Myocardial Injury after Non-Cardiac Surgery:

A Prevalence Study

By

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Declaration

I, Ettienne Coetzee, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Signed by candidate

E Coetzee

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Without their assistance in data-collection, this project would not have been possible.

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List of Abbreviations

ACC/AHA	American College of Cardiology and American Heart Association
aHR	adjusted hazard ratio
ASA	American Society of Anesthesiology
CCS	Canadian Cardiovascular Society
CI	confidence interval
cTnT	cardiac troponin T
CV	coefficient of variation
ECG	electrocardiogram
ESC/ESA	European Society of Cardiology and the European Society of Anaesthesiology
EuSOS	European Surgical Outcomes Study
HIV	human immunodeficiency virus
hs-cTnT	high sensitivity cardiac troponin T
IQR	inter quartile range
MACE	major adverse cardiac event
MAP	mean arterial pressure
METs	metabolic equivalents
MI	myocardial injury
MINS	myocardial injury in non-cardiac surgery
OR	odds ratio
RCRI	revised cardiac risk index
SASOS	South African Surgical Outcomes Study
SD	standard deviation
VISION	Vascular Events In Non-cardiac Surgery Patients Cohort Evaluation Study

WHO	World Health Organisation

Abstract

Background

Worldwide, the number of patients suffering from surgical complications account for a significant burden on healthcare systems. Myocardial injury after non-cardiac surgery (MINS) is a new entity that has recently been identified as an independent risk factor associated with 30-day all-cause mortality. The risk of death increases approximately 10 fold following MINS in the perioperative period. Diagnosing myocardial injury in nonsurgical patients often relies on specific symptomatology and clinical findings combined with special investigations. However, in surgical patients, more than 80% of patients with postoperative myocardial injury will be asymptomatic, and hence the majority of diagnoses will be missed. Studies identifying the prevalence and risk factors for MINS have been conducted in countries with a different surgical population to South Africa. The primary outcome of this study was to investigate the prevalence of MINS after non-cardiac, elective, elevated risk surgery in South Africa.

Methods

Patients undergoing elevated risk, elective, non-cardiac surgery ≥ 45 years of age were enrolled via convenience sampling. The new 5th generation, high sensitivity cardiac troponin T (hs-cTnT) blood test was used to identify MINS. Blood samples were taken between 24 to 72 hours after surgery. Exclusion criteria included patients with known renal disease, a recent cardiac event, pulmonary embolism or sepsis.

Results

A total of 244 patients were included in the study. The prevalence of MINS was 4.9% (95% CI 2.2-7.6) which was not significantly different (p=0.078) to reports from international prospective observational studies.

Conclusion

Elective, elevated risk surgical patients in South Africa have a similar incidence of MINS when compared to patients from international studies. As the risk profile of South African patients is significantly lower than other similar international observational studies, it is possible that the prevalence of MINS is more common in South Africa, when patients are adjusted for cardiovascular risk profile. The burden of MINS on public health morbidity is therefore likely to be proportionally more in South Africa when compared to international reports. This may suggest that the calibration of international cardiovascular risk prediction models is incorrect for South African patients, or there are confounding comorbidities which should be included in South African cardiovascular risk prediction models. Larger studies are required to confirm

this hypothesis however, and should also aim to address the need for appropriate cardiovascular risk predicting models in South Africa, to ensure timeous identification of patients at risk of MINS.

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Chapter 1 – Introduction and Literature Review

Burden of surgical complications

Weiser et al. (2008) estimated the global burden of surgery on healthcare systems to range between 187 and 281 million surgical cases per annum.[1] Of these patients, 7 million will have major perioperative complications and approximately a million will experience mortality per year, indicating a significant impact on global healthcare, to which cardiovascular-related mortality contributes about a third.[2] High-income countries appear to have a lower perioperative permanent disability- and death rate (0.4-0.8%), when compared to low and middle-income countries (5-10%), with general anaesthesia associated mortality as high as 1 per 150 cases in certain parts of sub-Saharan Africa.[1] According to the authors, nearly 50% of the perioperative complications were avoidable. Therefore, the significance of perioperative morbidity and mortality is a well-established concern, as is the need to investigate potential risk factors and mitigating actions to prevent these.

Elective and Non-elective surgical procedures

Non-elective surgery carries a higher risk of complications when compared to elective procedures, demonstrated by studies done in all socio-economic environments.[3–5] Many confounders, such as the inability to optimise medical co-morbidities and undiagnosed end-organ damage add risk during non-elective surgery. Planned, elective surgery would ideally allow for appropriate patient preparation and selection, in an effort to reduce the perioperative risk. In a large, multicentre, international study, both elective and non-elective patients have been extensively investigated for myocardial injury after non-cardiac surgery (MINS).[5] This study included patients from North- and South America, Europe, Australia and Asia. However, investigators in the South African context have only published data on a single vascular surgical cohort.[6–8] Since vascular surgery presents a specific high-risk profile, the data cannot simply be extrapolated to other surgical disciplines. The prevalence of MINS in elective, high-risk surgery, from all surgical disciplines, could provide new insight into perioperative medicine in the South African context. It could either reassure clinicians about the safety associated with elective surgery in South Africa, or it could raise concern and serve as a sobering push towards furthering research and developing preventative strategies to avoid MINS in the perioperative period.

