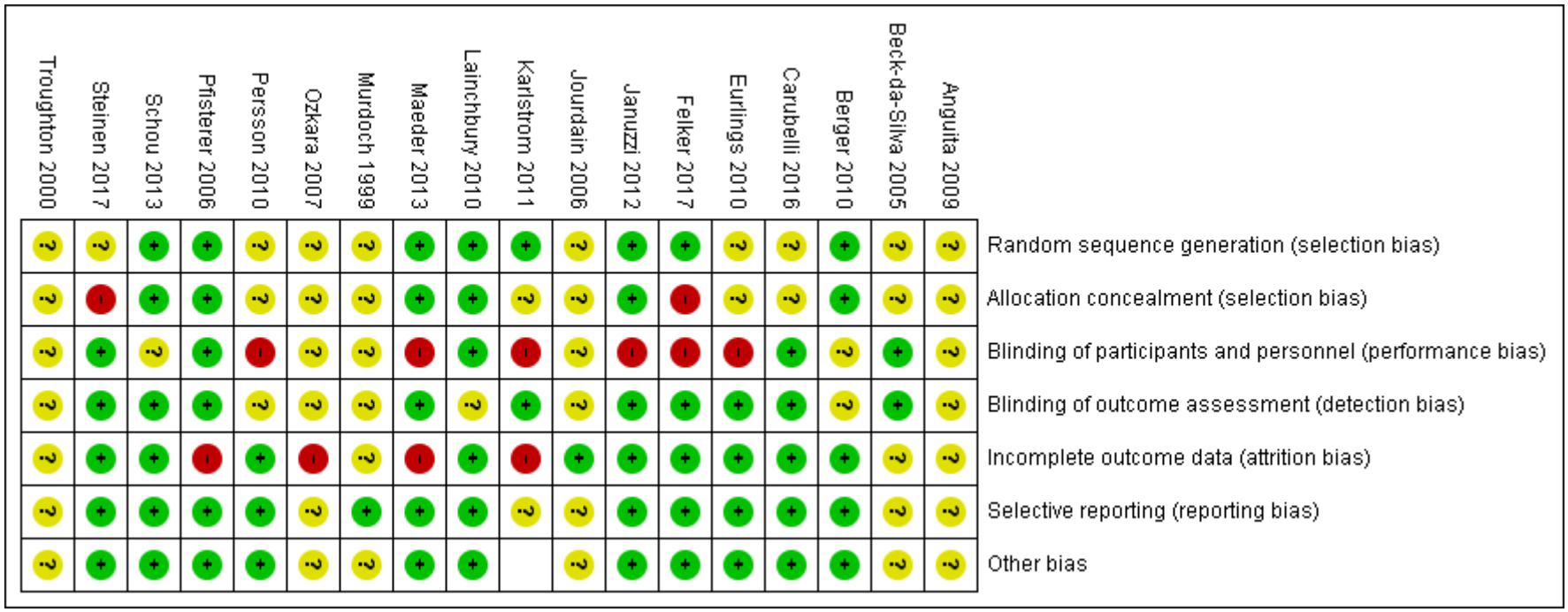

Fig. S2.1 Risk of bias summary

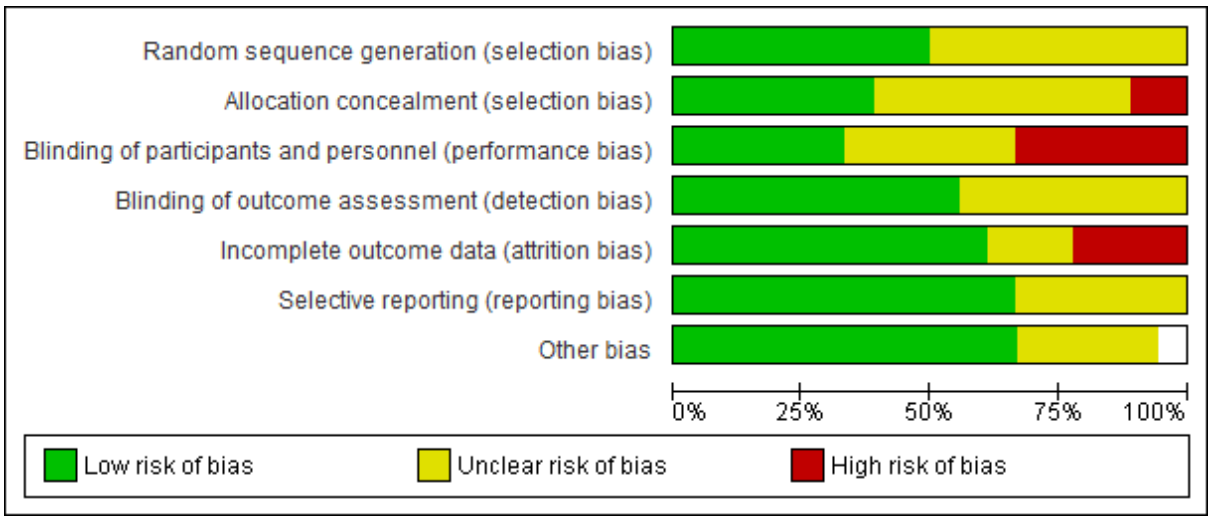

Fig. S2.2 Risk of bias graph

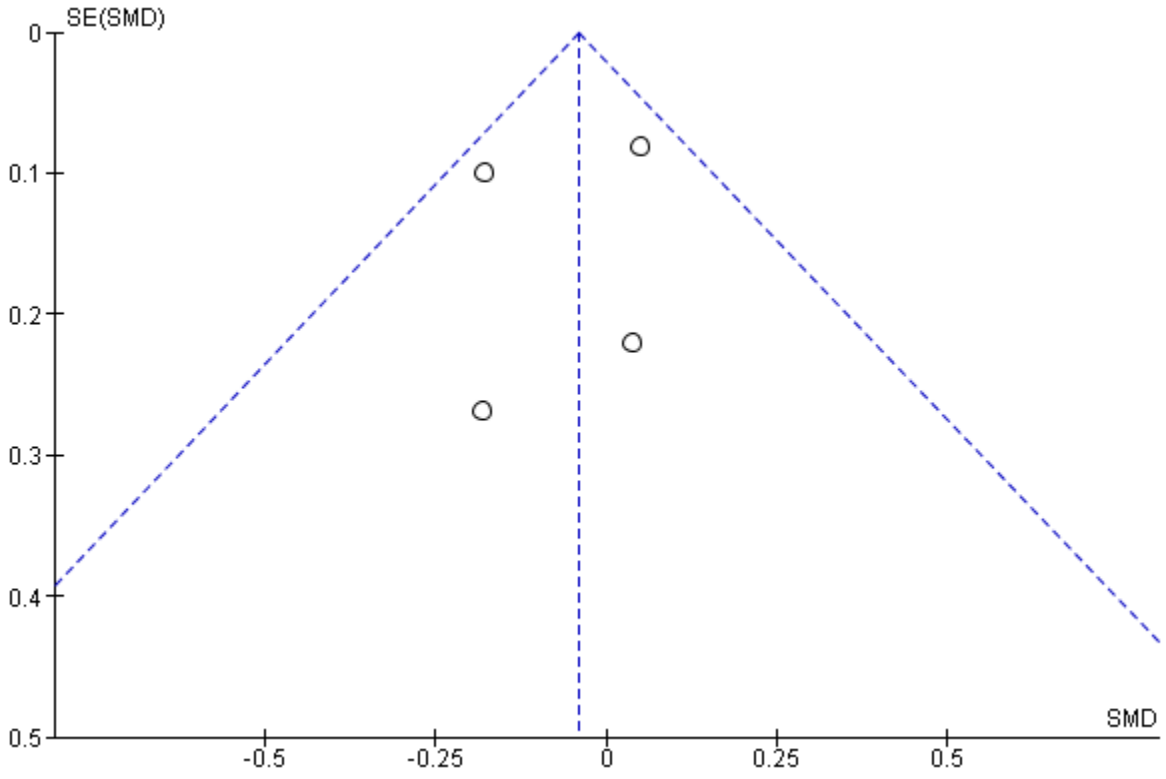

Fig. S2.3 Funnel plot for standard mean difference forest plot

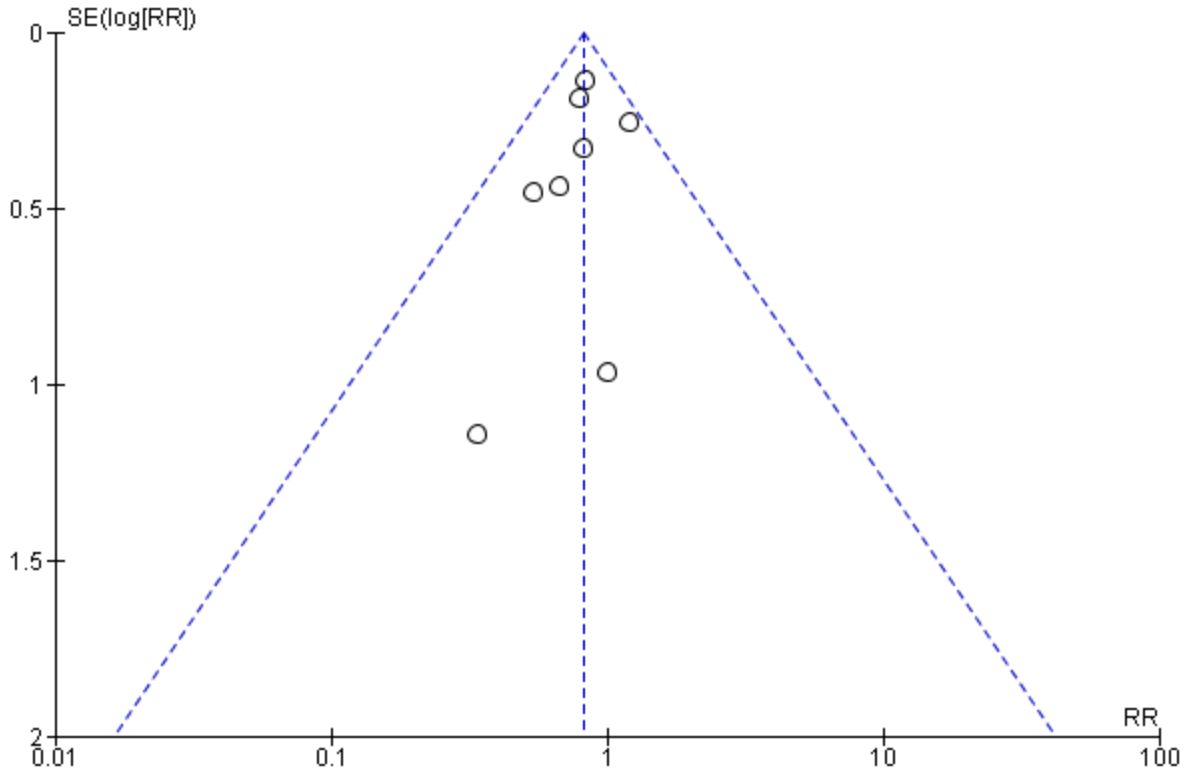

Fig. S2.4 Funnel plot for mortality at 4- and 6- months forest plot

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2.4 Chapter discussion

In this systematic review, we sought to determine whether NP-directed medical therapy decreases NP levels and increases survival in non-surgical patients with cardiac failure. We were unable to show conclusively that NP-directed therapy decreases NP levels in this study, although there was a six-month survival benefit. However, the complexity of clinical treatment approaches is highlighted. Although 18 clinical trials were reviewed, many of the trials could not be combined into a meta-analysis because of the heterogeneity between studies. This is highlighted in Table 2.2, which shows the patient selection criteria for each trial. Drug therapy and treatment approach varied between trials, making it difficult to derive a consistent approach to care in the intervention arm.

Ultimately, only four trials presented data on NP-reduction and mortality within six months of randomisation. The six-month target is questionable in its applicability to surgical patients; however, since these were trials in a non-surgical population, intervention and follow-up times were much longer, limiting the number of trials that could be included in the systematic review.

The demonstration of a reduction in mortality in the intervention arm raises many important questions for the role of NP-directed medical therapy in surgical patients. Does the intensification of care, unrelated to NP reduction, lead to a survival benefit? Is the NP level of little clinical utility beyond its initial use in the diagnosis of heart failure? These questions are relevant in a surgical population if intensification of care in the immediate preoperative period could improve postoperative cardiovascular outcomes.

It was difficult to identify a single drug regimen that would reduce NP levels (Table 2.4.1). An approach incorporating diuretics, angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers, and beta-blockers showed efficacy in four trials.[30-33]

Table 2.4.1 NP reduction with different classes of medical therapies

Intervention	Percentage reduction in intervention group	Absolute reduction in intervention group(pg/ml)	How many patients achieved the target
Diuretic:			
PRIMA	8.6%	254	No data
Carubelli	No data	No data	No data
Berger	No data	No data	No data
ACEI:			
Troughton	36%	79	No data
Murdoch	42%	47	4 (out of 10 patients)
ACEI/BB:			
STARBRITE	9%	41	37%
STARS-BNP	19%	68	33%
ARB:			
PROTECT*	52%	1219	44%
Combined therapies:			
BATTLESCARED	20%	402	52%
TIME-CHF (Pfisterer)	No data	No data	22%
TIME-CHF (Maeder)	No data	No data	No data
UPSTEP	3.6%	30	60%

2.5 Chapter conclusion

This chapter explored the possibility of preoperative optimisation in noncardiac surgery using NP-directed medical therapy through the lens of studies of non-surgical patients. Owing to the heterogeneity of therapeutic approaches adopted in these studies, it was difficult to find a consistent management approach that could be applicable to surgical patients. NP-directed medical therapy requires further enquiry and research to determine the optimal therapeutic strategy and duration necessary to realise potential survival benefit in surgical patients. Furthermore, defining an adequate response to therapy intensification still remains to be determined, as the systematic review failed to demonstrate a decrease in NP levels at six months.

Our next step was to explore the role of exercise therapy in lowering natriuretic peptide levels.

3 The role of cardiac rehabilitation using exercise to decrease natriuretic peptide levels in non-surgical patients: A systematic review

Publication reference: Alphonsus CS, Govender P, Rodseth RN, Biccard BM. The role of cardiac rehabilitation using exercise to decrease natriuretic peptide levels in non-surgical patients: a systematic review. *Perioperative Medicine* 2019;8(14). doi: 10.1186/s13741-019-0124-0

3.1 Declaration from author and co-authors

3.1.1 Declaration from author

The following co-authors contributed to the publication: Dr Pooveshnie Govender (PG), Professor Reitze Rodseth (RR), and Professor Bruce Biccard (BB).

The protocol was developed by CSA, RR, and BB. BB conducted the database searches. Screening, extraction of articles, and data extraction was done by CSA, PG, and BB. CSA prepared the manuscript and PG, RR, and BB provided critical revision for intellectual content and quality. All authors approved the final published version and agreed to be accountable for the accuracy or integrity of the work.

Signature removed

Christella S Alphonsus 16 August 2021

3.1.2 Declaration from co-authors

The undersigned hereby certifies that:

1. This declaration correctly reflects the nature and extent of the candidate's contribution to this work and the nature of the contribution of each of the co-authors.
2. The co-authors meet the criteria for authorship in that they have contributed to the conception, execution, interpretation, drafting, revision, and final approval of the publication.
3. The main author and co-authors take public responsibility for their part of the publication.
4. There is no other author of the publication according to these criteria.
5. Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit.

Location of data: Study-related material are stored on the author's (CSA) password-protected laptop.

Signature removed
Professor Bruce Biccard Date: 16 August 2021

Signature removed
Professor Reitze Rodseth Date: 16 August 2021

Signature removed
Dr Pooveshni Govender Date: 16 August 2021

3.2 Synopsis

3.2.1 Rationale for conducting the study

The role of exercise in cardiovascular health

The relationship between exercise and cardiovascular health has been studied over the past seven decades.[34] Lack of physical activity (along with uncontrolled hypertension and diabetes, smoking, obesity, and an abnormal blood lipid profile) is one of the key risk factors for cardiovascular disease.[35] Conversely, exercise can modify this cluster of risk factors by improving insulin sensitivity, reducing blood lipid levels and blood pressure.[36, 37]

Several epidemiological studies have noted the relationship between physical activity and cardiovascular disease.[38] Most recently, a large prospective observational study of 130,000 participants from 17 high-income, middle-income, and low-income countries studied the impact of physical activity, both recreational and non-recreational, on cardiovascular disease and mortality.[39] One week of total physical activity was assessed using the long-form International Physical Activity Questionnaire (IPAQ). Participants were recruited by approaching households or individuals, who were telephonically requested to visit their local clinics and followed up for a median of almost seven years.[39]

A dose-dependent benefit of physical activity from only 30 minutes a day for five days a week up to 1,250 minutes a week indicated any type of physical activity was beneficial. Moderate intensity (150–750 minutes per week) compared to low intensity (<150 minutes per week) physical activity was associated with a 28% lower risk of mortality and 20% lower risk of cardiovascular disease. High physical activity (>750 minutes per week) produced additional reduction of mortality by 19% and cardiovascular disease by 12%.[39]

Exercise in cardiac failure

Exercise has prognostic, diagnostic, and therapeutic implications in cardiac failure.[38] In patients with symptomatic heart failure, increasing physical inactivity is associated with an incremental increase in the risk of all-cause death.[40] Traditionally, exercise had been discouraged in heart failure patients.[38] Over time, we have come to understand that heart failure is a multi-system disease where the heart, lungs, skeletal muscle, vasculature, and neuro-hormonal systems are all involved in heart failure progression.[38] Exercise can positively modulate the evolution of heart failure.[41]

In 1988, Sullivan and colleagues produced the first work demonstrating improved exercise tolerance in 12 heart failure patients after exercise training.[42] The largest study, HF-ACTION, was a multicentre randomised controlled trial of safety and efficacy of aerobic exercise training in 2,331 patients with stable heart failure with reduced ejection fraction (HFrEF) and New York Heart Association classes II to IV.[43] This trial showed modest reductions in all-cause mortality/hospitalisation and cardiovascular mortality/heart failure hospitalisation (when adjusted for highly prognostic predictors of the primary outcome). Since HF-ACTION demonstrated that exercise was safe with some clinical benefit in heart failure, this led to the US Centers for Medicare and Medicaid Services including coverage for cardiac rehabilitation in selected patients who had similar criteria to patients in the HF-ACTION trial.[44]

Exercise is now a recommended therapy for people with heart failure.[45] These patients can be frail and have multiple comorbidities; therefore, exercise programmes may need to be tailored to be accessible and achievable.[46]

Motivation for this study in the PhD

Exercise training as preoperative rehabilitation in surgical patients with cardiac disease may provide a potentially non-invasive, and possibly cheaper, alternative to escalating drug therapy in people with heart failure. Exercise targets the same organ systems as multi-modal heart failure drug therapy and thus the physiological basis for this therapy is

sound. Improving preoperative cardiac function may mitigate the detrimental effects of the surgical stress response on cardiovascular function. This may lead to a reduction in perioperative cardiovascular complications and mortality.

In this study, we investigated the use of natriuretic peptide testing to monitor the impact of exercise training on cardiac function. A secondary goal of this study was to identify suitable exercise programmes to reduce NP levels.

3.2.2 Aim and objectives

Aim

To determine: (a) whether exercise therapy decreases NP levels in adult medical patients with cardiac failure and (b) whether an associated NP-level reduction is associated with increased survival.

Objectives

1. To determine whether exercise therapy can reduce NP levels in patients with cardiac failure.
2. To determine whether exercise therapy can reduce mortality and morbidity in cardiac failure patients.
3. To determine the shortest duration of time for reducing NP levels with exercise therapy in cardiac failure patients.
4. To determine which specific exercise regimens are effective in reducing NP levels in people with cardiac failure.

3.2.3 Main results

Sixty-four full-text articles were reviewed for potential inclusion and 16 trials met the inclusion criteria. Sixteen trials provided data for this review's outcomes.

Study characteristics of included trials:

- All trials included adult patients of 18 years and older.
- The trials were conducted in an outpatient setting and patients in the intervention group received supervised training.
- All trials included some form of aerobic exercise, either walking, bicycling, or running on a treadmill. Three trials included interval training and three trials included resistance training in addition to aerobic training in the intervention.
- Most trials were small, with a maximum of 40 patients in each arm, with the exception of the HF-ACTION trial, which included 477 patients.
- Most trials included patients with a reduced ejection fraction (EF<40%).

Study results:

NP levels can be lowered with supervised exercise training and this improvement is achievable within 12 weeks.

Below is the content of the published article followed by the references of the paper. *The context and meaning of the published paper are described in detail in the rest of the chapter*.