Defining surgical risk

Various international task forces have published guidelines and recommendations regarding the perioperative evaluation and care of patients for non-cardiac surgery. In 2007, the American College of Cardiology and American Heart Association (ACC/AHA), described their three risk categories based on the likelihood of developing significant perioperative major adverse cardiac events (MACE): low (less than 1%), intermediate (1 – 5%) and high (above 5%).[9] In 2014, a more pragmatic distinction between low (less than 1%) and elevated risk (greater than 1%) was used to describe the cumulative patient- and surgery-specific risk.[10]

Impact of MINS

In a large, multicentre study, Devereaux et al evaluated the association between myocardial injury after non-cardiac surgery and mortality (Vascular Events In Non-cardiac Surgery Patients Cohort Evaluation Study – VISION 2012).[5] Patients that suffered a troponin elevation had a significantly elevated risk of 30-day mortality. Myocardial injury was subsequently defined as an elevated cardiac troponin T (cTnT) which was attributed to myocardial ischaemia following noncardiac surgery.[12] Subsequent analysis of the data compared risk factors and identified a troponin elevation as the strongest predictor of mortality, with an odds ratio (OR) of 10.07 (95% confidence interval 7.84 – 12.94).[12] MINS occurred in 8% of patients.[12] One in ten patients that experienced MINS died within 30 days of surgery. The vascular surgical cohort that has been studied in South Africa, found an incidence of MINS of 13.5%.[13] The causes of death from the VISION study were found to be approximately equally divided between vascular- and non-vascular deaths. In other words, having an elevated cTnT during the acute post-operative period increased *all-cause mortality*. While the predictive power of post-operative troponin elevations are clear, an editorial in Circulation (2013) emphasised that practitioners should be aware of its lack of specificity in identifying the exact cause of death.[14] Troponin elevation was not able to demonstrate increased risk of cardiac death, but rather functioned as a marker of overall hazard. However, the VISION study investigators attempted a rational explanation for this phenomena. They concluded in their discussion that MINS is likely to contribute to mortality even if the eventual cause of death is non-vascular, such as pneumonia, and that a patient that develops MINS will likely be at a physiological disadvantage at dealing with additional perioperative complications, which might have been insignificant, should they have occurred in the absence of MINS. MINS is independently associated with both vascular- and non-vascular deaths.[12]

The impact of MINS has also influenced international perioperative management guidelines. In the 2007 ACC/AHA guidelines for non-cardiac surgery evaluation, post-operative troponin surveillance is only recommended in symptomatic patients *with* electrocardiogram (ECG) changes.[9,10] The European Society of Cardiology and the European Society of Anaesthesiology (ESC/ESA) guidelines of 2014, promotes the pre- and postoperative use of troponin screening, but only in high risk patients.[15] While the Third Universal Definition of Myocardial Infarction taskforce also imply that troponin surveillance in high risk patients might be considered, the ESC/ESA guidelines provide a definition for what they regard as high risk patients: poor functional capacity with metabolic equivalents (METs) of less than or equal to 4, or a revised cardiac risk index (RCRI) of greater than 1 for vascular surgery or greater than 2 for non-vascular surgery.[15,16] The European guidelines further note that troponin screening provides additional prognostic value. A review in 2016 stated that the majority of clinicians do not appreciate the significance of MINS, and suggested an approach to incorporate perioperative cTnT surveillance in daily practice.[17] However, in 2017, the Canadian Cardiovascular Society (CCS) provided perioperative guidelines that incorporated strong recommendations for postoperative troponin surveillance.[18] Troponin surveillance is recommended in patients above 45 years with additional risk factors (elevated RCRI or other cardiac biomarkers) and routinely in patients above 65 years of age. While the rest of the international guidelines are still ambivalent, the recent addition of cTnT surveillance to the 2017 CCS guidelines suggest that the international perioperative community is moving towards troponin surveillance becoming daily practice. Despite the availability of the cTnT test increasing in South Africa, it will likely be some time before this becomes common practice, especially in resource limited facilities. It is therefore important to investigate troponin screening in the South African context.

MINS – Pathophysiology, Clinical presentation and Diagnosis

Approximately 30% of mortality after non-cardiac surgery are as a result of cardiovascular complications.[2] A brief review of the pathophysiology of MINS aims to clarify its impact on the perioperative period.