3.3 Article published in Perioperative Medicine

The role of cardiac rehabilitation using exercise to decrease natriuretic peptide levels in non-surgical patients: a systematic review

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Abstract

Exercise is recommended in patients with cardiac failure. In the perioperative patient, exercise is also gaining popularity as a form of prehabilitation. In this meta-analysis, we examine if exercise is able to reduce natriuretic peptide levels. Natriuretic peptide has strong prognostic ability in identifying patients who will develop adverse postoperative cardiovascular outcomes. The protocol was registered with PROSPERO (CRD42017051468). The database search included MEDLINE (PubMed), CINAHL (EBSCO host), EMBASE (EBSCO host), ProQuest, Web of Science, and Cochrane database. The primary outcomes were to determine whether exercise therapy was effective in reducing NP levels as compared to control group, the shortest time period required to reduce NP levels after exercise therapy, and whether reducing NP levels decreased morbidity and mortality. Full texts of 16 trials were retrieved for this review. Exercise therapy showed a significant reduction in natriuretic peptide levels between the intervention and control groups (SMD – 0.45, 95% CI – 0.88 to – 0.03) with significant heterogeneity between the included trials. This was also shown within a 12-week period.

Keywords: Cardiac morbidity, Preoperative factors, Myocardial ischaemia

Introduction

Historically, exercise was commonly avoided in patients with heart failure. This has changed dramatically over the past 30 years with recommendations from international organisations such as the European Society of Cardiology and American College of Cardiology Foundation/American Heart Association for the use of exercise training to improve exercise tolerance and reduce morbidity and mortality.[1]

Exercise is now considered part of preoperative rehabilitation, also known as prehabilitation, for patients presenting for surgery. This is based on the philosophy that improving functional capacity may improve the patient's ability to withstand the surgical stress response and thereby improve postoperative outcomes. Outcomes such as hospital length of stay, postoperative pulmonary complications, and quality of life have been improved with this approach.[2]

There is currently no consensus on the type and duration of exercise needed to improve outcome in surgical patients[3] and non-surgical patients.[4] Furthermore, B-type natriuretic peptide (BNP) testing has been recommended to identify patients at high risk of perioperative cardiovascular events,[5] yet there remains limited data on the efficacy of exercise to decrease B-type natriuretic peptides[4] and decrease subsequent cardiovascular events.

The objective of this systematic review of clinical trials was to determine whether in adult, medical patients with cardiac failure, exercise therapy was able to decrease NP levels and whether this was associated with improved cardiovascular outcomes.

Methods

Protocol and registration

The protocol was registered with PROSPERO (CRD42017051468). The Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines were

adhered to.[6] This protocol included a meta-analysis on the effect of medical therapy on NP levels, which is presented in the accompanying paper (CS Alphonsus et al. 2019).

Eligibility criteria

The inclusion criteria for this systematic review have been described in the systematic review on natriuretic peptide-directed medical therapy which included exercise therapy trials.

In this systematic review, we report prospective randomised clinical trials of adult medical patients who were randomised to exercise as part of cardiac rehabilitation, where the subsequent changes in natriuretic peptide levels are reported. We excluded (i) trials that monitored natriuretic peptides for prognostic or diagnostic purposes, without a strategy to lower natriuretic peptide levels; (ii) reviews of natriuretic peptide or biomarker physiology; and (iii) trials reporting natriuretic peptides in patients with acute myocardial infarction, pulmonary hypertension, cardiac resynchronisation therapy, and left ventricular assist devices.

Information sources, search, *and study selection*

Three searches were conducted using search terms ‘brain natriuretic peptide’ AND ‘treatment’, ‘brain natriuretic peptide’ AND ‘heart failure’, and ‘brain natriuretic peptide’ AND ‘exercise’. The following databases were accessed: MEDLINE (PubMed), CINAHL (EBSCO host), EMBASE (EBSCO host), ProQuest, Web of Science, and Cochrane database. There were no filters used for year of publication or language. Non-English titles were not excluded. An example of the search is shown in Supplementary appendix 3.1. The initial search was conducted on 22 December 2016 and updated on 4 March 2018.

Data collection process

Titles were screened for potential inclusion by CA and PG. Abstracts of potential papers identified through the title search were then screened using inclusion and exclusion criteria by CA and PG. The full texts of potential trials were then extracted for full text

review and analysis. Reference lists were searched for additional papers that could be included in this review. Data extraction was done by one author (CA) and then checked by a co-author (BB). When required data was not presented in the publication, the authors were contacted for these data.

Data items

We extracted data on the NP reduction at the end of the exercise trials. Data was also extracted on the patient characteristics, the type of exercise intervention, the physical activity in the control group, and mortality and morbidity in the trials was also extracted.

Outcomes

The primary outcomes for this review were to determine (i) whether exercise therapy was effective in reducing NP levels as compared to control group, (ii) the shortest time period required to reduce NP levels after exercise therapy, and (iii) whether reducing NP levels decreased morbidity and mortality. The secondary outcome was to determine which specific exercise regimens were more effective in reducing NP levels.

Risk of bias in individual studies

Assessment of bias in the studies was conducted by CA and verified by BB following discussion. The Cochrane Collaboration risk of bias tool was used and assessed selection bias, concealment bias, performance bias, detection bias, attrition bias, and other biases. Studies were assessed as having low, unclear, or high risk of bias.

Summary measures and synthesis of results

Statistical analyses were conducted using Review Manager Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). For NP reduction, we tabulated the absolute NP change. NP levels which were reported as median and interquartile range (IQR) were converted to mean and SD.[7] As the included trials used either BNP or NT-proBNP to monitor therapeutic response we made use of standardised mean difference (SMD) for our meta-analysis. SMD addresses the difference in the effect size for an intervention when the units of measurement differ between trials, e.g. use of

BNP or NT-proBNP. The SMD is the difference between groups in mean end point divided by the SD of the control group (or pooled SD of the treatment and control groups).[8] These data are presented as a forest plot. Random effects models were used where the I^2 statistic >25% (representing significant heterogeneity), otherwise a fixed effects model was used.

Risk of bias across studies

Risk of publication bias across studies was assessed with funnel plots for NP reduction.

Results

Study selection

After the initial search, 64 articles were reviewed for potential inclusion. Twenty-six trials (27 publications) were selected and 8 trials added from references, of which 18 were trials of medical therapy interventions and 16 trials were of an exercise intervention

(Fig. 3.1). We evaluated 2 previous systematic reviews using the AMSTAR format (Supplementary appendix 3.2).

Study characteristics of included studies

Cardiac rehabilitation exercise trials were conducted in adult patients 18 years and older, in an outpatient setting (Table 3.1). The included cardiac rehabilitation exercise trials all included some form of aerobic exercise, either walking, bicycle, or treadmill. Trials that involved interval training were considered as a separate subgroup for analysis.[9-11] Three trials included resistance training in addition to aerobic training in the intervention group.[12-15] Most trials ran for up to 12 weeks, one trial for 20 weeks,[14] and another for 24 weeks.[12] Most trials were small, with a maximum of 40 patients in each arm, with the exception of 1 large trial (HF-ACTION) which included 477 patients.[16] Most trials included patients with an ejection fraction (EF) <40%, two trials had patients with EF 40–49%[17 18] and three trials

had patients with mixed categories of heart failure.[9] [10] [14] The exercise intervention protocols were not individualised to the NP levels, but the NP response to the exercise intervention was reported in all the trials.

The exercise intervention group received supervised exercise training in all the trials, except two where the exercises were home-based after participants were given instructions.[18] [19] The control group were given exercise information (except Brubaker[20]) but did not receive supervised exercise training.

Risk of bias within studies and across studies

The risk of bias of the included trials is shown in the Supplementary appendix 3.3: Fig. S3.1 and Supplementary appendix 3.4: Fig. S3.2. The random sequence generation was acceptable in three trials.[16] [17] [21] By virtue of the intervention (supervised exercise versus exercise recommendation), blinding of patients was impossible, and investigator blinding was poor. Outcome assessors were only blinded in two trials.[16] [20] The funnel plots for SMD (Fig. 3.2) did not suggest publication bias.

Results of individual studies and synthesis of results

All trials presented data on NP levels at the end of the intervention period.

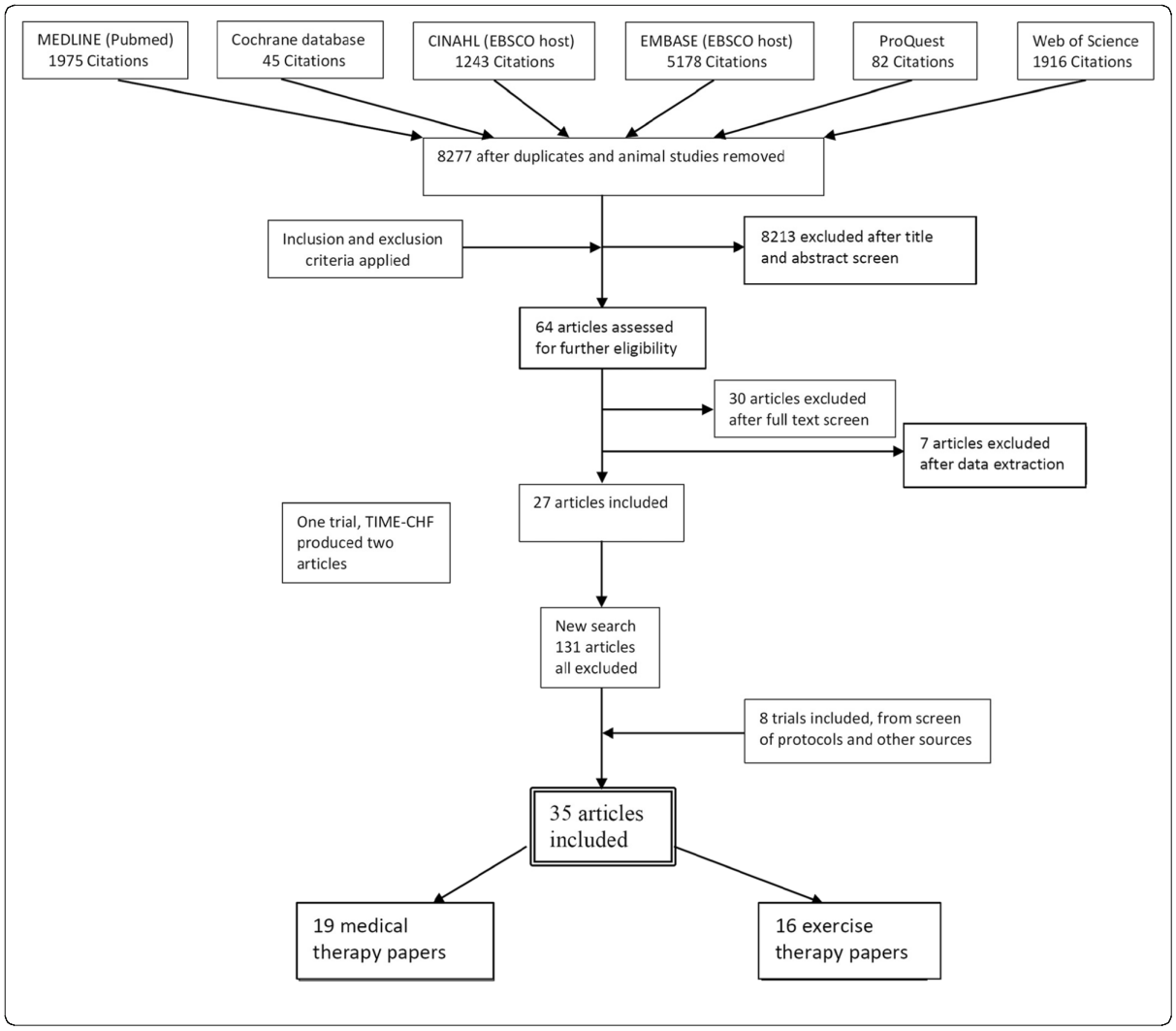

Fig. 3.1 PRISMA flow diagram

Is exercise therapy as effective in reducing NP levels as compared to control group?
The meta-analysis of the SMD in NP levels between the intervention and control group is shown in Fig. 3.3. The overall point estimate showed a significant reduction in NP levels between the intervention and control groups (SMD -0.45, 95% CI -0.88 to -0.03) with significant heterogeneity between the included trials. Neither the continuous aerobic, nor the interval training subgroup showed a significant reduction in NP.

What is the shortest time period required to reduce NP levels after exercise therapy?

An analysis of the trials with a 12-week intervention period (the shortest exercise intervention period in the eligible trials), showed a significant NP reduction (SMD -0.75, 95% CI -1.17 to -0.33) (Fig. 3.4).

Table 3.1 Trial characteristics of cardiac rehabilitation exercise trials

Author, year	Patient characteristics	Type of NP	Baseline NP in intervention group
			(pg/ml)
Kobayashi et al. 2003	Stable NYHA II-III. EF < 40%	BNP	281 ± 92
Meyer et al. 2004	Stable NYHAII-III. EF ≤ 40%	NT-proBNP	1092 ± 980
Jonsdottir et al. 2006	Patients previously hospitalised in past 3 years for heart failure	BNP	173.2 ± 180.4
Maria Sarullo et al. 2006	Stable CHF. EF < 40%	NT-proBNP	3376 pg/ml ± 3133
Brubaker et al. 2009	CHF. EF ≤ 45%	BNP	176 ± 38
Malfatto et al. 2009	Chronic heart failure	BNP	293 ± 115
Parrinello et al. 2010	Stable NYHAII-III. EF ≤ 45%	BNP	205.2 ± 46.5
Gary et al. 2011	Stable NYHA II-III, stable on medical therapy. EF 15 to 40%	BNP	184.4_151.6
Guazzi et al. 2012	Stable NYHA class II or III, stable on medical therapy. EF ≤ 45%	NT-proBNP	1088.1 ± 447.1
Norman et al. 2012	Volunteers, NYHAII-IV, ≥ 21 years, LVEF ≤ 40%, on optimal medical therapy	BNP	1088.1 ± 447.1
Sandri et al. 2012	Stable CHF. EF < 40%	NT-proBNP	≤55 years, 1675±354 ≥65 years, 1301±261
Eleuteri et al. 2013	Stable NYHA II, stable on medical therapy. EF ≤ 40%	NT-proBNP	1570.7 ± 3125.8
Ahmad et al. 2014, HF-ACTION sub-study	CHF patients with reduced left ventricular ejection fraction (< 35%)	NT-proBNP	960.6 ± 1114
Aksoy et al. 2015	NYHAII-III CHF on optimal medical therapy. EF 35 to 55%	NT-proBNP	Continuous aerobic exercise group 20.79 ± 12.8 Interval exercise group 24.00 ±18.27

NP natriuretic peptide, *CHF* chronic heart failure, *EF* left ventricular ejection fraction, *BNP* B-type natriuretic peptide, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *NYHA* New York Heart Association

Does reducing NP levels decreased morbidity and mortality?

Only four trials reported on mortality[10 14 16 20]. HF-ACTION trial[16] reported 189 (16%) deaths in the intervention group and 198 (17%) deaths in the control group, HR 0.96 (0.79–1.17), p=0.70, and a cardiovascular mortality at a median follow up of 30 months of 131 (11%) deaths in the intervention group and 143 (12%) deaths in the control group, 0.92 (0.74–1.15), p=0.47. Three other trials, Nilsson[10], Jónsdóttir[14] and Brubaker[20]

reported mortality. Nilsson et al. reported one death in the control group, Jónsdóttir et al. two each in intervention and control groups and Brubaker et al. one in each group. None of other trials reported mortality.

Secondary outcome: Where specific exercise regimens were more effective in reducing NP levels?

Neither supervised continuous aerobic exercise or interval training was independently associated with a significant reduction in NP levels. A preferable exercise regimen therefore cannot be determined.

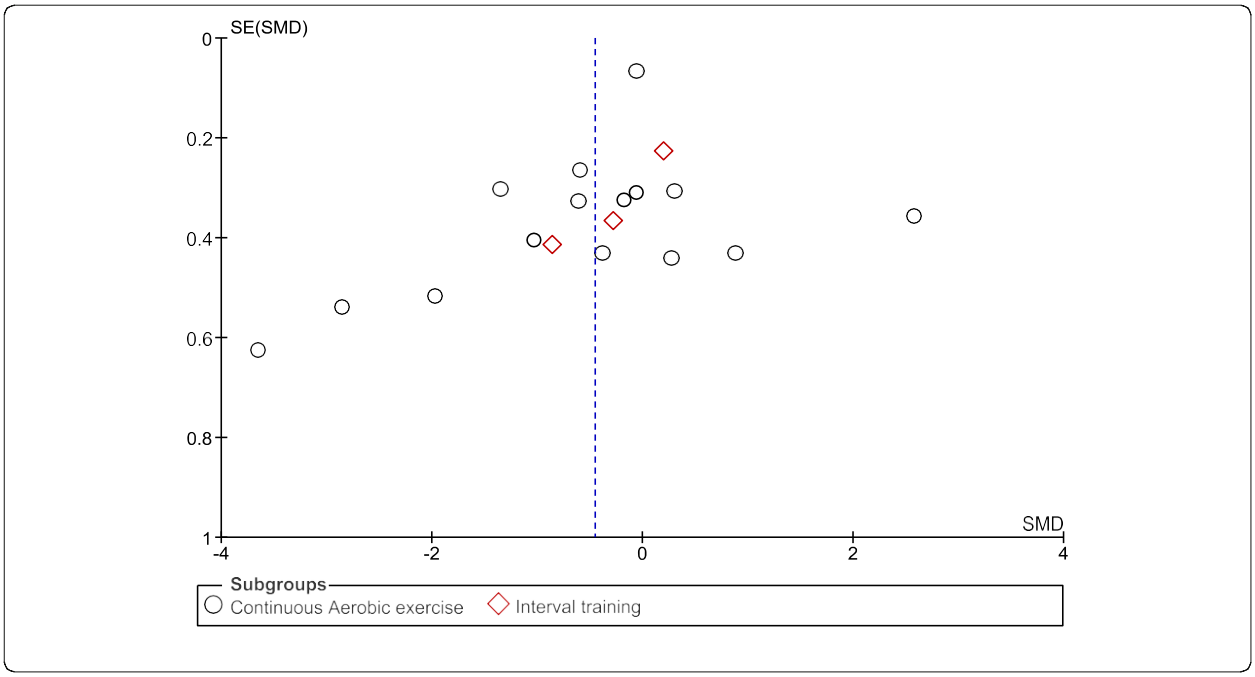

Fig. 3.2 Funnel plot for standardised mean difference forest plot. SMD– standardised mean difference

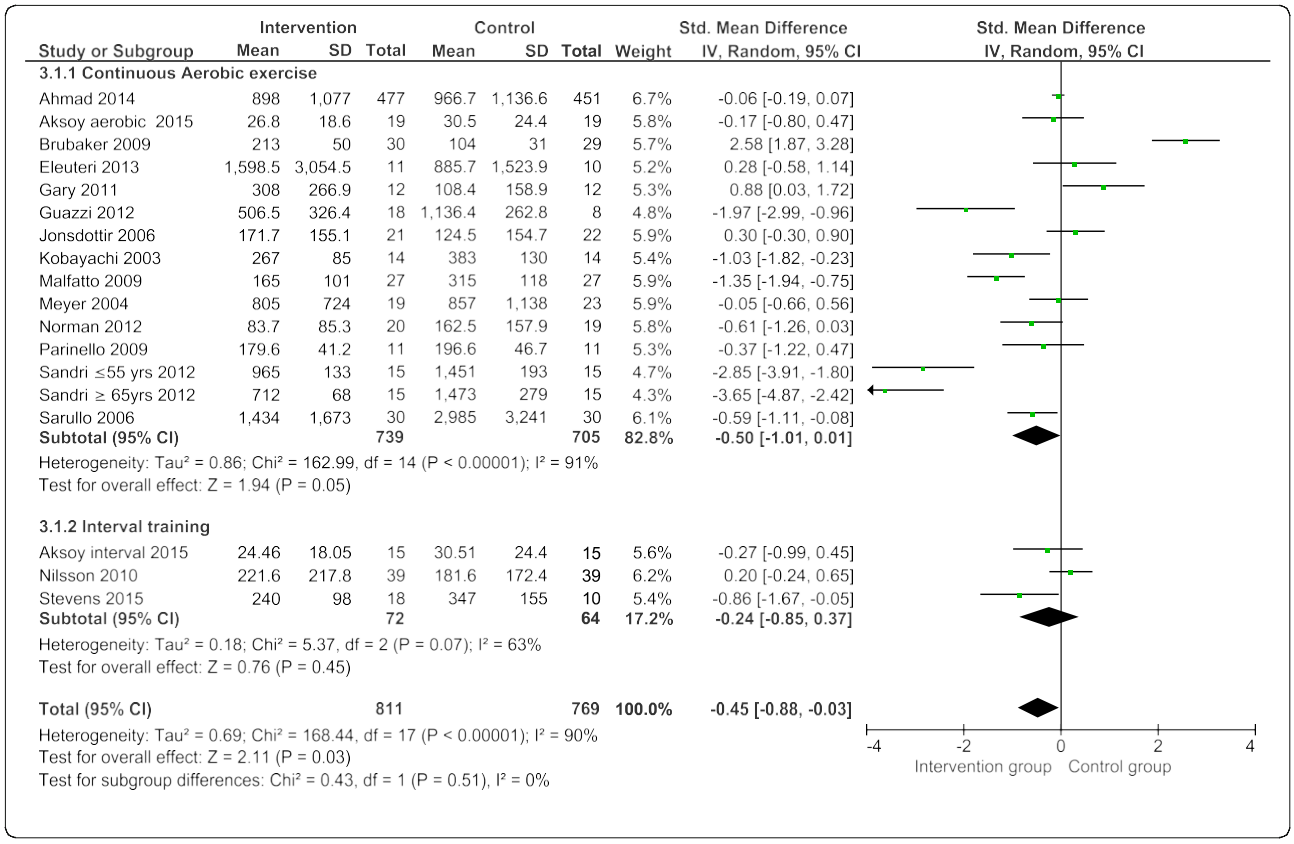

Fig. 3.3 Standardised mean difference in natriuretic peptide levels in exercise therapy. SD-standard deviation; CI-confidence interval