Myocardial injury (MI) is a term extensively used in medical literature, ranging from the emergency room to the operating theatre. The cause and clinical presentation can differ significantly. The primary event leading to MI might originate from a variety of pathological processes. Interrupted blood supply, imbalanced oxygen supply and demand, poorly

oxygenated blood and blood with inadequate oxygen carrying capacity can all result in MI.[16] They can occur as solitary events or in combination. A review article focusing on the pathophysiology of perioperative myocardial infarction noted the dissimilarity between medical patients with myocardial infarction and myocardial infarction during the perioperative period.[19] The vast majority of patients with acute myocardial infarctions that present to the emergency room, will suffer from an acute occlusive vascular cause, such as plaque rupture or thrombosis. This differs to most of the patients that suffer a perioperative myocardial injury. Post-mortem studies identified oxygen supply-demand imbalance as the major contributor to myocardial injury within the first 3 to 4 days after surgery, while plaque rupture occurred at random intervals within the first 17 days. This finding supports the hypothesis that MINS is likely as a result of a relative hypoperfusion of the coronary arteries, possibly aggravated by an increased myocardial oxygen demand in the first few days after surgery. This aggravation might be due to the increased basal metabolic rate associated with surgery, pain, post-operative respiratory complications, coagulation disturbances or anaemia. Recent publications have investigated perioperative haemodynamic effects on myocardial injury. Intraoperative hypotension, defined as a mean arterial pressure (MAP) of less than 55 mmHg, significantly increased the occurrence of myocardial injury. The magnitude of impact was also time-dependent, with a duration above 20 minutes resulting in a significant increase in 30-day mortality.[20] Another publication found a statistically significant association between preoperative baseline heartrate and myocardial injury.[21] The study concluded that elevated heart rate, especially above 96 beats per minute, increased the risk of myocardial injury and mortality within 30 days. Although plaque rupture appears to contribute to perioperative myocardial injury, it does not appear to occur more commonly in the early postoperative time.[19] Another finding was that patients with established coronary artery disease, had an increased risk of perioperative MI. The pathophysiological process behind perioperative MI is therefore different when compared to medical MI.

While the basic pathological process that result in MI is likely caused by lack of adequate oxygen supply to the myocardium, the way in which this presents can vary. MI seen in the emergency room is commonly associated with the clinical symptoms and signs defined by the Third Universal Definition of Myocardial Infarction.[16] This definition includes symptoms of ischaemia, ECG changes, altered cardiac imaging studies and deranged cardiac biomarkers. Of note, is the requirement of clinical symptoms and signs *in addition to* elevated biomarkers. MINS presents as a different clinical entity. Of great concern is the fact that the majority of

patients (more than 84%) that experience MINS, do not have ischaemic symptoms and therefore do not fulfil the diagnostic criteria.[12] ECG abnormalities occurred in less than 35% of patients with MINS, significantly reducing the predictive utility thereof.[12] If perioperative physicians were to rely on current guidelines to diagnose MI in the perioperative period, they will miss the majority of patients that experience MINS.[22] MINS was introduced as a new diagnostic entity because of its independent manner in which it influences perioperative outcome and its unique presentation.[12,22] Elevated cardiac biomarkers, specifically cTnT, therefore forms the cornerstone of diagnosing MINS in the perioperative phase.

Cardiac Troponin T

The physiological basis of muscle contraction applies to both skeletal- and cardiac muscle. Appropriate interactions between muscular structural proteins are required for contraction to occur. Troponin is one such protein. When injury occurs to myocardial muscle, these structural proteins are released into the circulation.[23] This troponin leak can then be quantified. Earlier generations of troponin tests had significant cross-reaction with skeletal muscle. Newer assays are now able to detect cardiac-specific troponin. The cardiac troponins T and I have been utilised as markers of myocardial damage. Both troponins have been implicated successfully in the diagnosis of MINS.[22] Universal standardisation of the Troponin I test have been a concern, hence Troponin T tests have been used more commonly.[24] With recent advances in technology, the sensitivity of troponin T detection has also increased.[25] Troponin tests prior to the latest 5th generation were unable to detect down to single digits in the ng/L range. This resulted in the inability to accurately quantify the true population normal. According to recommendations found in the universal definition of myocardial infarction, diagnostic cardiac biomarkers should be sufficiently sensitive to allow the calculation of the upper limit of normal (99th percentile) with a coefficient of variation (CV) of 10% or less.[16,24,26] The fourth generation cTnT test had a lower limit indicated by a result of <0.01 μg/L (<10 ng/L).[25] In other words, once the troponin level reached 10 ng/L or lower, the test was no longer representative. The upper reference of normal for the 4th generation cardiac troponin T was found to be 0.03 μg/L (30 ng/L).[27] Current 5th generation cTnT has a lower limit of 3-5 ng/L.[27] An upper limit of normal of 13 ng/L (10% CV), was calculated.[25,27] This had a significant impact on how the diagnosis of acute myocardial ischaemia was made. Troponin T levels above 13 ng/L are now regarded as elevated, a remarkable change from the World Health Organisation (WHO) definition of greater than 0.1 μg/L (>100 ng/L) from the 1970's.[27] Of

course, specific troponin cut offs will apply to specific clinical scenarios. A review article discussing the statistical implications of diagnostic tests highlights the importance of pre- and post-test probability, and how the need for a specific sensitivity or specificity can alter diagnostic test requirements.[28] Certain clinical scenarios would benefit from a more sensitive test as opposed to a test with greater specificity but reduced sensitivity. A good example would be an acute myocardial infarction in the emergency room. In a patient with risk factors for and clinical signs of myocardial ischaemia, the pre-test probability for a positive troponin leak would be high. A false negative might therefore have more harmful implications for patient care and prognosis as opposed to a false positive. Comparing the 4th generation cTnT with the latest 5th generation test, illustrates how it has evolved. The sensitivity of the diagnosis of acute myocardial infarction within nine hours of the event has increased from just over 80% to nearly 100%.[27] Specificity has reduced from approximately 99% to just over 75%. With a sensitivity of nearly 100%, the occurrence of false negatives is almost excluded. The hs-cTnT can therefore rule out the diagnosis of acute myocardial infarction with great accuracy at the cost of some specificity. The need to establish proper normal ranges, and a 99th percentile for specific population groups are therefore important. Statistical analysis revealed that a 4th generation cTnT of greater than 0.03 μg/L (>30 ng/L) were significant in predicting 30-day mortality (aHR 4.30; 95% CI, 2.68–6.91).[12]

To be able to utilise 5th generation cut offs for MINS a correlation with the 4th generation cTnT test is required. Some literature suggesting correlating values exist. Studies comparing 4th- and 5th generation cTnT tests suggest a 4th generation test value of 30 ng/L comparing to approximately 53 ng/L of the 5th generation test, while 20 ng/L (4th generation) compares to 40 ng/L (5th generation).[29,30] Another study investigated the proportion of patients that have elevated hs-cTnT after non-cardiac, elective surgery.[31] A 95th percentile was calculated for postoperative hs-cTnT of 33 ng/L, of which the prevalence matched the cumulative proportion with 4th generation cTnT above 30 ng/L. In the light of these developments, the prevalence of both 33 ng/L and 53 ng/L troponin leaks, using the 5th generation test, have been included in this study.

Troponin elevation from other causes

The pathophysiology of troponin leaks after myocardial ischaemia may be either from increased myocardial oxygen demand or decreased supply, and results in myocardial cellular dysfunction. This dysfunction can lead to cell damage or cellular death, and is followed by

troponin proteins leaking into the circulation. Non-ischaemic causes of troponin leaks are less well understood, while the predictive impact on perioperative mortality is unaffected.[32] Various associations with troponin elevation have been described, such as carbon monoxide poisoning, renal failure, heart failure, acute pericarditis, acute exacerbation of chronic obstructive airway disease, chemotherapy-related myocardial damage, pulmonary arterial hypertension, pulmonary embolism, sepsis (previously defined as severe sepsis or septic shock), stroke and sub arachnoid haemorrhage.[33–44] Within the context of a different cause of troponin elevation, its specificity for disease is lost, but its predictive power on mortality appears to remain intact. In a recent article, mortality and functional status were predicted with equal or improved accuracy, when compared to existing tests for evaluating the severity of pulmonary arterial hypertension.[41] However, in non-surgical patients with renal impairment, studies have shown that cTnT elevations occur without evidence of myocardial ischaemia.[34–36] Some studies also evaluated the prognostic value of elevated cTnT in renal patients and failed to demonstrate a significance during long-term follow-up. Whether this can be applied in the perioperative milieu is debatable since data from the VISION trial demonstrated that, regardless of estimated glomerular filtration rate, the prognostic value of cTnT elevation remained consistent in the perioperative setting.[5] The significance might be better demonstrated if one can distinguish between an acute postoperative cTnT elevation and a relative increase from an existing elevated cTnT at baseline. An acute elevation from undetectable levels to 500 ng/L (in other words, a change in cTnT of +500 ng/L) might herald a worse prognosis as opposed to an elevation from 480 ng/L to 500 ng/L (a change in cTnT of +20 ng/L). A recent study evaluated troponin changes during the perioperative period and found a significant proportion of high risk patients to have an elevated hs-cTnT even before surgery, which predicted the long- and short term postoperative morbidity and mortality in these patients.[45] The study also demonstrated an increased mortality risk when an absolute rise in pre-existing elevated cTnT occurred. In summary, a conclusion can be made that other disease entities may lead to an elevated cTnT. Although a large proportion of those disease states have shown that those elevated biomarkers have prognostically relevant data, it cannot be applied universally in non-surgical patients. In the perioperative period, troponin elevations appear to be a more robust prognostic marker, whether it be pre- or post-operatively. Ideally, cardiac troponin surveillance should commence before elevated risk surgery.