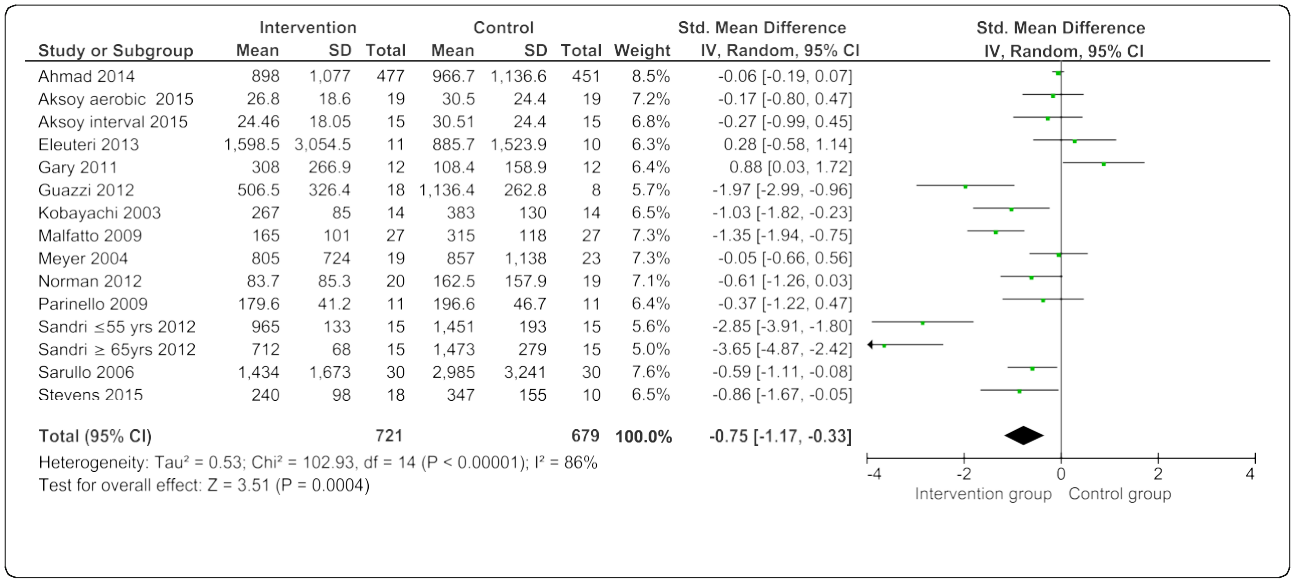

Fig. 3.4 Standardised mean difference in natriuretic peptide levels in exercise therapy within 12 weeks. SD-standard deviation; CI-confidence interval

Discussion

This meta-analysis examines exercise rehabilitation in adult patients with chronic heart failure in an outpatient setting. The principal finding was that exercise training can significantly decrease NP levels within 12 weeks in adult medical patients eligible for cardiac rehabilitation. The patients most likely to benefit from this intervention had stable chronic heart failure, with an EF which was predominantly <45% (Table 3.1). However, significantly heterogeneity exists between trials. Currently, there is insufficient data to determine whether this NP reduction is also associated with a survival benefit.

The characteristics of the exercise programmes were the following. Almost all trials included exercise programmes that were conducted under direct supervision. All the programmes had an aerobic component and varied in exercise intensity, duration and frequency. Few trials had interval training and resistance training. The exercise regimens were predominantly determined by patient specific physiological parameters, e.g. AT, VT and VO_2peak and were thus individualised. The duration of the exercise programme was 12 weeks in most trials. These findings are applicable to patients with cardiac failure of varying severity but considered stable on medication. It is important to note that NP levels were not a criterion for inclusion in these trials, and hence, we do not know the baseline NP level necessary to determine eligibility for a supervised exercise programme.

The strength of this meta-analysis is that it shows exercise training to be associated with a reduction in NP levels within 12 weeks from randomisation. There were no reports of morbidity associated with the supervised exercise programmes.

This review has some limitations. Firstly, the protocols differed between trials making it difficult to recommend a specific exercise programme. This may partly explain the significant heterogeneity in the included studies. However, despite the significant heterogeneity, the random effects meta-analysis suggests that the reduction in NP levels associated with exercise training is possible within 12 weeks. There remains limited mortality data in the trials of cardiac rehabilitation programmes which document NP level changes over time. It is thus impossible to determine whether a reduction in NP levels secondary to exercise therapy is associated with increased survival. It is possible that an exercise intervention may improve other patient reported outcomes, although these were not uniformly reported in the included trials. Finally, as all of the trials were not blinded to the patient or investigator, it is possible that there

may be co-intervention bias associated with the exercise arm of these trials.

Our review differs from the two previous systematic reviews which have examined NP levels in non-surgical patients after exercise therapy.[4 22] These reviews also found that NP levels were reduced after exercise therapy, with a high heterogeneity in the response. The strength of our review is that it updates the previous reviews[4] with more trials and only includes RCTs with aerobic exercise programmes.[22] We did not consider trials examining yoga, stretching, Tai-chi, functional electrical stimulation or inspiratory muscle training.[22]

Elevated preoperative NP levels have been independently associated with major adverse cardiac events and mortality following surgery.[23-25] Further investigation into the role of supervised preoperative exercise programme in the surgical population may provide insight into the relationship between exercise and NP levels in this cohort of patients.

Conclusion

This meta-analysis shows that NP levels can be lowered with supervised exercise training and can be achieved within a 12-week programme. An exercise prehabilitation programme of 12 weeks duration may lower NP levels, and possibly perioperative risk. It is unclear whether this will improve postoperative cardiovascular outcomes.

Supplementary information

Supplementary appendix 3.1: Example of search strategy for the systematic review. **Supplementary appendix 3.2:** AMSTAR evaluation of previous systematic reviews. **Supplementary appendix 3.3: Fig. S3.1.** Risk of bias graph. **Supplementary appendix 3.4: Fig. S3.2.** Risk of bias summary.

Abbreviations. AT: Anaerobic threshold; BNP: B-type natriuretic peptide; CI: Confidence interval; EF: Ejection fraction; HR: Hazard ratio; IQR: Interquartile range; NP: Natriuretic peptide; NT-proBNP: N-terminal pro-B-type natriuretic peptide; SD: Standard deviation; SMD: Standardised mean difference; VO_2: Maximum oxygen consumption; VT: Ventilatory threshold.

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Authors' contributions. The screening, extraction of articles, and data extraction were done by CSA, PG, and BMB. The manuscript was prepared by CSA, BMB, and RNR. All authors read and approved the final manuscript.

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Availability of data and materials. All articles available online and datasets are available from the corresponding author.

Ethics approval and consent to participate. Not applicable.

Consent for publication. Not applicable.

Competing interests. The authors declare that they have no competing interests.

Supplementary appendix 3.1

Example of search strategy for the systematic review. Search strategy: (peptide set AND therapy set) NOT surgery set Natriuretic Peptide, Brain (MeSH) OR Brain Natriuretic Peptide OR Type-B Natriuretic Peptide OR Type B Natriuretic Peptide OR B-type Ventricular Natriuretic Peptide OR B type Ventricular Natriuretic Peptide
AND

Therapeutics (MeSH) Therapeutics OR treatment OR therapy OR rehabilitation

NOT

General Surgery (MeSH) OR Surgical Procedures, Operative (MeSH) OR surgery OR surgical OR operative search strategy: (peptide set AND heart failure set) NOT surgery set Natriuretic Peptide, Brain (MeSH) OR Brain Natriuretic Peptide OR Type-B Natriuretic Peptide OR Type B Natriuretic Peptide OR B-type Ventricular Natriuretic Peptide OR B type Ventricular Natriuretic Peptide

AND

Heart Failure (MeSH) OR Coronary Artery Disease (MeSH) Heart failure OR cardiac failure OR heart decompensation OR myocardial infarction OR myocardial ischemia OR heart attack OR myocardial infarct

NOT

General Surgery (MeSH) OR Surgical Procedures, Operative (MeSH) OR surgery OR surgical OR operative search strategy: (peptide set AND exercise set) NOT surgery set Natriuretic Peptide, Brain (MeSH) OR Brain Natriuretic Peptide OR Type-B Natriuretic Peptide OR Type B Natriuretic Peptide OR B-type Ventricular Natriuretic Peptide OR B type Ventricular Natriuretic Peptide

AND

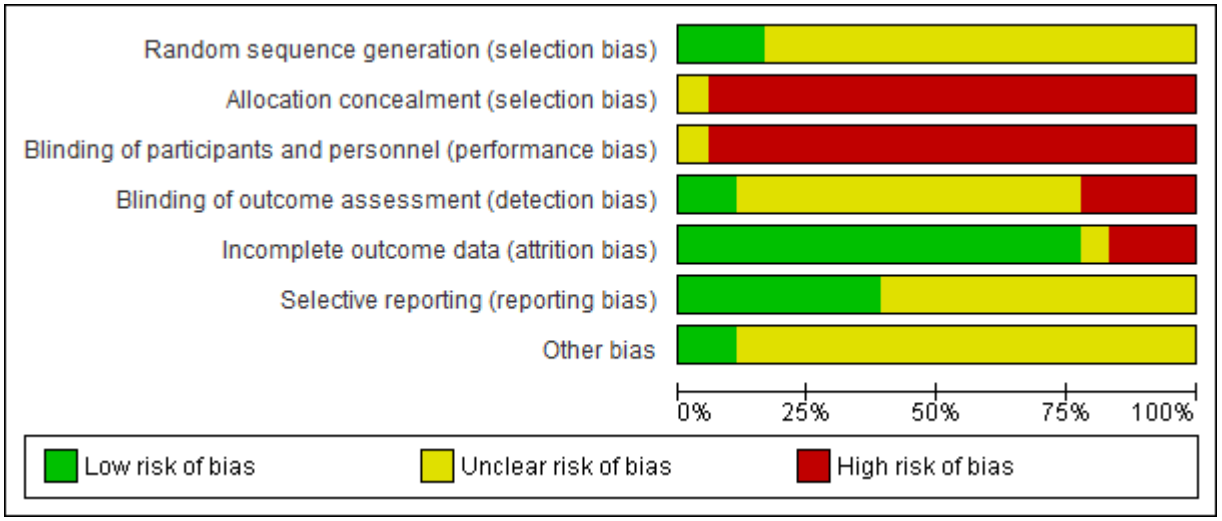
Exercise (MeSH) OR Physical Exertion (MeSH) OR Exercise OR physical exertion OR physical activity OR motor activity OR physical effort

NOT

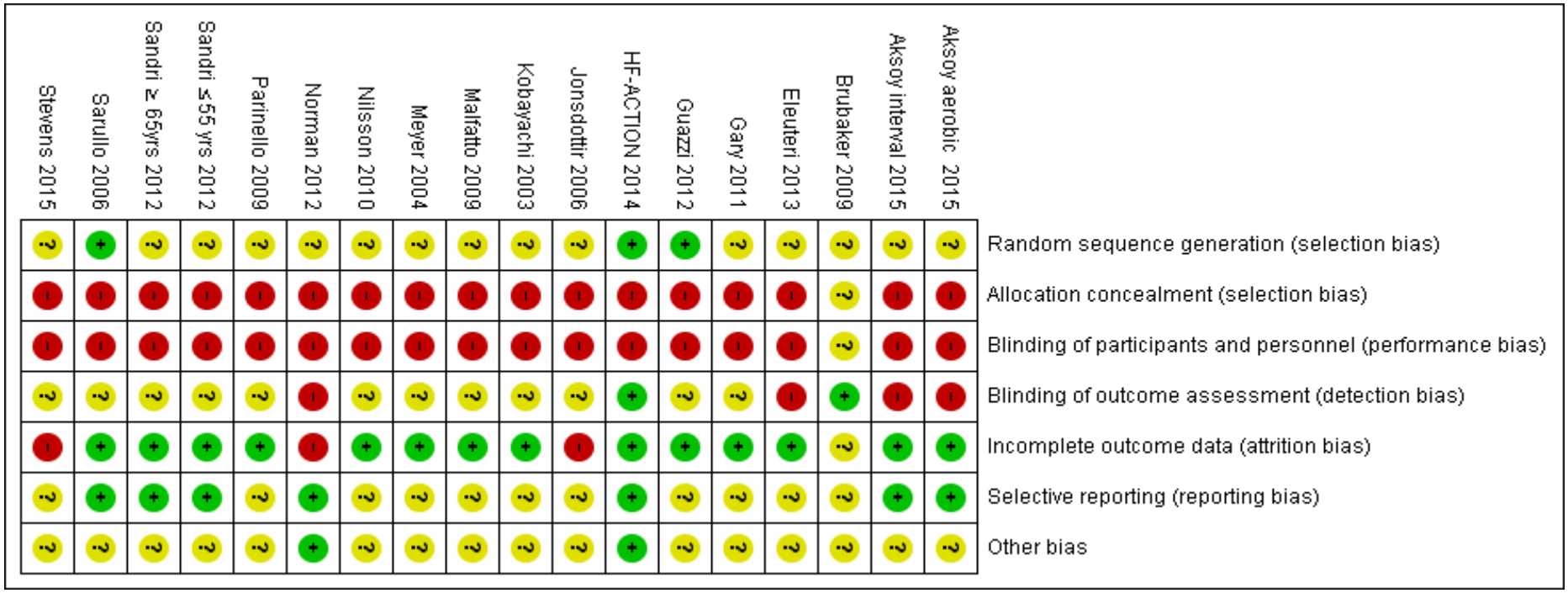
General Surgery (MeSH) OR Surgical Procedures, Operative (MeSH) OR surgery OR surgical OR operative

Supplementary appendix 3.2. AMSTAR evaluation of previous systematic reviews

Author	Journal	Comment	A priori design	Duplicate	Comprehensive review	Publication status	List of studies	Characteristics of studies	Scientific quality assessed	Quality with conclusions	Publication bias discussed
Smart, Steele[4]	International Journal of Cardiology 2009	Systematic review and individual patient meta-analysis	No	Yes	No	No	Yes	Yes	Yes	Yes	No
Pearson, King, Smart[22]	Open Heart 2018	Systematic review and meta-analysis	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes



Supplementary appendix 3.3. Fig. S3.1. Risk of bias graph



Supplementary appendix 3.4. Fig. S3.2. Risk of bias summary

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3.4 Chapter discussion

The findings of this systematic review are remarkable when considering the simplicity of using exercise to improve exercise tolerance and functional capacity in heart failure. Exercise targets the same organ systems as drug therapies used to treat heart failure. Although many of the trials were small, the reduction in NP levels is encouraging.

The relatively short time in which measurable improvement is evident with exercise training is also surprising. Although most patients had stable heart failure, many had a reduced ejection fraction (<45%). Appropriate patient selection for exercise therapy may be an important component that contributed to the success of exercise therapy in reducing NP levels in the studies included in this systematic review.

The major limitation with this intervention is that exercise programmes need to be tailored to the individual and have to be supervised. This may be difficult to achieve on a large scale in the preoperative environment. However, the cost reduction in drug therapy may be a potential benefit. It is also unknown whether the reduction in NP levels with exercise therapy is associated with a reduction in mortality. Specific exercise regimens were not identified as superior to others in this systematic review; however, all exercise programmes were built around an aerobic base programme.

3.5 Chapter conclusion

The finding that a minimum of 12 weeks of exercise therapy reduces NP levels suggests that this intervention may have utility in the preoperative arena. The potential for using exercise to improve preoperative functional capacity needs to be further explored, as does its impact on perioperative mortality.

4 The prevalence of elevated natriuretic peptide in high-risk patients presenting for adult noncardiac surgery in Western Cape hospitals

Publication Reference: Alphonsus CS, Jagga M, Crowther M, Coetzee E, Davies G, Fullerton Z, van Zyl HA, Reed A, Cloete E, Roos J, Roodt F, Rodseth RN, Biccard BM. A prospective observational study of preoperative natriuretic peptide testing in adult non-cardiac surgical patients in hospitals in Western Cape Province, South Africa. *South African Medical Journal* 2021;111(4):338–342.

4.1 Declaration from author and co-authors

4.1.1 Declaration from author

This was a multi-centre study that required the contribution of many people to achieve the recruitment of the patients and the objectives of the study. The following co-authors contributed to the paper: M Jagga, M Crowther, E Coetzee, G Davies, Z Fullerton, HA van Zyl, A Reed, E Cloete, J Roos, F Roodt, RN Rodseth, and BM Biccard.

In Chapter 4, the contributions by authors to the work were as follows: CS Alphonsus developed the protocol, collected, collated, and analysed data and was the main author of the manuscript. M Jagga, M Crowther, and E Coetzee helped develop the protocol; collected, collated, and analysed data; and reviewed drafts of the manuscript. G Davies, Z Fullerton, HA van Zyl, A Reed, E Cloete, J Roos, and F Roodt helped with data collection and reviewed drafts of the manuscript. RN Rodseth helped with protocol development and reviewed drafts of the manuscript. BM Biccard participated in protocol development, data collection, and data analysis and reviewed drafts of the manuscript. All authors approved the final published version and agreed to be accountable for the accuracy or integrity of the work.

Signature removed

Christella Alphonsus 16 August 2021

4.1.2 Declaration by supervisor on behalf of co-authors

The undersigned hereby certifies that:

1. The above declaration correctly reflects the nature and extent of the candidate's contribution to this work and the nature of the contribution of each of the co-authors.
2. The co-authors meet the criteria for authorship in that they have contributed to the design of the work. Furthermore, they have participated in patient recruitment, data collection, and data analysis for the study. They were involved in drafting or revision and final approval of the publication.
3. The main author and co-authors take public responsibility for their part of the publication.
4. There is no other author of the publication according to these criteria.
5. Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit.

Location of data: The original data are stored at the following location and will be held for at least five years from the date indicated below.

The paper clinical record form and source documents are stored in a locked cabinet in the Department of Anaesthesia and Perioperative Medicine research office. Statistical Package for the Social Sciences (SPSS) data analysis and any other study-related material are stored on the author's (C Alphonsus) password-protected laptop.

Signature removed

Professor Bruce Biccard Date: 16 August 2021

4.2 Synopsis

4.2.1 Rationale for conducting the study

Relevance of cardiovascular research in Africa and in surgical patients presenting for noncardiac surgery

Globally, cardiovascular disease is the leading cause of death.[27] The majority of these deaths occur in low- and middle-income countries, which include African countries.[47] The majority of research in cardiovascular medicine in LMIC is on congenital and inflammatory diseases. However, with increasing urbanisation, LMIC are undergoing an epidemiological transition, with growing numbers of patients with cardiovascular disease.[48] The absolute number of deaths related to cardiovascular disease in sub-Saharan Africa has increased to over 50% in the past three decades. Many experts have warned that soon, healthcare services in LMIC will be battling not only the diseases of poverty but also the diseases of urbanisation—with limited resources.[28] Available data projections suggest that in the next few decades, cardiovascular diseases and other non-communicable diseases will become the most frequent cause of death in sub-Saharan Africa.[29]

The presence of cardiovascular comorbidities in surgical patients can lead to adverse perioperative cardiovascular outcomes.[6] It follows that the growing cardiovascular disease burden in African countries will lead to a greater number of patients with cardiovascular disease presenting for noncardiac surgery. This will have an impact on perioperative outcomes, with many potentially suffering cardiovascular complications.[6]

Risk stratification in patients presenting for surgery in South African public hospitals

At present, we have little data on the proportion of patients with cardiovascular disease who are presenting for surgical intervention in South African hospitals.[49, 50] We have little data describing the burden of cardiovascular complications following noncardiac surgery in South Africa, and we have little data on the perioperative management of these patients, including compliance with recommended cardiovascular risk stratification guidelines.

Motivation for this study in the PhD

This PhD thesis was initially conceptualised to explore the clinical applicability of using B-type natriuretic peptide-directed medical therapy in surgical patients with cardiovascular comorbidities. The first step to investigate the efficacy of such an intervention is to identify those patients who may benefit from risk stratification. According to the Canadian guidelines,[18] patients with at least one of Lee's cardiovascular risk factors[11] should progress to the next step of risk stratification, which is natriuretic peptide testing.[18] The realisation that the process of risk stratification was not being implemented in South Africa emphasised the need for this work to help identify the at-risk cardiovascular patients in South Africa, before we could address risk stratification and perioperative medical therapy.

International guidelines emphasise the need to identify high-risk noncardiac surgical patients through preoperative risk stratification.[18] The poor performance of widely used clinical risk stratification tools, such as the Revised Cardiac Risk Index, has compelled clinicians to search for more reliable tests.[12] Raised preoperative B-type natriuretic peptides have a strong association with postoperative cardiac complications and are thus being used in the first step of screening for high-risk surgical patients.[51, 52,18] The benefit of preoperative B-type natriuretic testing is that it can used for the first step in risk stratification and subsequently in directing medical therapy, and thus, theoretically, also in risk modification.