South African surgical population and MINS

The European Surgical Outcomes Study (EuSOS) evaluated in-hospital mortality over a 7-day period. The study included over 40 000 patients from 28 European nations and excluded patients undergoing cardiac surgery.[3] The recent South African Surgical Outcomes Study (SASOS) closely matched the EuSOS in terms of patient selection and methodology.[4] The VISION trial included all surgeries performed on patients above 45 years of age and also reported on various risk factors and mortality.[5] A comparison between EuSOS and SASOS indicated that the South African surgical patients were significantly younger, had an overall lower American Society of Anesthesiology grading and a lower proportion of elevated risk surgery (all comparisons had a p value less than 0.01).[4] This could explain the elevated mortality witnessed in the EuSOS study (4.0% compared to 3.1%; p value is 0.006).[4] More South African patients underwent non-elective surgery when compared to both EuSOS and VISION data. To compare South African patients to the VISION data, we compared all patients >=45 years of age from the SASOS cohort with VISION. Statistical comparisons were done using X^2 with Yate's correction. South African patients were once again younger but more exposed to elevated risk surgery (see Table A). These comparisons illustrate the significant differences between elective surgical patients in South Africa and the rest of the world, which forms an important rationale for this study.

Table A. **Comparison between the >= 45 year old cohorts of the South African Surgical Outcomes Study (SASOS) and the Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Study** [5,4]

	SASOS >= 45 years (n=1698)	**VISION (n=15132)**	**p**
45-64 years n (%) [95% CI]	1117 (65.8) [63.5-68.0]	7436 (50.9) [50.1-51.2]	<0.001
65-75 years n (%) [95% CI]	337 (22.2) [20.2-24.2]	3779 (25) [24.3-25.7]	0.012
>75 years n (%) [95% CI]	204 (12.0) [10.5-13.6]	3657 (24.2) [23.5-24.8]	<0.001
Elevated risk n (%) [95% CI]	1135 (66.7) [64.6-69.1]	9168 (60.6) [59.8-61.4]	<0.001
Elective surgery n (%)	989 (58.2)	12991 (85.8)	<0.001

Current proposed management of MINS

Large, randomised controlled trials that evaluate specific treatment modalities for MINS, are currently lacking. Most recommendations are based on observational data. Currently, simple therapeutic measures are advocated to improve patient outcomes. A reanalysis of the data from the PeriOperative ISchemic Evaluation (POISE) trial of 2008 suggests that once MINS occurs, addition of aspirin and statin therapy could positively impact postoperative survival.[11] Another study investigated patient outcomes in a vascular cohort of 667 patients, all of which suffered MINS.[46] A comparison was made between those patients that received medical treatment intensification (defined as introducing or increasing any of these four cardiovascular drug groups; antiplatelet agents, β-blockers, statins, or angiotensin converting enzyme inhibitors) during the postoperative period, and those that did not. The cohort that did not receive intensified therapy had a hazard ratio (HR) of 1.77 (95% CI 1.13–2.42; p=0.004) of one-year mortality compared to those that were provided with treatment intensification.[46] Practice guidelines promote the involvement of other medical specialities to include a multidisciplinary team once MINS occurs.[17,18,22] Recommendations also suggest further investigational workup, increasing surveillance and providing haemodynamic optimisation for patients that are diagnosed with MINS. Trials on specific therapies for MINS are ongoing.[17] In summary, current treatment modalities involve simple therapeutic measures, such as the introduction of aspirin and a statin, increasing the monitoring of the patient (high care environment with continuous monitoring) and optimisation of myocardial oxygen delivery (treat hypotension, anaemia and pain).

Summary

The burden of complications after surgery has a significant impact on global healthcare. Studies indicate that cardiovascular complications play a significant role and suggest that a large proportion of those complications can be avoided. Myocardial injury after non-cardiac surgery (MINS) has been identified as a unique clinical entity with a significant impact on mortality. Its predominantly asymptomatic presentation renders clinical symptoms and signs less useful at establishing a diagnosis. Cardiac troponin elevation has been implicated as an accurate marker of MINS, although unable distinguish between vascular or non-vascular causes of death, its prognostic value in the perioperative field remains robust. Newer generations of the test have increased sensitivity and still provide significant predictive data

in the perioperative period. Most of the current data represent patient populations that differ from South Africa. South African patients appear to have different risk profiles. Investigating the prevalence of MINS in the non-cardiac, elective, elevated risk surgical population has not yet been conducted, and could provide a unique insight into South African surgical patients and their potential postoperative outcomes.

Appendices

Consent Form

Consent Form: Myocardial Injury after Non-cardiac Surgery: A Prevalence Study

HREC Reference number: 818/2014

Department of Anaesthetics
D23 Groote Schuur Hospital

Unique Participant Identification Number: _____

Patient Sticker

Consent Form : Myocardial Injury after Non-cardiac Surgery: A Prevalence Study

Please initial box/thumbprint

1. I confirm that I have read and understood the contents of the information sheet presented to me. I confirm that I have had an opportunity to consider the contents of the information sheet and to ask any question freely. I confirm that these questions have been answered clearly and that I am satisfied with the explanation that I have received. ☐
2. I agree that my participation in this study is voluntary. I understand that I may freely withdraw from this study at any point prior to any medication being given in theatre, without having to give any reason for the withdrawal; and that the withdrawal will not affect my medical care. ☐
3. I agree to take part in this study. ☐

Name of participant	Signature/thumbprint	Date
Name of person taking consent	Signature	Date
Name of witness	Signature	Date

If you have any questions about this study, please contact one of the investigators:

Dr Ettienne Coetzee	Tel: 0825561463	ettiennec@gmail.com
Veronica Francis	Tel: 083 244 9895	veronica.francis@uct.ac.za

If you have any questions or concerns about your rights or welfare as a research participant, please contact Prof Marc Blockman, Chairperson, University of Cape Town, Faculty of Health Sciences Human Research Ethics Committee on 021 406 6338; or email marc.blockman@uct.ac.za

Please complete in triplicate: Original remains with investigator for filing. One copy for the patient to retain and one for the patients' folder.

Data Sheet

Data Sheet: Myocardial Injury after Non-cardiac Surgery:
A Prevalence Study

HREC Reference number: 818/2014

Department of Anaesthetics
D23 Groote Schuur Hospital

Unique Participant Identification Number: _____

Please complete for each patient:
Surgery:

Anaesthetic:
□Spinal □Epidural □Combined spinal/epidural □Nerve Block □ General Anaesthetic

Patient Demographics:

Age:_____ Gender: □Male □Female

Weight:_____ Height:_____

Medical History:
□ Hypertension □Diabetes Mellitus □Smoking □Hypercholesterolaemia
□Heart failure □Previous myocardial infarction □Previous stroke
□Malignancy

□Other:_____

Patient Information Sheets

Myocardial Injury After Noncardiac Surgery - A Prevalence Study

Patient Information Sheet

Patient Participation

You have been asked to participate in this study because you and the operation you are about to have, match the group of patients that this study aims to investigate. The details will be explained below. Participation in this study is completely voluntary and at no point will your decision to either participate or not influence your level and standard of treatment. You can also choose to withdraw at any time without having to give an explanation.

Background and Purpose of the study

Currently, around 200 million operations are done on patients worldwide every year. More than 1 million of those patients will die within 30 days of their operation. Some of these deaths are because of damage occurring in the heart muscle cells caused by a problem with the blood supply to the heart's muscle. By using specific blood tests, patients at risk of developing those complications can be identified. You have been asked to participate because the type of operation you are about to undergo has a potential of 1 in a 100 or above of causing an injury to your heart.

Study Outline

A specific blood test, called high sensitivity troponin T (TropT) has been successfully used to identify injury to the heart. If you agree to participate, blood samples will be taken at 24 hours and 48 hours after your surgery (should you still be in hospital at 48 hours). These samples will be taken to a lab and tested only for TropT. As soon as the results are known, the blood samples will be discarded as per the usual protocol at the lab and you will be notified about the result. At that point your participation in the study will end. However, if your blood test is positive for injury to the heart, you will be referred to a heart specialist (cardiologist) for further management in an attempt to protect you from potential complications as mentioned above. Should you wish to be notified about the result of the study, we will do so at the completion thereof. A total of 300 patients are required to participate and the study will take about 3 to 4 months to complete.

Risks

This study is merely an observational study- that means that at no stage, during this study, do we do anything actively that is different from what's normally done, so your standard of care is not less. You will not receive any specific treatment. The drawing of blood carries with it very little risk (pain, bleeding and infection) because it is a well-known procedure and the team that will be taking samples have been sufficiently trained.

New Findings

Should any new information become available that might affect your decision to participate in this study, you will be notified as soon as possible.

Potential Benefits

There is no guarantee that you might benefit from this study. At the moment we do not test patients for heart damage or injury as a routine. By testing your blood we might be able to identify you earlier than usual as having a heart injury and by referring you to a heart specialist, further management might prevent potential complications.

Treatments

If your tests are negative, your participation in this study will end. Should any of your tests be positive, we will refer you to a heart specialist. He/she might ask your permission for further tests or recommend certain treatments. Since this is an observational study, we will neither give, nor withold any treatment as part of your participation in this study.

Costs and Payment for Participation

You will not receive any form of payment for participating in this study. Participation is completely voluntary. As mentioned before, you may withdraw from this study at any point, without influencing your treatment.

Confidentiality

All of your medical records will be treated confidentially. Information from this study will be submitted to the Medicines Control Council of South Africa. Medical records which identify you and the consent form signed by you, will be inspected and/or copied by the University of Cape Town Ethics Committee that has reviewed this research project to make sure the rights and confidentiality of the volunteers are never infringed. Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. Once the study is completed, its results and findings might be presented at meetings and journals. At no point however will your identity be revealed. You have the right to check your study records and request changes if the information is not correct.