However, in the South African context, it was unknown how many patients with significant cardiovascular disease scheduled for noncardiac surgery have raised B-type natriuretic peptides. Owing to our resource limitations, we felt it was necessary to understand the scope of the problem before making recommendations for B-type natriuretic peptide testing as part of preoperative screening. This will also help in the future to determine the cost-effectiveness of including natriuretic peptide screening for high-risk patients presenting for noncardiac surgery in our hospitals.

4.2.2 Aim and objectives

Aim

To describe the prevalence of, and associations with, abnormal (raised) NP in patients with clinical risk factors for cardiovascular disease undergoing intermediate- and high-risk surgery.

Objectives

1. The primary objective was to determine the prevalence of abnormal (raised) NP in patients with known clinical cardiovascular risk factors. Abnormal (raised) NP levels were defined according to the NP thresholds associated with major adverse cardiac events following noncardiac surgery, with a NT-proBNP level >300ng/L.[51]
2. The secondary objective was to develop a model to identify surgical patients who may benefit from preoperative NP screening.

4.2.3 Main results

Demographic information:
Patients were recruited from seven public sector hospitals in Western Cape province in South Africa: Paarl, Victoria, Mitchells Plain, George, Worcester, and New Somerset Hospitals (secondary-level hospitals) and Groote Schuur Hospital (tertiary-level). The inclusion criteria were as follows: ≥45 years old, scheduled for elective, non-obstetric, intermediate- to high-risk noncardiac surgery, with at least one of the following cardiovascular risk factors: a history of ischaemic heart disease or peripheral vascular disease (coronary equivalent); a history of stroke or transient ischaemic attack; a history of congestive cardiac failure; diabetes mellitus currently on an oral hypoglycaemic agent or insulin; and serum creatinine level >175 μmol/L (>2.0 mg/dL).

Population:
During data collection, 3,638 patients were screened and 200 patients fulfilled the inclusion criteria. Following this, 172 of the 200 (86%) eligible patients had blood samples drawn for NT-proBNP testing.

Study results:
In this study, 63 patients (37%) had abnormal (raised) NT-proBNP (≥300 pg/mL). The comorbidities that were independently associated with elevated NT-proBNP in the generalised linear mixed model were coronary artery disease (and coronary equivalent, peripheral vascular disease), congestive cardiac failure, and a creatinine level >175 µmol/L.

Below is the content of the published article followed by the references of the paper. The context and meaning of the published paper are described in detail in the rest of the chapter.

4.3 Article published in South African Medical Journal

A prospective observational study of preoperative natriuretic peptide testing in adult non-cardiac surgical patients in hospitals in Western Cape Province, South Africa

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Background. International guidelines recommend risk stratification to identify high-risk non-cardiac surgical patients. It is also recommended that all patients aged ≥45 years with significant cardiovascular disease should have preoperative natriuretic peptide (NP) testing. Abnormal preoperative B-type NPs have a strong association with postoperative cardiac complications. In South African hospitals, it is not known how many patients with significant cardiovascular disease scheduled for intermediate- to high-risk surgery will have raised NPs.

Objectives. To determine the prevalence of abnormal (raised) NPs in non-cardiac surgical patients with cardiac clinical risk factors. A secondary objective was to

develop a model to identify surgical patients who may benefit from preoperative NP screening.

Methods. The inclusion criteria were patients aged ≥45 years presenting for elective, non-obstetric, intermediate- to high-risk non-cardiac surgery with at least one of the following cardiovascular risk factors: a history of ischaemic heart disease or peripheral vascular disease (coronary equivalent); a history of stroke or transient ischaemic attack; a history of congestive cardiac failure; diabetes mellitus currently on an oral hypoglycaemic agent or insulin; and serum creatinine level >175 μmol/L (>2.0 mg/dL). Blood samples for N-terminal-prohormone B-type NP (NT-proBNP) were collected before induction of anaesthesia. The preoperative prognostic threshold for abnormal (raised) NT-proBNP was ≥300 pg/mL. A generalised linear mixed model was used to determine the association between the risk factors and an abnormal NT-proBNP level.

Results. Of 172 patients, 63 (37%) had an elevated preoperative NT-proBNP level. The comorbidities independently associated with elevated preoperative NT-proBNP were coronary artery disease or peripheral vascular disease, congestive cardiac failure, and a creatinine level >175 μmol/L.

Conclusions. We strongly recommend that non-cardiac surgical patients aged ≥45 years undergoing intermediate- or high-risk non-cardiac surgery with a history of coronary artery disease/peripheral vascular disease, congestive cardiac failure or elevated creatinine have preoperative NP testing as part of risk stratification.

Introduction

Every year ~230 million adults around the world undergo major non-cardiac surgery.[10] The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) study highlighted the incidence of perioperative cardiac complications in patients with cardiovascular comorbidities. The findings showed that in patients aged ≥45 years, the 30-day mortality rate was 2%,[5] and 8% had significant myocardial injury that contributed to subsequent morbidity.[11]

Current guidelines emphasise the need to identify high-risk non-cardiac surgical patients through preoperative risk stratification.[6] However, widely used clinical risk stratification tools such as the Revised Cardiac Risk Index (RCRI) do not perform as well as cardiovascular biomarkers, specifically natriuretic peptides (NPs).[7] Raised preoperative B-type NPs have a strong association with postoperative cardiac complications. This has been shown in observational studies and meta-analyses, and has been the impetus for including B-type NP screening for high-risk surgical patients.[8] [9]

Some preoperative international guidelines, such as the Canadian Cardiovascular Society (CCS) guidelines on perioperative cardiovascular risk assessment, advocate that all patient aged ≥45 years who have 'significant cardiovascular disease' and present for intermediate- to high-risk surgery should have preoperative NP testing.[6] 'Significant cardiovascular disease' is defined as a history of coronary artery disease, cerebrovascular disease, peripheral artery disease, congestive heart failure or severe pulmonary hypertension, or a severe obstructive intracardiac abnormality (severe aortic stenosis, severe mitral stenosis, or severe hypertrophic obstructive cardiomyopathy).[6]

The rationale for the present study was that in the South African (SA) context, it is unknown how many patients with significant cardiovascular disease scheduled for intermediate- to high-risk surgery will have raised NPs. This information is necessary to inform appropriate preoperative screening protocols for patients at risk of cardiovascular events following non-cardiac surgery. Indiscriminate preoperative NP testing would be inappropriate in a resource-limited environment. A data-informed approach to preoperative NP screening may reduce costs and focus efforts on those patients at greatest cardiovascular risk in the perioperative period.

Objectives

To describe the prevalence of and associations with abnormal (raised) NPs in patients with clinical risk factors for cardiovascular disease undergoing intermediate- and high-risk surgery.

Methods

This was a prospective, observational study conducted in seven public sector hospitals in Western Cape Province, SA. Paarl, Victoria, Mitchells Plain, George, Worcester and New Somerset hospitals are secondary-level hospitals and Groote Schuur Hospital is a tertiary-level hospital. Ethics approval was provided by the Human Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town (ref. no. 463/2019) and the trial was registered on ClinicalTrials.gov (ref. no. NCT 04114032). Approval was granted by the Western Cape Department of Health and the individual hospitals to conduct the study (provincial approval ref. no. WC_201909_006).

The primary objective was to determine the prevalence of abnormal (raised) NP levels in patients with clinical risk criteria. Abnormal (raised) NP levels were defined according to the NP thresholds associated with major adverse cardiac events following non-cardiac surgery, with an N-terminal-prohormone B-type NP (NT-proBNP) level >300 ng/L.[8] The secondary objective was to develop a model to identify surgical patients who may benefit from preoperative NP screening. The inclusion criteria were patients aged ≥45 years presenting for elective, non-obstetric, intermediate- to high-risk non-cardiac surgery with at least one of the following cardiovascular risk factors: a history of ischaemic heart disease or peripheral vascular disease (coronary equivalent); a history of stroke or transient ischaemic attack; a history of congestive cardiac failure; diabetes mellitus currently on an oral hypoglycaemic agent or insulin; and serum creatinine level >175 μmol/L (>2.0 mg/dL). Intermediate-risk surgery is defined as having a 30-day risk of cardiovascular death or non-fatal myocardial infarction of 1–5%, and high-risk surgery as exceeding 5%.[12] Emergency and day-case surgery were excluded. Patients were screened on the afternoon before surgery and provided written informed consent during preoperative anaesthesia assessment. Baseline demographic and clinical data included age, gender, preoperative haemoglobin, white cell count and serum creatinine. If a preoperative electrocardiogram was done, a copy was kept as a source document.

Blood samples for NT-proBNP testing were collected in theatre before induction of anaesthesia on insertion of the intravenous cannula for vascular access. The specimens were couriered to PathCare Laboratories and analysed within 2 hours of

the blood specimen being drawn. The team in theatre were blinded to the NT-proBNP result, since this was only available postoperatively. However, elevated NT-proBNP results that were of prognostic importance for postoperative cardiovascular events were declared to the surgeons postoperatively, and they were advised to do troponin screening for 3 days. The reporting of results to surgeons postoperatively would allow for institution of supportive strategies (e.g. management of tachycardia,[13] optimisation of haemoglobin if necessary,[14] administration of aspirin and statin therapy)[15] and monitoring for progression to myocardial infarction, and cardio-vascular risk modification could be advocated following discharge.

In order to evaluate the association between five clinical risk factors and an abnormal (raised) NT-proBNP level in a binary logistic regression model, a sample that included at least 50 patients with an abnormal level would be required. To ensure that we fulfilled this requirement, we estimated the sampling cohort as follows. Based on previous observational studies in the Western Cape, we expected to screen ~ 800 elective surgical patients in all centres over a 4-week period, of whom we expected that 160 would fulfil clinical and surgical criteria for NP testing, and that of these ~ 65 would have abnormal (raised) NPs. The sample size was derived on an estimated prevalence of a raised NP level of 40% (95% confidence interval (CI) 33–48). Sixty-five patients with raised NPs would provide sufficient power to allow for a regression that included the five clinical risk factors of the RCRI, and would not violate the 10 events (raised NPs) per variable rule.[16]

A generalised linear mixed model using a logit link was used to identify independent risk factors for the binary outcome. These included a one-level and a hierarchical two-level model to account for the expected correlation in outcomes within hospitals. We excluded patients with missing values for potential risk predictors, and only used complete case analysis as <1% of the dataset was incomplete for a potential clinical risk predictor.[17] Results are reported as adjusted odds ratios with 95% CIs. All the RCRI factors were entered into the models, with the exception of the type of surgery, as all patients were scheduled for intermediate- or high-risk surgery. The potential independent predictors entered into the model were a history of ischaemic heart disease or peripheral vascular disease (coronary equivalent); a history of stroke or transient ischaemic attack; a history of congestive cardiac failure; diabetes mellitus

currently on an oral hypoglycaemic agent or insulin; and serum creatinine level >175 μmol/L (>2.0 mg/dL). The independent variables associated with an abnormal NP level would be used to build a model to predict which patients should undergo preoperative NP testing prior to intermediate or major surgery.

Continuous data are reported as mean and standard deviation (SD) or median and interquartile range, and categorical data as number and percentage. The Statistical Package for the Social Sciences version 24 (SPSS Inc. USA) was used for data analysis.

Results

The patients recruited into the study are shown in the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) diagram in Fig. 4.1. The trial was extended to 8 consecutive weeks in each hospital over the months beginning October 2019 to end of March 2020 in order to reach the sample size required for the study. The study was stopped because of the curtailment of elective surgery during the COVID-19 pandemic lockdown, with 63/172 patients (37%) with an abnormal (raised) NT-proBNP level, 2 patients fewer than our target. The baseline patient characteristics are set out in Table 4.1. Only one preoperative creatinine value was missing from the data set, since no renal function test was done for the patient preoperatively.

The prevalence of abnormal (raised) NT-proBNP in patients with clinical risk criteria was 37%. Table 4.2 shows recruitment across the study sites. The highest recruiting sites were Groote Schuur, Paarl and Victoria hospitals.

The comorbidities that were independently associated with elevated NT-proBNP in the generalised linear mixed model were coronary artery disease (and coronary equivalent, peripheral vascular disease), congestive cardiac failure, and a creatinine level >175 μmol/L (Table 4.3).

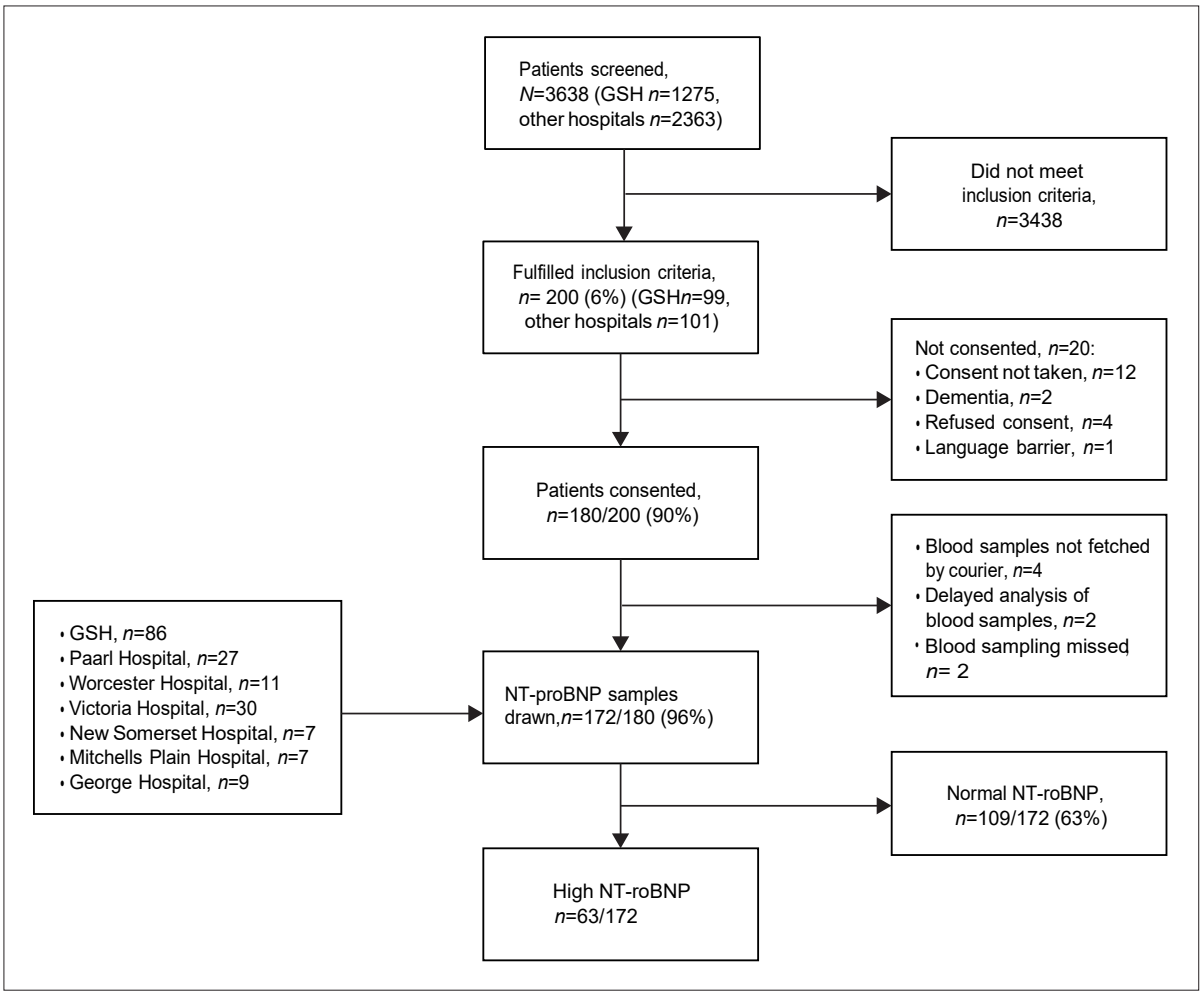

Fig. 4.1. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) diagram. (NT-proBNP = N-terminal-prohormone B-type natriuretic peptide; GSH = Groote Schuur Hospital)

Table 4.1 Baseline characteristics of patients

	Whole cohort (*N*=172)	**High NT-proBNP* (*N*=63; 37%)**	**Normal NT-proBNP (*N*=109; 63%)**	***p*-value**
Age (years), mean (SD)	63.5 (9.8)	65.4 (10.2)	62.4 (9.4)	0.0523
Gender female, *n* (%)	92 (54)	28 (44)	64 (59)	0.0423
Comorbidity, *n* (%)				
CAD/PVD	76 (44)	33 (52)	43 (39)	0.1087
CCF	17 (10)	12 (19)	5 (9)	0.0033
Diabetes mellitus	97 (56)	35 (56)	62 (57)	0.8886
Stroke/TIA	25 (15)	5 (5)	20 (18)	0.0739
Creatinine >175 µmol/L	15 (8.7)	10 (16)	5 (5)	0.3340

NT-proBNP = N-terminal-prohormone B-type natriuretic peptide; SD = standard deviation; CAD/PVD = coronary artery disease/peripheral vascular disease; CCF = congestive cardiac failure; TIA = transient ischaemic attack. High NT-proBNP >300 ng/L.

Table 4.2 Patient recruitment characteristics per hospital

Hospital	**Patients for elective surgery, *N***	**Patients fulfilling study inclusion criteria (RCRI ≥1), *n* (%)**	**Raised NT-proBNP, *n* (%)**	**No consent, no blood sample taken, *n***
Groote Schuur	1 275	99 (8)	33 (33)	13
Paarl	431	27 (6)	10 (37)	0
Worcester	264	12 (5)	1 (8)	1
Victoria	483	37 (8)	11 (30)	6
New Somerset	486	13 (3)	2 (15)	4
Mitchells Plain	206	2 (1)	0	0
George	493	10 (2)	6 (60)	1

RCRI = Revised Cardiac Risk Index; NT-proBNP = N-terminal-prohormone B-type natriuretic peptide.

Table 4.3 Multivariable association with a prognostically important elevated NT-proBNP

Comorbidities (predictors)	***p*-value**	**OR**	**95% CI**
CAD/PVD	0.006	3.295	1.410–7.698
CCF	0.001	8.016	2.293–28.020
Stroke/TIA	0.195	0.455	0.137–1.504

Diabetes	0.080	2.099	0.914–4.817
Creatinine >175 µmol/L	0.001	8.901	2.422–32.713

NT-proBNP = N-terminal-prohormone B-type natriuretic peptide; OR = odds ratio: CI =confidence interval; CAD/PVD = coronary artery disease/peripheral vascular disease; CCF = congestive cardiac failure; TIA = transient ischaemic attack.

Table 4.4 Preoperative risk calculator

Preoperative variables from derivation model	Coefficients	Probability of high NT-proBNP, %
Baseline	–3.570	3
CAD/PVD	1.192	8
CCF	2.081	18
Creatinine >175 µmol/L	2.186	20

NT-proBNP = N-terminal-prohormone B-type natriuretic peptide; CAD/PVD = coronary artery disease/peripheral vascular disease; CCF = congestive cardiac failure.

Risk equation:

$$p = \frac{1}{1+e^{-(-3.570+(CAD/PAD)+(CCF)+(CREATININE))}}$$

$$p = \frac{1}{1+e^{-(-3.570+1.192+2.081+2.186)}}$$

The preoperative risk calculator (Table 4.4) shows that the presence of coronary artery disease/peripheral vascular disease is associated with an 8% probability of a high NT-proBNP level, congestive cardiac failure with a 18% probability, and elevated creatinine with a 20% probability. The baseline probability in the cohort is 3%. The risk equation to derive the probability of high NT-proBNP appears alongside, below Table 4.4.

Discussion

The main finding of this study was that of SA patients aged ≥45 years with clinical cardiovascular risk factors scheduled for intermediate- or high-risk non-cardiac surgery, 1 in 3 will have an abnormal (raised) NT-proBNP level. In addition, patients with a history of congestive cardiac failure or a creatinine level >175 µmol/L have a >15% probability of a high preoperative NT-proBNP level. Previous studies have

shown that high preoperative NPs are prognostic of perioperative cardiovascular complications.

Study strengths and limitations

The strengths of this study are that it was a prospective, pragmatic study, which provides information for preoperative risk stratification of SA surgical patients scheduled for intermediate- and high-risk non-cardiac surgery. In the SA resource-limited environment, these findings suggest that it is justifiable to conduct preoperative NP testing in patients with coronary artery disease/ peripheral vascular disease, congestive cardiac failure, and an elevated creatinine level scheduled for intermediate- and high-risk surgery.

Since we recruited patients who already had at least one of the RCRI risk factors, this patient cohort represents a high-risk group.

A further strength of this study is that it was a multicentre study that included hospitals serving different demographic areas. Controlling for the hospital clusters suggests that the findings are robust and generalisable to patients from different healthcare facilities in the Western Cape. Furthermore, controlling for the clusters may explain the difference between the lack of association of diabetes mellitus with an abnormal NT-proBNP level on univariate analysis, but not on multivariate analysis.

The weakness of the study is that we did not follow up these patients for cardiovascular outcomes. However, a large observational cohort study suggests that an abnormal (raised) preoperative NP level is an important independent predictor of postoperative cardiovascular morbidity and mortality.[14] We therefore believe that our findings are of clinical relevance in preoperative cardiovascular risk stratification in SA.

Studies have also shown that the addition of NP testing to existing clinical risk indices, such as the RCRI, improves prognostic performance. However, clinical risk factors are not equally weighted and some clinical risk factors may have a greater impact on patient outcomes. In our study, three of the five traditional preoperative cardiovascular risk factors, coronary artery disease/peripheral vascular disease, congestive cardiac

failure and elevated creatinine, were found to be independently associated with NP elevation. This study supports the CCS guidelines in using clinical risk predictors as a screening tool to identify which patients should have preoperative NP screening.

The cardiovascular disease burden per site in Table 4.2 can be used to plan for resource allocation and funding for NT-proBNP screening in high-risk patients.

Recommendations

Our recommendation is that surgical patients scheduled for intermediate- and high-risk non-cardiac surgery with a history of coronary artery disease/peripheral vascular disease, congestive cardiac failure or an elevated creatinine level should have preoperative NP testing done. We recommend that patients with an abnormal (raised) NT-proBNP level should also have postoperative troponin screening. Patients with a normal level do not require additional postoperative monitoring for cardiovascular events.[4] The small number of patients with a history of stroke or transient ischaemic attack would suggest that a larger study is required in order to determine whether a history of stroke or transient ischaemic attack is independently associated with an abnormal (raised) NT-proBNP level. Furthermore, the role of NT-proBNP screening on the basis of age alone remains uncertain in SA, where further research is needed. To understand the full implications of these findings for clinical practice in SA, a cost-effectiveness analysis would be beneficial.

Future research should focus on preoperative optimisation of patients with elevated NPs.

Conclusions

We recommend that SA surgical patients scheduled for intermediate- and high-risk non-cardiac surgery with a history of coronary artery disease/peripheral vascular disease, congestive cardiac failure or an elevated creatinine level have preoperative natriuretic testing done as part of risk stratification. We suggest that if these surgical patients have a history of stroke or transient ischaemic attack, they may also benefit

from preoperative natriuretic testing. Patients with an abnormal (raised) NT-proBNP level should have postoperative troponin screening.

Declaration. The research for this study was done in partial fulfilment of the requirements for CSA's PhD degree at the University of Cape Town.

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Author contributions. CSA: protocol development, data collection, data collation, data analysis, writing the manuscript. MJ, MC, EC: protocol development, data collection, data collation, reviewed drafts of the manuscript. GD, ZF, HAvZ, AR, EC, JR, FR: data collection, reviewed drafts of the manuscript. RNR: protocol development, reviewed drafts of the manuscript. BMB: protocol development, data collection, data analysis, reviewed drafts of the manuscript.

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Conflicts of interests. None.

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4.4 Chapter discussion

The development of an integrated clinical pathway for the perioperative management of surgical patients with cardiovascular comorbidities must begin by identifying patients who may be high-risk. In this study, we were able to define the scope of the problem through preoperative NT-proBNP testing.

During the eight weeks over which the study was conducted, 3,638 surgical patients were screened in seven hospitals in the Western Cape. We found 200 patients with one cardiovascular risk factor (6%) undergoing intermediate- to high-risk surgery. This is important because it means that the next step in risk stratification, NP testing, which is not routine at the moment, is feasible in noncardiac surgery. Of this high-risk group, we were able to find that a significant proportion (37%) had elevated NT-proBNP and are thus at risk of developing cardiovascular complications. These patients carry substantial risk and will derive benefit from focused risk stratification and management efforts to improve outcomes.

In this study, by defining this group of patients at significant risk, it is possible that focused care is achievable for these patients to mitigate their mortality and long-term morbidity.

4.5 Chapter conclusion

This chapter provides the context in which perioperative management of surgical patients with cardiovascular comorbidities should take place. It gives some understanding of the cardiovascular risk burden of patients presenting for surgery in public sector hospitals in the Western Cape of South Africa. This study also demonstrates that risk stratification and possibly optimisation of patients with natriuretic peptide testing can be achieved in a LMIC. Focusing our efforts on the small group of patients undergoing intermediate- to high-risk surgery and with one cardiovascular risk factor, yielded a large proportion of patients with an elevated NT-proBNP. These patients carry a high proportion of morbidity and mortality risk in the

surgical population. A future potential approach in these patients could be risk modification through preoperative optimisation.

The preceding two chapters evaluated optimisation of patients using natriuretic peptide-directed medical therapy and exercise therapy. This chapter of the thesis identifies which patients may be eligible for medical optimisation using B-type natriuretic peptide-guided therapy. The next chapter will explore the wider context of cardiovascular disease in Africa through the African Surgical Outcomes Study (ASOS) and will give insight into the disease burden and need for implementation of risk stratification on a larger scale across the continent.

5 Towards the quantification of perioperative cardiovascular risk in the African context: A sub-analysis of the South African Surgical Outcomes Study and the African Surgical Outcomes Study

Publication reference: Alphonsus CS, Kluyts H-L, Gobin V, Elkhogia A, Madzimbamuto FD, Tumukunde J, Omigbodun AO, Youssouf C, Mehyaoui R, Munlemvo DM, Basenero A, Antwi-Kusi A, Ashebir DZ, Ndonga AK, Ngumi ZW, Sani CM, Samateh A, Madiba TE, Pearse RM, Biccard BM, African Surgical Outcomes Study (ASOS) investigators. Towards the quantification of perioperative cardiovascular risk in the African context: a sub-analysis of the South African Surgical Outcomes Study and the African Surgical Outcomes Study. *South African Medical Journal* 2021;111(11):1065–1069. https://doi.org/10.7196/SAMJ.2021.v111i11.15848

5.1 Declaration from author and co-authors

5.1.1 Declaration from author

This was a sub-study of data from the African Surgical Outcomes Study (ASOS) and South African Surgical Outcomes Study (SASOS). The following co-authors contributed to the paper: H-L Kluyts, V Gobin, A Elkhogia, FD Madzimbamuto, J Tumukunde, AO Omigbodun, C Youssouf, R Mehyaoui, DM Munlemvo, A Basenero, A Antwi-Kusi, DZ Ashebir, AK Ndonga, ZW Ngumi, CM Sani, A Samateh, TE Madiba, RM Pearse, and BM Biccard.

In Chapter 5, the contributions by authors to the work were as follows: CS Alphonsus participated in data collection for the original studies, developed the protocol for the sub-study, and was the main author of the manuscript. BM Biccard developed the protocol, data collection, and data analysis for the original studies; and participated in protocol development and performed the data analysis for this sub-study. H-L Kluyts, V Gobin, A Elkhogia, FD Madzimbamuto, J Tumukunde, AO Omigbodun, C Youssouf, R Mehyaoui, DM Munlemvo, A Basenero, A Antwi-Kusi, DZ Ashebir, AK Ndonga, ZW

Ngumi, CM Sani, AL Samateh, TE Madiba, RM Pearse, and BM Biccard helped collect data for the original studies and reviewed drafts of the manuscript for this sub-study. All authors approved the final published version and agreed to be accountable for the accuracy or integrity of the work.

Signature removed

Christella Alphonsus 16 August 2021

5.1.2 Declaration by supervisor on behalf of co-authors

The undersigned hereby certifies that:

1. The above declaration correctly reflects the nature and extent of the candidate's contribution to this work and the nature of the contribution of each of the co-authors.
2. The co-authors meet the criteria for authorship in that they have contributed to the design of the work. Furthermore, they have participated in patient recruitment, data collection and data analysis for the study. They were involved in drafting or revision and final approval of the publication.
3. The main author and co-authors take public responsibility for their part of the publication.
4. There is no other author of the publication according to these criteria.
5. Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit.

Location of data: The original data are stored at the following location and will be held for at least five years from the date indicated below.

The paper clinical record form and source documents are stored in a locked cabinet in the Department of Anaesthesia and Perioperative Medicine research office. Statistical Package for the Social Sciences (SPSS) data analysis and any other study-related material are stored author's (C Alphonsus) password-protected laptop.

Signature removed

Professor Bruce Biccard Date: 16 August 2021

5.2 Synopsis

5.2.1 Rationale for conducting the study

Cardiovascular disease on the African continent

Non-communicable diseases (NCDs) such as cardiovascular disease, cancers, chronic respiratory diseases, chronic kidney disease, diabetes, and mental illnesses contribute significantly to disability and deaths worldwide.[53] The United Nations (UN) has recognised this as a major concern and aims to reduce premature deaths due to NCDs by 30% by 2030 as one of the Sustainable Development Goals. [54]

Sub-Saharan Africa (SSA) is expected to have one of the greatest increases in mortality due to NCDs.[55] Risk factor surveillance for NCDs in SSA shows exposure to at least one risk factor, including tobacco consumption, harmful alcohol use, unhealthy diet, physical inactivity, obesity, or high blood pressure, in most adults.[56] However, a study of disability caused by NCDs estimates a 67% increase in the all-age disability-adjusted life years from 1990 to 2017 attributable to NCDs in SSA.[53] Despite these preliminary data on increasing risk factors to NCDs, large-scale surveillance and population-level data are lacking.[55]

Perioperative cardiovascular outcomes in Africa

Data on surgical outcomes in Africa is sorely lacking and presents a blind spot in population health data from the continent. Data on the burden of cardiovascular disease in patients presenting for noncardiac surgery on the African continent is similarly lacking. The few available studies are predominantly in vascular surgical patients from South Africa, which represent a very specific high-risk group.

The African Surgical Outcomes Study (ASOS)[57] and South African Surgical Outcomes Study (SASOS)[58] provided a snapshot of the incidence of adverse events after surgery. The findings were not reassuring. Poor outcomes were largely occurring in young healthy patients who should have otherwise recovered and become fully functional postoperatively.

Motivation for this study in the PhD

In the previous chapter, we sought to understand the scope of the problem in Western Cape hospitals in South Africa through identifying how many patients with cardiovascular risk were presenting for noncardiac surgery, and by extension, how many patients will need natriuretic peptide testing. In this chapter, we broaden the question to the African continent. Cardiovascular disease was previously a lesser concern on the African continent, but as discussed in the previous chapter and this chapter, it is becoming a greater public health problem with epidemiological transition in Africa.

In this study, we present the results of an investigation to establish the scope of the problem on the African continent using data from two large observational studies. Both the ASOS and SASOS collected data on patients presenting for surgery in African hospitals over a one-week period. These data can be used to estimate the cardiovascular disease burden and surgical outcomes on the continent.

5.2.2 Aim and objectives

Aim

This sub-study collated data on comorbidities and surgical outcomes from two large observational studies, ASOS and SASOS, to investigate the prevalence of cardiovascular disease in elective surgical patients and the risk of postoperative cardiovascular complications in this population.

Objectives

1. To define the cardiovascular disease burden in patients aged ≥45 years presenting for surgery in the combined ASOS and SASOS data set.
2. To determine the relative risk (RR) of developing postoperative cardiovascular outcomes in the ASOS/SASOS cohort.
3. To determine the utility of the RCRI for preoperative cardiovascular risk stratification of elective, noncardiac surgical patients in Africa aged ≥45 years.

5.2.3 Main results

Demographic information:
The original SASOS study comprised 3,927 patients and ASOS 11,422 patients from 25 countries. Although 3,045 patients were included in the sub-analysis, a substantial proportion of the patients (2,048) were from South Africa.

Population:
The analysis for the primary outcome included 3,045 patients after 810 patients were excluded due to missing data (Figure 5.1).

Study results:
The prevalence of cardiovascular disease in the population was as follows: hypertension 41.3%, coronary artery disease 4.7%, congestive cardiac failure 1.9%, diabetes mellitus 15%, stroke 1.4%, and chronic renal disease 2.8%. Patients with major cardiac complications were significantly older, with a higher prevalence of hypertension, coronary artery disease, or congestive cardiac failure, and underwent major surgery. In-hospital mortality was 1.2%. The discrimination of the RCRI for major cardiac complications shows an area under the curve of 0.68 (95% CI 0.57–0.79).

Below is the content of the published article followed by the references of the paper. The context and meaning of the published paper are described in detail in the rest of the chapter

5.3 Article published in South African Medical Journal

Towards the quantification of perioperative cardiovascular risk in the African context: A sub-analysis of the South African Surgical Outcomes Study and the African Surgical Outcomes Study

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Background. The burden of cardiovascular disease in patients requiring non-cardiac surgery in Africa is not known. These patients are at increased risk for postoperative cardiovascular complications.

Objectives. In this sub-study, to use data on comorbidities and surgical outcomes from two large observational studies, the South African Surgical Outcomes Study (SASOS) and the African Surgical Outcomes Study (ASOS), to investigate the prevalence of cardiovascular disease in elective surgical patients and the risk of postoperative cardiovascular complications in this population.

Methods. SASOS and ASOS were both prospective, observational cohort studies that collected data over 1 week in each participating centre. The primary outcome was in-hospital postoperative complications, which included prespecified and defined cardiovascular complications. We defined the cardiovascular disease burden of patients aged ≥45 years presenting for surgery (main objective), determined the relative risk of developing postoperative cardiovascular complications (secondary objective) and assessed the utility of the Revised Cardiac Risk Index (RCRI) for preoperative cardiovascular risk stratification of elective, non-cardiac surgical patients in Africa (third objective).

Results. The primary outcome analysis of 3 045 patients showed that patients with major cardiac complications were significantly older, with a higher prevalence of hypertension, coronary artery disease or congestive cardiac failure, and had undergone major surgery. In-hospital mortality for the cohort was 1.2%.

Conclusions. The substantial burden of cardiovascular disease in patients presenting for non-cardiac surgery in Africa is shown in the principal findings of this study. The RCRI has moderate discrimination for major cardiac complications and major adverse cardiac events in African patients undergoing non-cardiac surgery.

Introduction

Cardiovascular disease is the leading cause of death worldwide. In surgical patients, the Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) study1 showed that patients with cardiovascular comorbidities had an increased incidence of perioperative cardiac complications. The 30-day mortality rate was 2% in patients aged ≥45 years,[1] and 8% had significant myocardial injury that contributed to subsequent morbidity.[2]

The number of patients presenting for surgery in Africa with cardiovascular disease is not known. Two large observational studies, the South African Surgical Outcomes Study (SASOS)[3] and the African Surgical Outcomes Study (ASOS),[4] collected demographic and clinical data that could provide insight into this problem. Both studies were conducted in a similar manner, as a 7-day snapshot of patients aged ≥18 years undergoing any inpatient surgery. The South African (SA) cohort comprised 3 927 patients, and the African cohort 11 422 patients from 25 countries. The data presented in this article will show the burden of cardiovascular disease in patients presenting for elective surgery and the risk of developing postoperative cardiovascular complications.

Defining perioperative risk requires steps to identify high-risk patients who will develop adverse outcomes. This is done prior to surgery through risk stratification, where patient comorbidities and clinical data are used in risk scores and indices. The Revised Cardiac Risk Index (RCRI) is a commonly used risk stratification tool and is

recommended in international guidelines for preoperative cardiovascular risk stratification.[5-7] However, the RCRI only provides moderate discrimination to predict postoperative cardiac complications.[8,9] The RCRI was derived from a single-centre cohort study,[10] and a systematic review of the utility of the RCRI including 24 cohort studies from across the globe did not include studies from African countries.[8] The utility and calibration of the RCRI are therefore unknown in African surgical patients.

Objectives

In this sub-study, we defined the cardiovascular disease burden in patients presenting for surgery on the African continent and the incidence of postoperative cardiovascular complications. We also used the RCRI to quantify perioperative risk for complications in these patients.

Methods

Data were pooled from two large observational studies. SASOS was registered on ClinicalTrials.gov (NCT02141867) and collected data from 19 May to 26 May 2014 in 50 hospitals in the public sector. ASOS was registered on the South African National Health Research Database (KZ_2015RP7_22) and ClinicalTrials.gov (NCT03044899). All participating sites received local ethics and regulatory approval for participating in SASOS and ASOS. ASOS used a convenience sampling strategy in participating African countries between February and May 2016. Each country collected data from at least 10 hospitals, or at least half the surgical centres if there were <10 surgical hospitals in the country. Data on all patients undergoing elective and emergency surgery procedures that required at least an overnight stay in hospital were collected.[4] The primary objective in SASOS was in-hospital mortality and the need for critical care admission in patients, although some hospitals collected in-hospital complications for the International Surgical Outcomes Study (ISOS).[11] The primary objective in ASOS was in-hospital complications and the secondary objective was in-hospital mortality. Ethics approval for this sub-study was given by the Human Ethics Research Committee, University of Cape Town, on 6 September 2019 (ref. no. HREC 615/2019).

In this sub-study, the primary objective was to define the cardiovascular disease burden of patients aged ≥45 years presenting for surgery in the combined SASOS and ASOS data set. Data were pooled from hospitals which collected data on the following comorbidities associated with adverse cardiovascular outcomes: hypertension, diabetes mellitus, stroke, coronary artery disease, congestive cardiac failure and chronic renal failure.[6,10]

The secondary objective was to determine the relative risk (RR) of developing postoperative cardiovascular outcomes in the SASOS/ASOS cohort. The cardiovascular outcomes defined in SASOS/ASOS were myocardial infarction, arrhythmias, pulmonary oedema, pulmonary embolism, stroke and cardiac arrest. As a comparison, we also used the outcomes defined in the RCRI, which are myocardial infarction, pulmonary oedema, ventricular fibrillation or primary cardiac arrest, and complete heart block. The data collected in SASOS/ASOS were not standardised for cardiovascular outcomes, so the definitions are not uniform but overlap with the RCRI in some instances.

The third objective was to determine the utility of the RCRI for preoperative cardiovascular risk stratification of elective, non-cardiac surgical patients in Africa aged ≥45 years. The preoperative RCRI risk factors were defined in the original derivation cohort by Lee *et al*.[10] as a history of coronary artery disease, a history of congestive cardiac failure, preoperative use of insulin, a history of stroke, a preoperative creatinine level >2 mg/dL, and high-risk surgery. The equivalent definitions of these risk factors in ASOS were a history of coronary artery disease, a history of congestive cardiac failure, a history of diabetes mellitus, a history of chronic renal disease, and major surgery. The outcome for the third objective was a composite of myocardial infarction, pulmonary oedema, and cardiac arrest and arrhythmia.

The discrimination of the RCRI for cardiac complications was described using the receiver operating characteristic (ROC) and area under the curve (AUC). The calibration between the original derivation cohort[10] and the ASOS cohort[4] was compared using the RR for cardiac complications in the African cohort for each RCRI risk factor. The likelihood ratios for low- (0 RCRI risk factors), intermediate- (1–2 RCRI risk factors) and high-risk (≥3 RCRI risk factors) categories were calculated.

Data are presented as number (proportion). In order to compare the characteristics of the patient groups with and without cardiac complications, the categorical variables were compared using the χ2 or Fisher's exact test, as appropriate. Continuous variables were tested for normality and summarised using mean and standard deviation or median and interquartile range, as appropriate. An independent-samples *t*-test was used to compare normally distributed data. Risk is presented as RR with 95% confidence intervals (CIs) using MedCalc (https://www.medcalc.org/calc/relative_risk.php). Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 25 (IBM, USA). The level of significance (α) was set at 0.05.

Results

The primary outcome analysis included 3 045 patients (Fig. 5.1), with 810 patients having been excluded owing to missing data. In this cohort, 2 048 patients were from South Africa: 989 patients from SASOS and 1 059 from ASOS. Table 5.1 shows the baseline characteristics of the cohort. Patients with major cardiac complications were significantly older, with a higher prevalence of hypertension, coronary artery disease or congestive cardiac failure, and underwent major surgery. In-hospital mortality for the cohort was 1.2%.

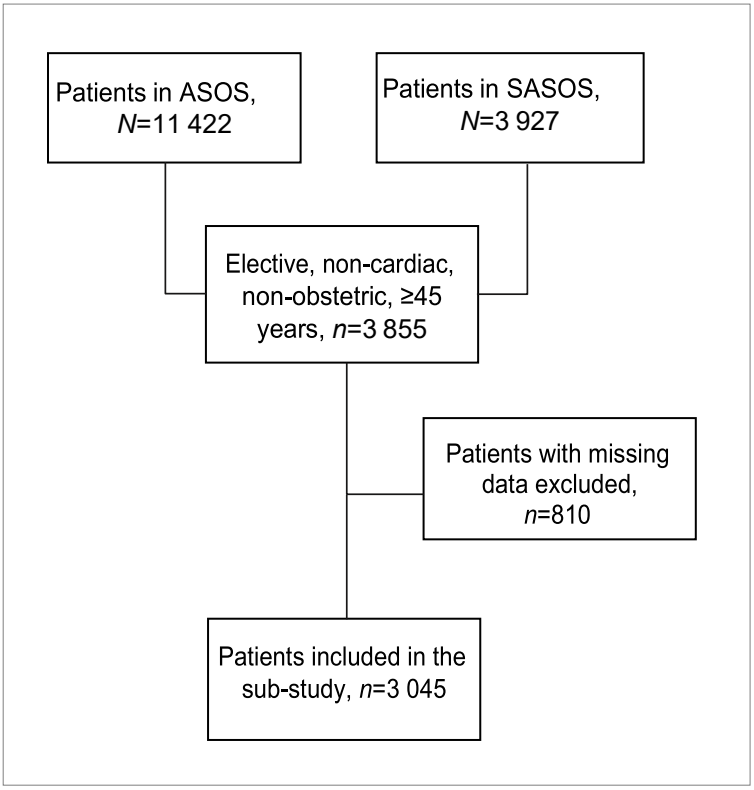

Fig. 5.1 STROBE diagram of the ASOS and SASOS patients included in the sub-study. (ASOS=African Surgical Outcomes Study; SASOS=South African Outcomes Study)

The prevalence of cardiovascular disease in the population was as follows: hypertension 41.3%, coronary artery disease 4.7%, congestive cardiac failure 1.9%, diabetes mellitus 15.0%, stroke 1.4% and chronic renal disease 2.8% (Table 5.1). Table 5.2 shows the relative risk of developing cardiovascular complications using two different definitions. Coronary artery disease, congestive cardiac failure and major surgery were significantly associated with adverse cardiovascular events under both the SASOS/ASOS and RCRI outcome definitions. Stroke, diabetes and chronic renal disease were not associated with cardiovascular outcomes.