If you experience a complication as a direct result of participation in this study

The University of Cape Town (UCT) has insurance cover for the event that research-related injury or harm results from your participation in the trial. The insurer will pay all reasonable medical expenses in accordance with the South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI) in the event of an injury or side effect resulting directly from your participation in the trial. You will not be required to prove fault on the part of the University.

The University will not be liable for any loss, injuries and/or harm that you may sustain where the loss is caused by

- The use of unauthorised medicine or substances during the study
- Any injury that results from you not following the protocol requirements or the instructions that the study doctor may give you
- Any injury that arises from inadequate action or lack of action to deal adequately with a side effect or reaction to the study medication
- An injury that results from negligence on your part

By agreeing to participate in this study, you do not give up your right to claim compensation for injury where you can prove negligence, in separate litigation. In particular, your right to

pursue such a claim in a South African court in terms of South African law must be ensured. Note, however, that you will usually be requested to accept that payment made by the University under the SA GCP guideline 4.11 is in full settlement of the claim relating to the medical expenses.

An injury is considered trial-related if, and to the extent that, it is caused by study activities. You must notify the study doctor immediately of any side effects and/or injuries during the trial, whether they are research-related or other related complications.

UCT reserves the right not to provide compensation if, and to the extent that, your injury came about because you chose not to follow the instructions that you were given while you were taking part in the study. Your right in law to claim compensation for injury where you prove negligence is not affected. Copies of these guidelines are available on request.

Contact Details of Study Coordinators

At any point you can call anyone of the study coordinators with questions or queries regarding this study.

Dr Ettienne Coetzee at 0825561463

Proffessor Bongani Mayosi at 021 406 6200

If you feel you have a significant research-related injury that requires immediate or urgent medical attention, do not hesitate to call or go to the closest emergency department.

Questions regarding your rights as a volunteer may be addressed to the Research Ethics Committee University of Cape Town that reviewed the ethical aspects of this study at **021 406 6338**. Do not sign this consent form unless you have had a chance to ask questions and have received acceptable answers to all of your questions.

Human Research Ethics Committee Reference Number: 818/2014

Ethics Approval Letters

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

11 November 2014

HREC REF: 818/2014

Dr N Meyersfeld
Anaesthesia
D23
NGSH

Dear Dr Meyersfeld

PROJECT TITLE: MYOCARDIAL INJURY AFTER NON-CARDIAC SURGERY: A PREVALENCE STUDY (MMed-candidate-Dr E Coetzee)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

Thank you for an excellent protocol. It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th November 2015.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the MMed Student, Dr Ettienne Coetzee will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical

HUMAN RESEARCH ETHICS COMMITTEE
09 DEC 2015
UNIVERSITY OF CAPE TOWN

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HEALTH SCIENCES FACULTY

0001838)

erves as notification of annual approval, including any documentation described below

☑ Approved | annual progr | Approved | wal date: 30.11.2016

☐ Not approved | ee attac

9/12/15

Principal Investigator to complete the following:

1. Protocol Information

nen submitting this fo	30/11/2015
EF	8182014
title	Myocardial injury after non-cardiac surgery: A prevalence study
Inv	N Meyerowitz
epartment / Offic s Mail	Anaesthesia D23 NGH
s this	☐ Yes √No

2. Protocol status (tick √)

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lease indicate (in the block below) the titles and URF gistry/repositio cts currently making

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4. Signature

		Date	8/12/15

Hospital Approval Letter

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL

Enquiries: Dr Bernadette Eick
E-mail : *Bernadette.Schmitz@westerncape.gov.za*

Dr N. Meyersfeld
Anaesthetics Department
D23 – New main Building

E-mail: nmeyersfeld@gmail.com / Justiaan.Swanevelder@uct.ac.za

Dear Dr Meyersfeld

RESEARCH PROJECT: Myocardial Injury After Non-Cardiac Surgery: A Prevalence Study (MMed Dr E. Coetzee)

Your recent letter to the hospital refers.

You are hereby granted permission to proceed with your research.

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) No hospital consumables and stationary may be used.
d) **No patient folders may be removed from the premises or be inaccessible.**
e) Please introduce yourself to the person in charge of an area before commencing.
f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
g) Confidentiality must be maintained at all times.

I would like to wish you every success with the project.

Yours sincerely

DR BERNADETTE EICK
CHIEF EXECUTIVE OFFICER
Date: 19th December 2014

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Chapter 2 – Publication ready manuscript: The South African Medical Journal

Myocardial injury after non-cardiac surgery: A prevalence study

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Abstract

Background

Worldwide, the number of patients suffering from surgical complications account for a significant burden on healthcare systems. Myocardial injury after non-cardiac surgery (MINS) is a new entity that has recently been identified as an independent risk factor associated with 30-day all-cause mortality. The risk of death increases approximately 10 fold following MINS in the perioperative period. Diagnosing myocardial injury in nonsurgical patients often relies on specific symptomatology and clinical findings combined with special investigations. However, in surgical patients, more than 80% of patients with postoperative myocardial injury will be asymptomatic, and hence the majority of diagnoses will be missed. Studies identifying the prevalence and risk factors for MINS have been conducted in countries with a different surgical population to South Africa. The primary outcome of this study was to investigate the prevalence of MINS after non-cardiac, elective, elevated risk surgery in South Africa.