Table 5.1 African surgical patients aged ≥45 years

Risk factor	Total patients	Patients with major cardiac complications*	Patients without major cardiac complications*	*p*-value
Age (years), mean (SD)	60.83 (10.88)	67.39 (12.24)	60.62 (10.77)	<0.001
Female, *n*/*N* (%)	1 172/2 235 (52.4)	22/38 (57.9)	1 150/2 197 (52.3)	0.52
Smoking, *n*/*N* (%)	417/2 202 (18.9)	4/37 (10.8)	413/2 165 (19.1)	0.29
Comorbidities, *n*/*N* (%)				
Hypertension	822/1 988 (41.3)	21/35 (60.0)	801/1 953 (41.0)	0.04
Coronary artery disease	106/2 232 (4.7)	7/38 (18.4)	99/2 194 (4.5)	0.002
Congestive cardiac failure	43/2 232 (1.9)	7/38 (18.4)	36/2 194 (1.6)	<0.0001
Stroke	32/2 232 (1.4)	1/38 (2.6)	31/2 194 (1.4)	0.43
Diabetes mellitus	335/2 232 (15.0)	10/38 (26.3)	325/2 194 (14.8)	0.63
Chronic renal disease	56/1 990 (2.8)	1/35 (2.9)	55/1 995 (2.8)	1.00
Major surgery, *n*/*N* (%)	637/2 235 (28.5)	23/38 (60.5)	614/2 197 (27.5)	<0.0001
ASA, *n*/*N* (%)				
Class 1	672/2 220 (30.2)	2/37 (5.4)	670/2 183 (30.7)	0.0004
Class 2	1 117/2 220 (50.3)	12/37 (32.4)	1 105/2 183 (50.6)	0.03
Class 3	403/2 220 (18.2)	19/37 (51.4)	384/2 183 (17.6)	0.0001
Class 4	28/2 220 (1.3)	4/37 (10.8)	24/2 183 (1.1)	0.001
Type of procedure, *n*/*N* (%)				
Orthopaedic	420/ 2 234 (18.8)	7/38 (18.4)	413/2 196 (18.8)	1.0
Breast	100/2 234 (4.5)	2/38 (5.3)	98/2 196 (4.5)	0.69
Obstetrics†	4/2 234 (0.2)	0	4/2 196 (0.2)	0.64
Gynaecology	272/2 234 (12.2)	3/38 (7.9)	269/2 196 (12.2)	0.62
Upper gastrointestinal	82/2 234 (3.7)	3/38 (7.9)	79/2 196 (3.6)	0.16
Lower gastrointestinal	175/2 234 (7.8)	2/38 (5.3)	173/2 196 (7.9)	0.76
Hepatobiliary	89/2 234 (4.0)	1/38 (2.6)	88/2 196 (4.0)	1.0
Urology	345/2 234 (15.4)	5/38 (13.2)	340/2 196 (15.5)	0.82
Vascular	54/2 234 (2.4)	3/38 (7.9)	51/2 196 (2.3)	0.06
Head and neck	151/2 234 (6.8)	3/38 (7.9)	148/2 196 (6.7)	0.74
Plastics	127/2 234 (5.7)	1/38 (2.6)	126/2 196 (5.7)	0.72
Thoracic	2/2 234 (1.6)	2/38 (5.3)	33/2 196 (1.5)	0.12
Neurosurgery	42/2 234 (1.9)	2/38 (5.3)	40/2 196 (1.8)	0.16
Other	306/2 234 (13.2)	0	306/2 196 (13.9)	0.0007

SD = standard deviation; *n* = number of patients affected; *N* = total population; ASA = American Society of Anesthesiologists.

*Major cardiac complications were defined as a composite of myocardial infarction, pulmonary oedema and cardiac arrest. Denominators may vary owing to missing data.

†Obstetric patients who underwent non-cardiac surgical procedures that were not caesarean sections.

Table 5.2 Relative risk for cardiovascular complications using SASOS/ASOS outcome definition and RCRI outcome definition

Comorbidities	SASOS/ASOS definition	RCRI definition
Female	1.10 (95% CI 0.55–2.22); *p*=0.77	1.10 (95% CI 0.55–2.22); *p*=0.77
Smoking	0.52 (95% CI 0.18–1.46); *p*=0.21	0.66 (95% CI 0.23–1.88); *p*=0.43
Hypertension	2.13 (95% CI 1.09–4.16); *p*=0.03	1.89 (95% CI 0.9–3.97); *p*=0.09
Coronary artery disease	4.5 (95% CI 2.04–10.04); *p*=0.0002	4.8 (95% CI 2.02–11.54); *p*=0.0004
Congestive cardiac failure	11.5 (95% CI 5.36–24.64); *p*<0.0001	12.27 (95% CI 5.31–28.38); *p*<0.0001
Stroke	1.86 (95% CI 0.26–13.13); *p*=0.53	1.06 (95% CI 0.07–17.01); *p*=0.97
Diabetes mellitus	2.02 (95% CI 0.99–4.12); *p*=0.053	1.36 (95% CI 0.56–3.28); *p*=0.50
Chronic renal disease	1.02 (95% CI 0.14–7.29); *p*=0.99	1.29 (95% CI 0.18–9.3); *p*=0.80
Major surgery	3.85 (95% CI 2.02–7.32); *p*<0.0001	3.44 (95% CI 1.7–6.98); *p*=0.0006

SASOS = South African Surgical Outcomes Study; ASOS = African Surgical Outcomes Study; RCRI = Revised Cardiac Risk Index; CI = confidence interval.

The incidence of postoperative cardiovascular complications according to the RCRI definition is shown in Tables 5.3 and 5.4. Missing data necessary to generate the RCRI outcome resulted in 28 patients with the data necessary for these analyses. The incidence of postoperative cardiovascular complications per point increase in the RCRI was 0.7%, 1.5%, 4.3% and 15% for 0, 1, 2 and ≥3 points, respectively (Table 5.3). The original index in 1999 showed a risk estimate of 0.4%, 0.9%, 6.6% and 11%.[10]

Table 5.3 Risk estimate for each point of the RCRI (≥45 years) for composite outcome in the SASOS/ASOS cohort compared with the original RCRI cohort*

RCRI	African surgical cohort risk estimate, %	Original 1999 RCRI cohort, %
0 point	0.7 (95% CI 0.23–1.20)	0.4 (95% CI 0.05–1.50)
1 point	1.5 (95% CI 0.62–2.4)	0.9 (95% CI 0.30–2.10)
2 points	4.3 (95% CI 0.90–7.60)	6.6 (95% CI 3.90–10.30)
≥3 points	15 (95% CI 0.65–30.70)	11 (95% CI 5.80–18.40)

SASOS = South African Surgical Outcomes Study; ASOS = African Surgical Outcomes Study; RCRI = Revised Cardiac Risk Index; CI = confidence interval.

*Composite outcome of myocardial infarction, pulmonary oedema and cardiac arrest and arrhythmia.

Table 5.4 Risk estimate per category of the RCRI

RCRI category	*n*/*N*	Risk estimate, %	LR
Low risk (0 points)	8/1 092	0.73 (95% CI 0.23–1.24)	0.52
Intermediate risk (1–2 points)	17/863	1.97 (95% CI 1.04–2.89)	1.4
High risk (≥3 points)	3/20	15 (95% CI 0–30.65)	10.6

RCRI = Revised Cardiac Risk Index; *n* = number affected; *N* = total population; CI = confidence interval; LR = likelihood ratio.

The incidence of postoperative cardiovascular complications according to the RCRI categories was 0.73% in the low-risk category, 1.97% in the intermediate-risk category, and 15% in the high-risk category (Table 5.4). The likelihood ratios for each risk category are shown. The discrimination of the RCRI is shown in the ROC curve for major cardiac complications (Fig. 5.2). It shows an AUC of 0.68 (95% CI 0.57–0.79). In the original cohort, the AUC was 0.78 (95% CI 0.73–0.82).[10]

Discussion

This study examined the cardiovascular disease burden of patients presenting for non-cardiac surgery on the African continent. In this cohort, a large proportion of patients had hypertension (41.3%), a history of smoking (18.9%) and diabetes mellitus (15.0%). Patients who were older with hypertension, coronary artery disease or congestive cardiac failure or were exposed to major surgery had an increased risk of postoperative cardiac complications. The RCRI demonstrated moderate discrimination for postoperative cardiovascular complications in African patients undergoing non-cardiac surgery, with an AUC of 0.68.

Previous studies have identified the concerning increase in non-communicable disease on the African continent.[12] Hypertension, smoking and diabetes mellitus are known risk factors for atherothrombotic cardiovascular disease, and this cohort had a very high prevalence of these risk factors.[12]

Additionally, in previous studies, the overall management of these cardiovascular risk factors from diagnosis to treatment and long-term control was shown to be poor.[12] This poor management is probably due to insufficient human and financial resources and lack of infrastructure in low- and middle-income countries.[13] A recent review of

cardiovascular disease in sub-Saharan Africa notes a paucity of data on the prevalence of ischaemic heart disease and cardiac failure.[12] The data on mortality caused by ischaemic heart disease and cardiac failure in sub-Saharan Africa are thought to be an underestimate owing to lack of biomarker and other diagnostic capabilities.[14,15] In the present sub-study, cardiac failure and ischaemic heart disease were significant causes of postoperative cardiovascular complications. Stroke and diabetes mellitus did not show a significant association with complications (Table 5.2); however, it is likely that this is due to an inadequate sample size in this sub-study to demonstrate this association.

A large proportion of the data on cardiovascular disease in in the present study came from the SA cohort of patients. Despite this limitation, the main message is that cardiovascular comorbidities present an additional risk for postoperative cardiovascular complications. This increased risk was shown across different populations in the VISION study.[1]

In order to relate our findings to the commonly used tool for cardiovascular risk stratification, the RCRI, we applied the RCRI in this cohort of patients. However, we could not perform an external validation of the RCRI in the SASOS/ASOS cohort owing to differences in risk factor and outcome definitions. As the SASOS/ ASOS studies did not use routine troponin screening as part of postoperative detection of myocardial injury after non-cardiac surgery, it is likely that the incidence of postoperative cardiovascular complications is under-reported in our cohort.[2,16] Nevertheless, the presence of coronary artery disease, congestive cardiac failure and major surgery were strong predictors of postoperative cardiovascular complications despite different study outcome definitions.

The utility of the RCRI to risk-stratify patients at cardiovascular risk is becoming more controversial. It appears to provide good discrimination for patients at low risk (with no RCRI risk factors), as reflected by a low likelihood ratio.[9] However, in the most concerning group, which is patients with one or more RCRI risk factors who are consequently at higher risk for complications, the performance of the RCRI is poor.[9] As a result, the Canadian Cardiovascular Society[7] and the American College of Cardiology/American Heart Association[5] recommend further risk stratification of

patients with one or more risk factors. The data from the SASOS/ASOS cohort would also suggest that the utility of the RCRI in an African cohort is at best moderate, and unlikely to be satisfactory for the risk stratification of patients with one or more risk factors. Further recommendation is limited in this sub-study by the small sample size and wide CIs in the high-risk category of patients.

Future studies in this cohort of patients with cardiovascular comorbidities need to focus on cardiovascular outcomes, risk stratification and optimisation before surgery.

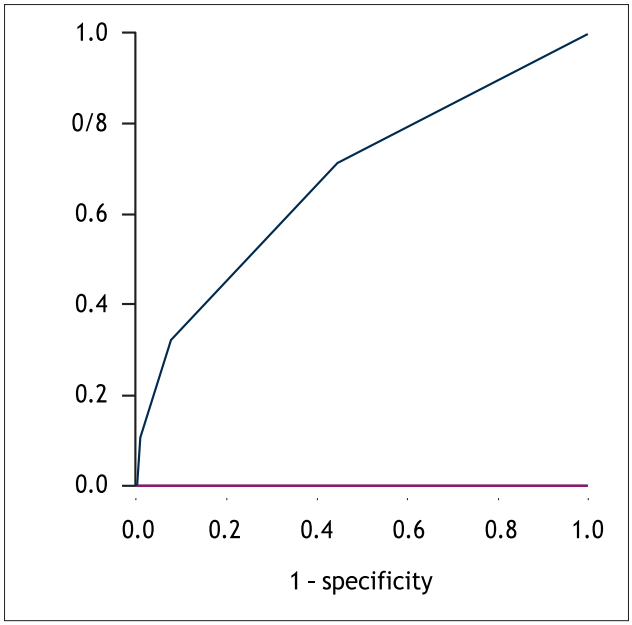

Fig. 5.2 Receiver operating characteristic curve of the Revised Cardiac Risk Index and major cardiac complications in elective African surgical patients aged ≥45 years

Conclusions

In this sub-study, we have shown that a substantial proportion of patients with cardiovascular disease present for non-cardiac surgery on the African continent. These comorbidities contribute to postoperative complications and adverse outcomes. The RCRI potentially provides moderate discrimination for preoperative cardiac risk stratification in African patients undergoing non-cardiac surgery.

Declaration. The research for this study was done in partial fulfilment of the requirements for CSA's PhD (Anaesthesia) at the University of Cape Town.

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Author contributions. CSA: protocol development, data collection, data collation, data analysis, wrote manuscript. H-LK, VG, AE, FDM, JT, AOO, CY, RM, DMM, AB, AA-K, DZA, AKN, ZWN, CMS, ALS, TEM, RMP, BMB: protocol development, data collection, data collation, reviewed drafts of manuscript.

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Conflicts of interest. RMP has received research grants and/or honoraria from Edwards Lifesciences, Intersurgical and GlaxoSmithKline. The other authors declare that they have no conflict of interest.

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5.4 Chapter discussion

Currently, this study provides the most comprehensive outcomes data on the cardiovascular burden and poor associated outcomes in elective, noncardiac surgical patients in Africa. This study demonstrated that perioperative cardiovascular complications were independently associated with age, hypertension, coronary artery disease, congestive cardiac failure, and major surgery. However, these risk factors potentially carry different proportional risk, as there is a 3.5 times increased risk of developing a cardiovascular complication if the patient has coronary artery disease (Table 5.2) and a 2.8 times increased risk in patients undergoing major surgery. The risk for patients with congestive cardiac failure is exponentially higher (about 10 times greater). Whether there are truly different proportional risks between these risk factors cannot be determined, as the confidence intervals overlap between the independent risk factors. However, patients presenting with these comorbidities are at increased risk of developing adverse outcomes on the African continent.

Following the conclusion of Chapter 4, we were concerned about the broader applicability of our findings. Natriuretic peptide testing may not be readily available in all hospitals in South Africa or Africa. We needed to place the problem of perioperative cardiovascular complications in a wider context to help motivate for this type of testing more broadly across Africa. We also need to motivate for consistent risk stratification to make sure these high-risk cardiovascular patients are not missed.

This study adds impetus to the need to change the usual rhetoric that cardiovascular disease in Africa is not common. It also lends importance and motivation to collect data on the continent in a structured and consistent way over time. Tracking this problem over time will help tailor cardiovascular risk prediction and modification strategies specific to regions and countries.

5.5 Chapter conclusion

This chapter provides a larger vision for perioperative cardiovascular medicine by expanding to include the African continent. We have demonstrated that patients with

cardiovascular comorbidities face an increased risk of postoperative mortality in Africa. These outcomes need to be mitigated through solutions in an African context related to the needs of African patients.

6 South African cardiovascular risk stratification guideline for noncardiac surgery

Publication reference: Alphonsus CS, Naidoo N, Motshabi Chakane P, Cassimjee I, Firfiray L, Louwrens H, van der Westhuizen J, Malan A, Spijkerman S, Kluyts H, Cloete NJ, Kisten T, Nejthardt MB, Biccard BM. South African cardiovascular risk stratification guideline for non-cardiac surgery. *South African Medical Journal* 2021;111(10b):1019–1025.

6.1 Declaration from author and co-authors

6.1.1 Declaration from author

In developing these national guidelines for South Africa, we collaborated with anaesthesia and vascular surgical specialists from seven academic institutions in the country. Each of the collaborators are co-authors who contributed to the paper: CS Alphonsus, N Naidoo, P Motshabi Chakane, I Cassimjee, L Firfiray, H Louwrens, J van der Westhuizen, A Malan, S Spijkerman, H Kluyts, NJ Cloete, T Kisten, MB Nejthardt, and BM Biccard.

In Chapter 6, the contributions by authors to the work were as follows: CS Alphonsus developed the guidelines and the first draft of the manuscript, and is the main author of the guidelines. BM Biccard helped develop the guidelines and first draft of the manuscript. CS Alphonsus, N Naidoo, P Motshabi Chakane, I Cassimjee, L Firfiray, H Louwrens, J van der Westhuizen, A Malan, S Spijkerman, H Kluyts, NJ Cloete, T Kisten, MB Nejthardt, and BM Biccard participated in the Delphi consensus process, critical review of guidelines, and design of guidelines. All authors approved the final published version and agreed to be accountable for the accuracy or integrity of the work.

Signature removed

Christella Alphonsus 16 August 2021

6.1.2 Declaration by supervisor on behalf of co-authors

The undersigned hereby certifies that:

1. The above declaration correctly reflects the nature and extent of the candidate's contribution to this work and the nature of the contribution of each of the co-authors.
2. The co-authors meet the criteria for authorship in that they have contributed to the design of the work. Furthermore, they have participated in patient recruitment, data collection, and data analysis for the study. They were involved in drafting or revision and final approval of the publication.
3. The main author and co-authors take public responsibility for their part of the publication.
4. There is no other author of the publication according to these criteria.
5. Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit.

Location of data: The original data are stored at the following location and will be held for at least five years from the date indicated below.

The paper clinical record form and source documents are stored in a locked cabinet in the Department of Anaesthesia and Perioperative Medicine research office. Statistical Package for the Social Sciences (SPSS) data analysis and any other study-related material are stored on the author's (C Alphonsus) password-protected laptop.

Signature removed

Professor Bruce Biccard Date: 16 August 2021

6.2 Synopsis

6.2.1 Rationale for conducting the study

International guidelines on preoperative risk assessment for noncardiac surgery

Three major guidelines from the American College of Cardiology/American Heart Association (ACC/AHA),[59] the European Society of Cardiology/European Society of Anaesthesiology (ESC/ESA),[60] and the Canadian Cardiovascular Society (CCS)[18] provide an approach to preoperative risk assessment for high-risk cardiac patients. These guidelines are similar in that an algorithm is used and common themes are covered: all patients must have a focused history and examination, then undergo risk stratification using various methods and undergo further preoperative testing if necessary.[61] However, the priorities and focus of each guideline are different.[61]

The CCS guidelines have the end goal of identifying patients at risk of MINS and the recommendations are based on the approach that will increase the probability of doing this.[18] The pooled risk estimates from external validation studies of the RCRI over the past 15 years (studies which monitored perioperative troponin measurements and reported events) are reported to be higher in patients with one or more risk factors at, around 5%.[6] The ACC/AHA and ESC/ESA are not focused on MINS and use a lower and older estimate for adverse outcomes of 1%.[59, 60] The ACC/AHA and the ESC/ESA guidelines also rely on risk calculators and assessment of exercise and functional capacity.[59-61] In contrast, the CCS guidelines place an emphasis on blood tests for biomarkers, BNP or NT-proBNP in the preoperative period and troponin in the postoperative period.[18] Risk calculators and functional capacity are of reduced importance in the CCS guidelines because of their poor prognostic capability in identifying patients at risk of MINS.[18]

Challenges of developing perioperative guidelines in low- and middle-income countries and Africa

The limitations of developing preoperative risk stratification guidelines, similar to the European and North American guidelines discussed above, in low- and middle-income

countries (LMIC) include a lack of large data sets and studies in the perioperative cohort of patients and a lack of resources for large-scale testing. Cardiopulmonary exercise testing and other cardiac diagnostic testing are not readily available. A lack of resources and understanding of the baseline prevalence of disease in the population makes the implementation of guideline recommendations from high-income countries (HIC) difficult in LMICs.

Motivation for this study in the PhD

In Chapters 4 and 5, the prevalence of cardiovascular comorbidities and elevated natriuretic peptides in patients presenting for surgery was demonstrated. These patients are at greater risk for cardiovascular complications, which presents a need for a structured and evidence-based approach to manage and modify this cardiovascular risk. The development of guidelines for a LMIC like South Africa was a starting point in acknowledging that collective and coordinated efforts need to be taken nationally in managing high-risk patients for noncardiac surgery. The CCS guidelines were adopted and simplified for the local context. Gaps in knowledge and future areas for research were highlighted, along with acknowledgment that a lack of availability of biomarker testing could affect implementation of guidelines.

As part of the final chapter of the PhD, these guidelines detail a course of action for addressing the concerns raised about managing high-risk cardiac patients for noncardiac surgery. The guidelines have been developed and appraised by collaborators at seven universities in South Africa. This collaboration has produced evidence-based, pragmatic, context-driven guidelines for South Africa.

6.2.2 Aim and objectives

Aim

To develop perioperative cardiovascular risk stratification and management practice guidelines for South African cardiac patients presenting for elective noncardiac surgery.

Objectives

1. To update and revise the most recent evidence-based perioperative cardiovascular risk stratification and management guidelines, the Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery, based on more recent publications.
2. To further revise the guidelines according to South African or African perioperative cardiovascular epidemiological publications.
3. To achieve consensus using a Delphi method, which is an accepted method for achieving convergence of opinions concerning knowledge solicited from experts within specific fields.[62]

6.2.3 Main results

Relevant publications to update guidelines:
Three international publications were identified which presented new data to update the CCS guidelines. Twelve publications presented data on risk factors and the incidence of cardiovascular complications following noncardiac surgery in South African or African patients.

Collaborators in the Delphi consensus process:
The first draft of the guidelines was critically evaluated by the lead vascular surgeon and lead anaesthetist for preoperative assessment at seven South African universities over a two-round consensus process.

Study results:
Four main recommendations were made addressing which patients need preoperative risk stratification, the place of non-invasive testing, the need for natriuretic peptide testing, and postoperative troponin screening.

Below is the content of the published article followed by the references of the paper. The context and meaning of the published paper are described in detail in the rest of the chapter.

6.3 Article published in South African Medical Journal

South African cardiovascular risk stratification guideline for non-cardiac surgery

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Executive summary

The South African (SA) guidelines for cardiac patients for non-cardiac surgery were developed to address the need for cardiac risk assessment and risk stratification for elective non-cardiac surgical patients in SA, and more broadly in Africa.

The guidelines were developed by updating the Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Non-cardiac Surgery, with a search of literature from African countries and recent publications. The updated proposed guidelines were then evaluated in a Delphi consensus process by SA anaesthesia and vascular surgical experts.

The recommendations in these guidelines are:

1. We suggest that elective non-cardiac surgical patients who are 45 years and older with either a history of coronary artery disease, congestive cardiac failure, stroke or transient ischaemic attack, or vascular surgical patients 18 years or older with peripheral vascular disease require further preoperative risk stratification as their predicted 30-day major adverse cardiac event (MACE) risk exceeds 5% (conditional recommendation: moderate-quality evidence).
2. We do not recommend routine non-invasive testing for cardiovascular risk stratification prior to elective non-cardiac surgery in adults (strong recommendation: low-to-moderate-quality evidence).
3. We recommend that elective non-cardiac surgical patients who are 45 years and older with a history of coronary artery disease, or stroke or transient ischaemic attack, or congestive cardiac failure or vascular surgical patients 18 years or older with peripheral vascular disease should have preoperative natriuretic peptide (NP) screening (strong recommendation: high-quality evidence).
4. We recommend daily postoperative troponin measurements for 48–72 hours for non-cardiac surgical patients who are 45 years and older with a history of coronary artery disease, or stroke or transient ischaemic attack, or congestive cardiac failure or vascular surgical patients 18 years or older with peripheral vascular disease, i.e. (*i*) a baseline risk >5% for MACE 30 days after elective surgery (if no preoperative NP screening), or (*ii*) an elevated B-type natriuretic

peptide (BNP)/*N*-terminal-prohormone B-type natriuretic peptide (NT-proBNP) measurement before elective surgery (defined as BNP >99 pg/mL or a NT-proBNP >300 pg/mL) (conditional recommendation: moderate-quality evidence).

Additional recommendations are given for the management of myocardial injury after non-cardiac surgery (MINS) and medications for comorbidities.

Keywords: non-cardiac surgery; preoperative risk stratification; natriuretic peptide testing.

Introduction

The population in low- and middle-income countries (LMIC) is five times greater than in high-income (HIC) countries.[3] The focus in LMIC has largely been on communicable diseases; however, increasing urbanisation has led to a greater burden of cardiovascular diseases.[3] Globally, an estimated 200 million adults undergo surgical procedures annually and ~ 1/20 patients suffer myocardial injury/ infarction or cardiac arrest or death within 30 days of major non-cardiac surgery. Perioperative cardiac complications account for one-third of all perioperative deaths.[4,5]

However, despite this burden of disease, there are no evidence-based guidelines for perioperative risk stratification and management of cardiac patients for non-cardiac surgery in LMIC. Developing guidelines for LMIC is challenging due to a lack of resources and funding for essential tests and services.

Recent publications have documented the burden of cardiovascular complications in South African (SA) and African surgical patients. Vascular surgery, in particular, is one of the highest-risk procedures leading to perioperative adverse cardiac events.[6] The risk of vascular surgery patients experiencing myocardial injury after non-cardiac surgery (MINS) is 1 in 5.[7] Furthermore, 7.1% (*n*=12/68) of vascular patients who are 45 years or older developed in-hospital major adverse cardiac event (MACE) in Africa (African Surgical Outcomes Study (ASOS).[8] The burden of peripheral arterial disease (PAD) is substantial in LMIC.[9]

The objective of this paper was to develop perioperative cardiovascular risk stratification and management practice guidelines for SA cardiac patients presenting for elective non-cardiac surgery.

Methods

The initial aim of this publication was to create a consensus statement for the perioperative cardiovascular risk stratification and management of PAD in SA. However, we hope that these guidelines may have a broader applicability in Africa.
The most recent evidence-based perioperative cardiovascular risk stratification and management guideline was used as a template based upon the robust methodology used in the generation of these guidelines.[10] These guidelines were critically appraised, and then either endorsed, or updated and revised based on more recent publications, and revised according to SA or African perioperative cardiovascular epidemiological studies.

A Medline search was conducted on 16 July 2019 with search terms: 'perioperative' (or 'postoperative' or 'surgical'), 'outcome/s' (or 'complication/s'), and 'cardiac' (or 'heart') and Africa/n (all African countries) not 'paediatric/s' (English and American spelling). Potentially relevant SA and African publications which described the incidence of cardiovascular complications following surgery were identified by authors CA and BMB. The incidence of MACE and associated patient risk factors were extracted where possible by CA and BMB. Further data describing the incidence of MACE for various patient risk profiles was extracted from the African Surgical Outcomes Study (ASOS)[8] dataset. Where the extracted data only described the in-hospital event rate, the predicted 30-day MACE rate was derived by a factor of 1.416 of the in-hospital incidence.[11] The search was updated on 8 May 2020.

These guidelines were developed using a Delphi technique. CA and BMB produced the first draft of the guidelines, which was then critically evaluated by the lead vascular surgeon and lead anaesthetist for preoperative assessment at each SA university over a two-round consensus process. The main target-users of these guidelines are explicitly anaesthetists and surgeons who perform vascular surgery; however, the group consensus was that these guidelines could be adopted for cardiovascular risk

stratification and management of all cardiac patients for non-cardiac surgery (as opposed to only patients with PAD), as the studies on which these recommendations are based are predominantly from mixed non-cardiac surgery studies. The feedback from participants regarding the challenges in implementing these guidelines has been highlighted in context boxes as well as suggestions for future research to investigate strategies to overcome these challenges.

In international guidelines, preoperative cardiovascular risk stratification and management is determined by one demographic risk variable (i.e. age), cardiovascular risk factors (i.e. comorbidities) and a surgical risk variable (i.e. intermediate to high-risk surgery). The interplay of these three variables selects the high-risk population who require further testing, specific monitoring, and intervention.[10] We have followed these requirements in our analysis of unpublished ASOS data, by only selecting patients who underwent intermediate and high-risk surgery and then analysing the data according to age and comorbidities. Furthermore, we have looked at two vascular cohorts from two SA observational studies due to the powerful signal for cardiovascular complications.[12,13] The event rate is reported as in-hospital MACE and predicted 30-day MACE (Table 6.1). The ASOS study only reported in-hospital MACE. We calculated the 30-day MACE based on a calculation derived from the VISION study, which showed that 70% of complications occur before discharge and a further 30% occur within 30 days after surgery. Therefore, we have estimated the 30-day event rate by a correction to in-hospital events of 10/7.[4]

All recommendations in these guidelines are based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) rating system with grading as strong or conditional recommendation based on high-, moderate-, low-, or very low-quality evidence.[14]

In these guidelines, we did not survey or reference opinions from the public or patients.

Table 6.1 Incidence of cardiac events in African and South African patients undergoing elective intermediate- to high-risk surgeries

Clinical risk category	Type of surgery	Outcome	Reported in-hospital events *n/N* (%; 95% CI)	Predicted 30-day events (%)/ Reported 30-day events *n/N* (%; 95% CI)
≥65 years* (ASOS)	All non-cardiac surgery	MACE	15/482 (3.1; 1.6–4.7)	4.4
≥45 years with significant CVD* (ASOS)	All non-cardiac surgery	MACE	4/81 (4.9; 0.2–9.7)	7.0
Coetzee *et al.*[19]	All non-cardiac surgery	MINS	12/244 (4.9; 2.2–7.6)	7.0
Van Zyl *et al.*[25]	Arthroplasty	MINS	68/160 (42; 34.8–50.1)	60
RCRI ≥1 (≥45 years* (ASOS))	All non-cardiac surgery	MACE	50/1 543 (3.2; 2.4–4.1)	4.5
≥18 years (SA MRC cohort)	Vascular surgery	MINS and death		136/749 (18.1; 15.4–20.9)
≥18 years (SA cohort, HIV sub- study)[13]	Vascular surgery	MINS and death		11/73 (15.1; 6.9–23.3)

ASOS = African Surgical Outcomes Study; CVD = cardiovascular disease; RCRI = revised cardiac risk index; CI = confidence interval; MACE = major adverse cardiac events (defined as death, non-fatal myocardial infarction, and cardiac arrest); MINS = myocardial injury after non-cardiac surgery; MRC = medical research council.

Significant cardiovascular disease = coronary artery disease, stroke or transient ischaemic attack, congestive cardiac failure, or peripheral arterial disease.

*Recommendations in the CCS guidelines.

Results

The search results produced 1 071 articles, of which 11 were publications that presented data on risk factors and the incidence of cardiovascular complications following non-cardiac surgery in SA or African patients,[12,13,15-23] and three publications [2,7,24] presented new data which may lead to revision of the Canadian Cardiovascular Society (CCS) guidelines. Thus, we reviewed 14 new or South African/African publications for these guidelines. The updated search yielded one new publication[25]

for review, bringing the total to 15 publications. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram is shown in Fig. 6.1.

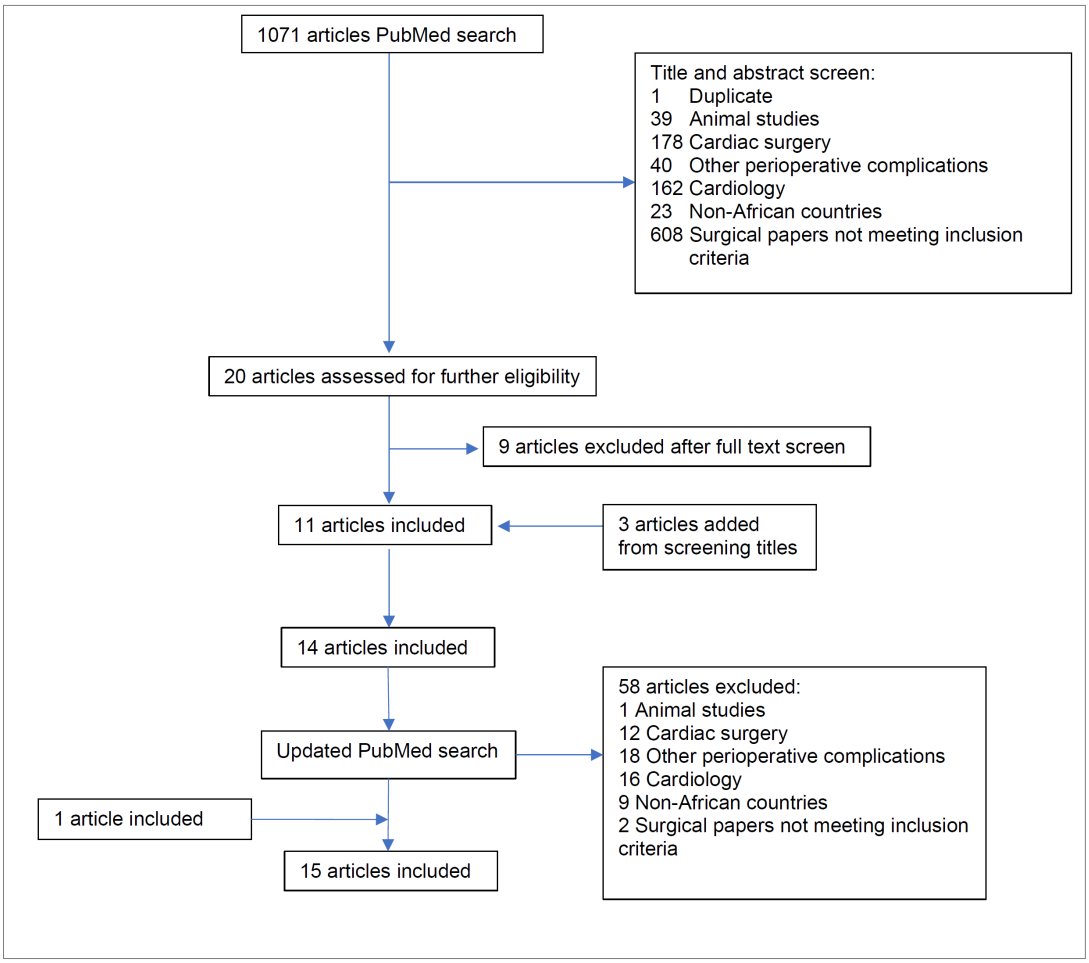

Fig. 6.1 PRISMA flow diagram

Clinical cardiac risk assessment

Risk assessment provides a pathway for patient management. Not only does risk assessment provide a context (considering the patient's current physiological state in the presence of comorbidities and the extent of the surgical injury), but it also provides means for communicating the risk to patients and multidisciplinary teams necessary for planning of surgery and anaesthesia.[10]

There are certain tools available to help with risk assessment and stratification.

Risk stratification of patients at significant risk of major adverse cardiac events

The recent CCS Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Non-cardiac Surgery advocate for risk stratification of patients who have >5% risk of MACE within 30 days of elective surgery.[10]

The incidence of MACE >5% reported in an African cohort of patients includes (*i*) non-cardiac surgical patients 45 years and older with a history of coronary artery disease, or stroke or transient ischaemic attack, or congestive cardiac failure (Table 6.1);[8] and (*ii*) vascular surgical patients who are 18 years or older with peripheral vascular disease,[10] including HIV-positive patients undergoing vascular surgery.[13] Significant cardiovascular disease is defined as a history of coronary artery disease, or stroke or transient ischaemic attack, or congestive cardiac failure.

In summary, only patients with significant cardiovascular disease and 45 years or older, or patients undergoing vascular surgery (or with established PAD) who are 18 years or older with peripheral vascular disease consistently have a risk for a MACE >5% at 30 days following elective non-cardiac surgery. The use of age and the revised cardiac risk index (RCRI) does not add important additional information in the prediction of MACE risk in the African cohort (Table 6.1).

Recommendation 1: We suggest that all elective non-cardiac surgical patients 45 years and older with a history of coronary artery disease, or stroke or transient ischaemic attack, or congestive cardiac failure; or patients 18 years or older with peripheral vascular disease undergoing vascular surgery require further preoperative risk stratification as their predicted 30-day MACE risk >5% (conditional recommendation: moderate-quality evidence).

Recommendation in context: This recommendation is based on observational studies conducted in elective surgery patients requiring at least one-night stay in hospital who were scheduled for intermediate to high-risk surgery. Thus, the need for further risk stratification will only apply to adult patients who fulfil both clinical (history of coronary artery disease, or stroke or transient ischaemic attack, or congestive

cardiac failure or peripheral arterial disease) and surgical (intermediate to high-risk surgery) criteria. This recommendation does not apply to patients undergoing low risk surgery, and surgery which does not require overnight hospital admission.

Future areas for research: The available data in SA is dominated by research focusing on high-risk patients who are presenting for vascular surgery. There is a paucity of data in the greater cohort of non-cardiac surgery patients from LMIC and this requires urgent attention. This recommendation can be strengthened through research focused on perioperative cardiovascular outcomes in non-cardiac surgical patients in developing countries, particularly in Africa.

The role of non-invasive testing in risk stratification

We have endorsed the recommendations of the CCS Guidelines regarding non-invasive testing.[10] The non-invasive tests discussed below do not add any further incremental value to risk stratification of elective non-cardiac surgical patients. Our search did not identify any further evidence which would change these recommendations.

Self-reported functional capacity

Patient-reported ability to exercise is an inaccurate and biased measure of physical fitness. This was shown in systematic reviews and confirmed in a recent, large prospective observational study (strong recommendation: moderate-quality evidence, Grade 1B).[2,26]

Resting echocardiography, coronary computed tomographic angiography, pharmacological stress echocardiography and radionuclide imaging

The above investigations are not recommended as a means of cardiovascular risk assessment. Resting echocardiography is an inferior risk-assessment tool compared with cardiac biomarkers (strong recommendation: low-quality evidence).[27] Resting echocardiography is not recommended unless there is a clinical suspicion of intracardiac lesion (mitral or aortic stenosis or hypertrophic obstructive cardiomyopathy) or severe pulmonary hypertension.

Coronary computed tomographic angiography leads to overestimation of risk and unnecessary cardiac intervention (strong recommendation: moderate-quality evidence).[28] Both stress echocardiography (strong recommendation: low-quality evidence) and radionuclide imaging (strong recommendation: moderate-quality evidence) have been studied in small cohorts of patients and there is little evidence on the utility of these preoperative tests.[10]

Exercise stress testing and cardiopulmonary exercise testing

Current evidence does not support the use of the above tests for cardiovascular risk assessment (strong recommendation: moderate-quality evidence, Grade 1B).[2,10]

Recommendation 2: We do not recommend routine non-invasive testing for cardiovascular risk stratification prior to elective adult non-cardiac surgery (strong recommendation: low- and moderate-quality evidence).

Recommendation in context: Current evidence does not support large-scale, non-invasive testing for cardiac risk stratification. This recommendation does recognise the clinician's autonomy to conduct further testing based on clinical findings, where these investigations may guide subsequent management.

Future areas for research: To establish robust evidence on the utility of non-invasive testing in a low-resource environment, we must be cognisant of the clinical experience and the context in which care is delivered. The lack of resources for adequate quality care for surgical patients was highlighted by the ASOS I study, which found high mortality and morbidity in young healthy patients.

Currently, there are limited data on the outcomes for high-risk patients presenting for non-cardiac surgery in Africa. Outcomes data are urgently needed before one can adequately further evaluate the role of non-invasive testing in this environment.

The role of natriuretic peptide testing in risk stratification

Natriuretic peptide (NP) testing has been shown to be a good predictor of perioperative adverse cardiac events,[29,30] and is significantly better than the RCRI (Table 6.2). This has also been confirmed in SA vascular surgical patients. A prospective cohort study

of 788 patients found that B-type natriuretic peptide (BNP) significantly improved risk prediction of patients who did and did not develop postoperative cardiac complications.[15]

Based on recommendation 1, the SA Practice Guidelines for cardiac patients for elective non-cardiac surgery recommends the following patients for NP screening: all patients 45 years and older with a history of coronary artery disease, or stroke or transient ischaemic attack, or congestive cardiac failure; or patients who are 18 years or older with peripheral vascular disease undergoing vascular surgery require further preoperative risk stratification using preoperative NP screening.

The incidence of MACE and utility of various NP thresholds is shown in Table 6.3. A BNP level above 99 pg/mL and *N*-terminal prohormone B-type natriuretic peptide (NT-proBNP) above 300 pg/mL are predictive of >5% risk of developing MACE.[30,31]

Table 6.2 AUC for BNP and RCRI in predicting perioperative outcomes (*N* = 632)[29]

Outcome	BNP, AUP (%); 95% CI	RCRI, ACU (%); 95% CI
MACE	80.5; 75.1 – 85.8	64.5; 56.6 – 72.3
Cardiac death	80.0; 71.5 – 88.6	67.1; 53.8 – 80.5
Non-fatal MI	78.6; 72.2 – 85.5	62.3; 52.8 – 71.7
All-cause mortality	71.4; 60.7 – 82.2	63.8; 53.2 – 74.3

AUC = area under the curve receiver operating characteristics; BNP = B-type natriuretic peptide; RCRI = revised cardiac risk index; CI = confidence interval; MACE = major adverse cardiac events (defined as death, non-fatal myocardial infarction, and cardiac arrest); MI = myocardial infarction.

Table 6.3 Preoperative NP thresholds for predicting the composite outcome of 30-day mortality and non-fatal myocardial infarction

Type of surgery	Type of NP	NP level (pg/mL)	MACE, % (95% CI)	Likelihood ratio
Mixed non-cardiac surgery[30]	BNP	0 – 99	5.3 (3.2 – 7.2)	0.58
		100 – 250	11.6 (4.3 – 18.8)	1.38
		≥250	26.9 (17.1 – 35.5)	3.88

NT-proBNP	0 – 300	5.2 (4 – 6.8)	0.42
	301 – 900	16.1 (12 – 20.2)	1.46
	901 – 3 000	26 (18.3 – 33.7)	2.68
	>3 000	39.5 (26.3 – 52.6)	4.97

NP = natriuretic peptides; BNP = B-type natriuretic peptide; CI = confidence interval; NT-proBNP = *N*-terminal pro-brain natriuretic peptide; MACE = major adverse cardiac events.

Recommendation 3: We recommend that all elective non-cardiac surgical patients who are 45 years and older with a history of coronary artery disease, or stroke or transient ischaemic attack, or congestive cardiac failure, or patients who are 18 years or older with peripheral vascular disease undergoing vascular surgery should have preoperative NP screening (strong recommendation: high-quality evidence).

Recommendation in context: We recognise that resource constraints could limit the ability to conduct preoperative NP testing in some hospitals. This recommendation is aspirational in resource-limited settings. Patients with raised NP present with a spectrum of symptoms (from asymptomatic to overt symptoms and signs of cardiovascular pathology). The presence of raised NP has prognostic utility in the preoperative period. Failure to identify these patients may have serious implications on postoperative outcomes.

There are currently few data to guide a cheap alternative to NP testing in a resource-limited environment. The current data would support the Duke Activity Status Index[2] as a potential candidate, but this would require further research with NP screening used as the ‘gold standard’.

Future areas for research: The increase in cardiovascular disease due to chronic comorbid conditions in SA and Africa as a whole, places a great deal of strain on already under-resourced healthcare systems. It follows then, that if there is a lack of evidence for non-invasive testing, resources could be allocated for a potentially robust test such as a NP test. Research is needed to determine whether the availability of NP

testing informs the management of high-risk patients for non-cardiac surgery, improves the quality of care and patient outcomes in developing countries.

The role of postoperative troponin screening

Myocardial injury after non-cardiac surgery (MINS) is defined as a postoperative troponin elevation with no evidence of a non-ischaemic aetiology of troponin elevation. The classic signs and symptoms of MI are often absent, with no chest pain or absent or minor electrocardiogram changes. It commonly occurs within the first 48 hours after surgery and can usually only be detected through daily troponin screening.[32] The diagnostic definition of MINS with 5th generation high-sensitivity troponin T (hsTnT) is an absolute change of at least 5 ng/L, if the level is between 20 to <65 ng/L, or a hsTnT level of at least 65 ng/L.[33]

The VISION (Vascular events In non-cardiac Surgery patIents cOhort evaluatioN) prospective observational study of 15 000 patients who were 45 years or older showed that ~1:20 patients suffer myocardial injury/infarction or cardiac arrest or death within 30 days of major non-cardiac surgery. Perioperative cardiac complications accounted for one-third of all perioperative deaths.[4,32]

In the vascular cohort of patients from the VISION study, the incidence (95% confidence interval (CI)) of MINS was 19.1% (15.7–22.6). The 30-day mortality was higher in patients with MINS (12.5%; 95% CI 7.3–20.6) compared with patients without MINS (1.5%; 95% CI 0.7–3.2; p <0.001). MINS was independently associated with 30-day mortality (odds ratio 9.48; 95% CI 3.46–25.96). The proportion of vascular surgery patients who suffered MINS without overt evidence of myocardial ischaemia was 74.1% (95% CI 63.6–82.4).[7] The reported incidence of MINS in SA vascular surgical patients was similar to the VISION study (17.3%; 95% CI 14.6–19.9).[12]

In a SA cohort of patients aged ≥45 years presenting for elective elevated-risk non-cardiac surgery (defined as all intra-abdominal, non-cardiac thoracic, joint replacement, major orthopaedic and vascular surgery) had an incidence of in-hospital MINS of 4.9% (95% CI 2.8–8.5).[19]

Recommendation 4: We recommend daily postoperative troponin measurements for 48–72 hours for all non-cardiac surgical patients 45 years and older with: (*i*) a history of coronary artery disease, stroke or transient ischaemic attack, congestive cardiac failure, or patients who are 18 years and older with peripheral vascular disease undergoing vascular surgery, i.e. a baseline risk >5% for major adverse cardiac events at 30 days after surgery (if no preoperative NP screening); or (*ii*) an elevated NT-pro BNP/BNP measurement before surgery (defined as BNP >99 pg/mL or a NT-proBNP >300 pg/mL) (conditional recommendation; moderate quality evidence).

Recommendation in context: The diagnosis of MINS has prognostic implications. Current evidence suggests that simple supportive strategies may be associated with improved outcomes, which can be easily managed by surgical teams. However, ~3 out of 4 patients requiring these interventions will not be identified without troponin screening. The cost implications of troponin screening have not been studied in SA. A cost-consequence study based on the VISION study shows favourable cost implications for patients at high risk of MINS.[1]

Management by a multidisciplinary team would only be required for select patients. This is an area which requires much research in both acute management of MINS, the timing and role of multidisciplinary teams, and the place of subsequent cardiovascular risk modification at the primary healthcare level.

The South African Practice Guidelines for non-cardiac surgery algorithm in cardiac patients is shown in Fig. 6.2.

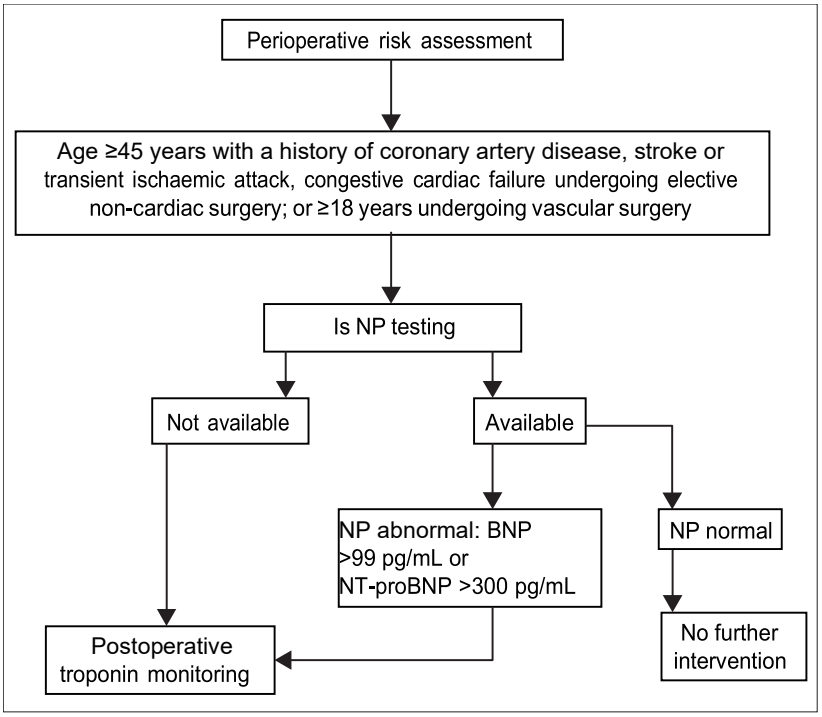

Fig. 6.2 South African Cardiac patient for non-cardiac surgery practice guidelines algorithm. (NP = natriuretic peptide; BNP = B-type natriuretic peptide; NT-proBNP = N-terminal prohormone B-type natriuretic peptide)

Additional recommendations: Management of MINS

The management of patients with MINS is supportive. Adequate treatment of tachycardia, hypotension, hypoxia, and bleeding (anaemia) is needed. An electrocardiogram should be done and a cardiologist should be notified if there is ST elevation, new left-bundle branch block (LBBB) or anterior ischaemic changes, as these clinical signs significantly increase mortality.[32] Statin and aspirin therapy should be started or continued[34] and beta-blockers should be continued if the patient is haemodynamically stable.[35]

The MANAGE (Management of myocardial injury After Non-cArdiac surGEry) study showed that anticoagulation, in this case dabigatran for up to 2 years after surgery, was protective against death, non-fatal MI and thrombotic complications. Dabigatran should be considered for patients who have had MINS. The suggested recommendation is that for patients who have had MINS but are stable and have no risk of subsequent surgical bleeding, anticoagulation should be started within 30 days of the MINS event (strong recommendation: high-quality evidence).[24] Arterial components of the primary composite outcome (MI, non-haemorrhagic stroke,

peripheral arterial thrombosis, amputation, and vascular death of unknown origin) and per-protocol analysis censoring 7 days after discontinuation of therapy both support the intervention as indicated by the hazard ratio of 0.73 (95% CI 0.55–0.96) and (0.57; 95% CI 0.41–0.79), respectively.

Recommendation in context: The management of MINS encompasses many interventions that are already part of good postoperative surgical care. The infrastructure and follow-up plan to safely anti-coagulate patients who have had MINS might not be available at all centres. However, the high-quality evidence demonstrating that anticoagulation is protective for MINS in the long-term cannot be ignored. The implementation of anticoagulation for these patients requires further collaborative work. Currently, dabigatran is of limited availability in the public sector. Although other anticoagulants may offer protection against MINS, there is currently no evidence from clinical trials to support this.

Additional recommendations: Chronic medication

Acetylsalicylic acid

There is no evidence of primary prevention of cardiovascular events in the perioperative period. Acetylsalicylic acid (ASA) should be stopped at least 3 days before surgery, and ASA can be restarted when there is minimal risk of surgical bleeding (strong recommendation: high-quality evidence).[36] Perioperative withdrawal of chronic ASA therapy does not increase cardiac or other arterial thrombotic events.[36] There are limited data in vascular surgical patients, although the findings of the vascular sub-study are consistent with the main trial, that ASA should be stopped in the perioperative period.[37]

This recommendation does not apply to patients who have had recent coronary stents, bare-metal stents within 3 months or drug-eluting stents within 1 year, and patients who are going for carotid endarterectomy. Continuation of ASA is recommended in these patients (strong recommendation: moderate-quality evidence).[38]

Beta-blockade

It is recommended that chronic beta-blocker medication is continued throughout the perioperative period (conditional recommendation: low-quality evidence).[39] Beta-

blocker therapy should not be started immediately before surgery (strong recommendation: high-quality evidence).[40]

Alpha-agonist

There is no recommendation to start this medication in the immediate preoperative period (strong recommendation: high-quality evidence).[41]

Calcium channel blocker

There is no recommendation to start this medication in the immediate preoperative period although chronic medication can be continued (conditional recommendation: low-quality evidence).[10]

Angiotensin-converting enzyme inhibitor/ angiotensin II receptor blocker

It is recommended that the above medication is stopped 24 hours before surgery and restarted when risk of hypotension has passed (strong recommendation: low-quality evidence).[10,42,43] The POISE-3 trial (NCT03505723) may provide high-quality evidence on how to manage antihypertensive agents in the perioperative period.

Statins

It is recommended that statins are continued in the perioperative period (strong recommendation: moderate-quality evidence).[44,45]

Conclusion

These cardiovascular risk stratification guidelines have been developed to provide context for risk stratification in elective non-cardiac surgery in SA. Future guidelines will need to include a broader group of participants from different surgical and medical disciplines, as well as input from patients. These guidelines would need to be updated when sufficient evidence has been generated in LMIC. Future work will also need to include assessment of guidelines implementation, adherence to recommendations, and associated patient outcomes.

Declaration. None.

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6.4 Chapter discussion

A significant number of South African patients with elevated risk for perioperative cardiac complications present for surgery at South African hospitals. These guidelines present the first South African evidence-based collaboration on risk stratification for cardiac patients for noncardiac surgery. The guidelines present the evidence in the context of a resource constrained setting, acknowledging the limitations under which clinicians work. When considering these resource constraints, it was important to rationalise recommendations to essential tasks that had the greatest utility in identifying high-risk patients.

Research in HIC provided data on the poor performance of exercise testing and other cardiac diagnostic investigations to identify risk in these patients. This poor performance, and the cost of setting up and maintaining such testing and investigations in South African hospitals meant that these approaches were given less importance than natriuretic peptide and troponin testing, which were also more robust screening tools.

The need for more research, large data sets, and more studies in high-risk populations in South Africa and Africa was highlighted throughout the development of the guidelines. The knowledge gap highlighted in the guidelines lends much needed direction for future research and projects within this field.

The collaboration with seven universities in South Africa also provides the cooperative platform needed for the implementation of these guidelines in the country.

6.5 Chapter conclusion

This chapter provides a summation of the work thus far in the risk stratification of high-risk cardiac patients in a low-resource setting. This work is relevant in our setting, yet much needed further epidemiological research work is still required. Collaboration and cooperation will be needed to implement these guidelines and provide context-specific feedback on the implementation of this work.

7 Conclusion and recommendations

In the final chapter of this thesis, I will summarise the key findings from each chapter and make recommendations for further research and implementation of these findings.

7.1 Overview of key findings

The first systematic review showed that despite many years of using natriuretic peptide-directed medical therapy, a clear reduction in natriuretic peptide levels could not be shown over the course of the directed medical therapy, although a reduction in mortality was demonstrated. It was unclear whether the lack of reduction in natriuretic peptides was due to the patients already being stabilised before recruitment and thus getting no further benefit from this clinical approach. Furthermore, the paradoxical finding of a reduction in mortality (despite an absence of a reduction in natriuretic peptide levels) may be ascribed to an increase in care. These findings made it difficult to translate a natriuretic peptide-directed medical therapy approach to surgical patients with cardiac comorbidities and raised preoperative natriuretic peptides.

The second systematic review showed that exercise is a possible method of lowering natriuretic peptide levels in non-surgical patients. All patients in the intervention group had a structured, supervised exercise plan, mostly involving aerobic training. Given the contradictory finding in the previous systematic review, it was useful to know that a non-drug therapy approach could be beneficial in cardiac failure patients.

Both the above systematic reviews raised the questions of which patients in our context, i.e. a low- and middle-income country, could benefit from preoperative natriuretic-peptide directed interventions—either medical therapy or exercise—and how many high-risk cardiac patients presenting for elective, noncardiac surgery had a raised natriuretic peptide level.

The prospective observational study that investigated natriuretic peptide levels in high-risk cardiac patients presenting for noncardiac surgery at seven hospitals in the Western Cape, South Africa showed that a substantial cohort of patients with high

natriuretic peptide levels were presenting for surgery and could potentially benefit from risk stratification and natriuretic peptide-directed interventions.

The next question was: What were the postoperative outcomes in these high-risk patients? Showing that these patients have adverse outcomes would add greater weight to identifying risk and implementing interventions to improve these outcomes. The sub-study of ASOS and SASOS data showed an in-hospital mortality of 1.2% and showed that these patients had an increased relative risk of suffering adverse outcomes.

Finally, the South African risk stratification guidelines were developed to provide the first step towards mitigating the cardiovascular risk in elective, noncardiac surgical patients in South Africa, and more broadly, in Africa. This step also lays the foundation for future research in this field. A structured, collaborative, and coordinated effort to identify and risk stratify high-risk patients will lead to formalising the preoperative preparation of these patients and lead to further work on natriuretic peptide-directed medical therapy.

7.2 Recommendations

7.2.1 Recommendations for further research

There are many gaps in research that have become evident throughout this thesis. The following suggestions are for studies that would be a continuation of the work presented in this thesis.

Establishment of databases:

- To investigate the prevalence of cardiovascular disease patients presenting for noncardiac surgery. There is a lack of robust data that could help direct management and resources for these patients. The disease burden at different hospitals may vary throughout South Africa and Africa.
- To collect country- and hospital-specific data on high-risk patients with elevated natriuretic peptide levels who are undergoing surgery in South African and

African hospitals. The perioperative period is a continuum, and there is a lack of national- and hospital-specific data on postoperative cardiovascular outcomes. Importantly, those high-risk patients need postoperative troponin screening, and the compliance with this postoperative investigation is unknown, which also hampers an understanding of the true burden of postoperative cardiovascular complications in Africa, as they are predominantly silent.

Risk stratification and optimisation studies:

- It is not known if patients can be optimised preoperatively through natriuretic peptide-directed medical therapy to reduce myocardial strain. This needs to be further investigated through a randomised clinical trial. Clinicians will not be able to be blinded to the randomisation, but the primary outcome assessors must be blinded.
- There is also the possibility of optimising patients using exercise therapy. This would also need to be further explored through a randomised clinical trial using similar methods as above.

Q*uality improvement studies:*

- We need observational data documenting the medical therapy management of chronic cardiovascular conditions in patients presenting for surgery and whether these conditions are being adequately managed preoperatively. If poorly managed, we need to probe the patients' understanding of their chronic comorbidities, factors associated with medication compliance, and the availability of medication to treat these conditions.
- We also need observational data on the quality of the perioperative care of high-risk patients presenting for noncardiac surgery. Furthermore, we need to understand the availability of resources to assess and risk stratify patients, the availability of natriuretic peptide and troponin testing, and the resources to manage these patients in the perioperative period. Finally, cardiovascular monitoring and focused care to maintain haemodynamic stability is imperative, but it is unknown whether these strategies are implemented.
- An analysis of the cost-benefit of the risk stratification and modification strategies mentioned above needs to be undertaken.

Implementation studies:

- Formalisation and implementation of the risk stratification process in all noncardiac surgery patients as part of routine clinical practice is a fundamental future aspect of this work. This is currently not being done, and it will need everyone working in the perioperative sphere, including surgeons, to work as a team to achieve this objective. The first step will be to audit current practice among all members of the multidisciplinary team. Then, protocols will need to be created, and education and engagement will need to be carried out. This will loop back to reauditing and team feedback. The goal is to provide consistency and continuity in patient management, which is not done at present.
- Increasing access to and availability of natriuretic peptide testing, as well as promoting its use, is an important step in the risk stratification process. Again, this will require education, training, and feedback from clinicians, since most clinicians are not using this test and do not understand its utility. A collaborative effort will help this process.
- The development of the South African risk stratification guidelines was a major achievement toward bringing this work the attention it needs. The participation of collaborators from around the country helped develop the working group for these guidelines. This working group will receive feedback regarding the guidelines from perioperative clinicians around the country. The guidelines will also need to be updated in the next few years and thus will keep evolving as this work moves forward.
- The development of a national and African perioperative cardiovascular research group will help the development of national and pan-African registries and further large-scale studies. There is great interest in this research throughout Africa, and the development of a pan-African group is underway.

7.2.2 Recommendations for supervision and mentorship of upcoming PhDs and MMEDs

It is envisioned that while this avenue of research grows, future postgraduate work through masters and PhDs in medicine can be developed. The potential studies highlighted above could be drawn into a larger research framework, which might

include (a) perioperative cardiovascular research in South Africa and Africa; (b) community-directed work in perioperative cardiovascular research; (c) education and training of perioperative clinicians and surgeons in risk stratification and perioperative optimisation; (d) implementation studies of evidence-based strategies of cardiovascular management in the perioperative period; and (e) development of the pre-anaesthesia clinic in perioperative preparation of the cardiac patient for noncardiac surgery.

7.2.3 Recommendations for collaboration

- *Development of multidisciplinary teams:* This work has already led to close collaboration with the Vascular Surgery Department at Groote Schuur Hospital. As awareness grows, further collaboration with orthopaedics, gynaecology, urology, and other surgical disciplines is anticipated. Further to this, collaboration with nursing teams, physiotherapy, family medicine, internal medicine, and cardiology would also assist this process.
- *Development of pre-anaesthetic clinic services:* This work also opens up the work of risk stratification and optimisation of high-risk patients in the preoperative anaesthesia clinic. This is an environment that allows a safe environment for communication, counselling, and developing a relationship, which allows for a longer preoperative period of regular consultations to optimise the patient.
- *Collaboration with clinicians in South Africa:* The development of the South African risk stratification guidelines showed the capacity for collaboration within South Africa. This working group is a step in the right direction for growing this work.
- *Collaboration on the African continent:* There is great interest in African collaboration, and this avenue will definitely be explored further.

7.3 Conclusion

About 3 million people annually will undergo noncardiac surgery on the African continent. Patients 45 years and older with cardiovascular comorbidities have a 2 to

10 times greater risk of developing cardiovascular complications, depending on their baseline comorbidity. These outcomes can be mitigated through a structured, evidence-based approach that starts with risk stratification.

The series of studies in this thesis have addressed the importance of perioperative cardiovascular research in South Africa, and more broadly, in Africa. The implementation of evidence garnered through scientific work in this field is contextual, and this thesis has described our understanding thus far, and consequently, the deficiencies that need to be investigated to move this work forward. This work lays the foundation to improve outcomes in surgical patients with cardiovascular disease, which is projected to increase on the African continent.

This thesis opens up further discussions in this field and research opportunities that will be best served through a collaborative approach.

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