Methods

Patients undergoing elevated risk, elective, non-cardiac surgery ≥ 45 years of age were enrolled via convenience sampling. The new 5th generation, high sensitivity cardiac troponin T (hs-cTnT) blood test was used to identify MINS. Blood samples were taken between 24 to 72 hours after surgery. Exclusion criteria included patients with known renal disease, a recent cardiac event, pulmonary embolism or sepsis.

Results

A total of 244 patients were included in the study. The prevalence of MINS was 4.9% (95% CI 2.2-7.6) which was not significantly different (p=0.078) to reports from international prospective observational studies.

Conclusion

Elective, elevated risk surgical patients in South Africa have a similar incidence of MINS when compared to patients from international studies. As the risk profile of South African patients is significantly lower than other similar international observational studies, it is possible that the prevalence of MINS is more common in South Africa, when patients are adjusted for cardiovascular risk profile. The burden of MINS on public health morbidity is therefore likely to be proportionally more in South Africa when compared to international reports. This may suggest that the calibration of international cardiovascular risk prediction models is incorrect for South African patients, or there are confounding comorbidities which should be included in South African cardiovascular risk prediction models. Larger studies are required to confirm

this hypothesis however, and should also aim to address the need for appropriate cardiovascular risk predicting models in South Africa, to ensure timeous identification of patients at risk of MINS.

Introduction

Recent reports estimate the global, annual perioperative morbidity and mortality rates at approximately 3% and 0.5% respectively.[1] To appreciate the impact on healthcare systems, those proportions translate into major perioperative complications in approximately 7 million patients, of which mortality occurs in 1 million in the immediate perioperative period per annum, since over 200 million surgeries are performed worldwide per year.[1] Studies from high-income countries suggest that 50% of major adverse perioperative events could be avoided.[1] Research on the cause- and prevention of perioperative complications can therefore benefit global healthcare.

Perioperative risk has recently been redefined according to the American College of Cardiology and American Heart Association (ACC/AHA) task force on perioperative cardiac evaluation and management publication.[2] Cumulative patient- and procedure specific risk for developing a major cardiac adverse event (MACE), such as death or cardiac arrest, can be divided into low- (less than 1% risk) or elevated risk (equal to or below 1% risk).

Cardiovascular deaths contribute a third to non-cardiac perioperative mortality.[3] A large, multicentre, international study investigated more than 15 000 patients from North- and South America, Australia, Europe and Asia (Vascular Events In Non-cardiac Surgery Patients Cohort Evaluation Study – VISION 2012).[4] 30-day mortality was found to be independently associated with an elevated cardiac biomarker, specifically cardiac troponin T (cTnT). It was not only the strongest predictor of mortality, but the magnitude of troponin elevation also correlated with risk. Subsequently, myocardial injury after non-cardiac surgery (MINS) was defined as an elevated cTnT, predicting mortality with an odds ratio (OR) of 10.07 (95% CI 7.84 – 12.94).[5]

Medical- and perioperative patients differ in terms of the clinical presentation of myocardial ischaemia.[6] Non-surgical guidelines rely on clinical symptoms and signs *in addition to* positive special investigations (electrocardiogram, cardiac biomarkers, cardiac imaging studies) to diagnose myocardial infarction.[7] Unfortunately, approximately 84% of perioperative patients with myocardial injury will be asymptomatic, resulting in clinicians missing the diagnosis in the vast majority of patients with MINS.[5] A recent review suggests that its silent presentation and the lack of high grade evidence for therapeutic interventions, could explain perioperative clinicians' hesitance towards adopting MINS as a significant perioperative event.[8] However, it is clear that MINS is associated with a significant public health burden associated with mortality and significant morbidity.[5]

Cardiac biomarkers utilised for the diagnosis of myocardial infarction require pre-defined reference limits. These limits or cut-off values are derived from healthy individuals.[9–11] With technological advances, the sensitivity of more recent generations of cTnT has increased.[11,12] For the first time, the 99th percentile, or upper reference of normal, can be determined in reference populations by using the latest 5th generation high sensitivity cardiac troponin T (hs-cTnT) test.[12] Only the latest hs-cTnT test satisfies the current guidelines' suggestion that the upper reference limit should be calculated as the 99th percentile from a reference population with a coefficient of variation (CV) of 10% or less.[7,12] This 99th percentile has been calculated by various studies and found to be approximately 14 ng/L.[11,12] While this has increased the sensitivity of the test remarkably, it has done so at the cost of specificity.[11] In terms of the diagnosis of acute myocardial infarction in medical patients, the sensitivity has increased to nearly 100%, almost eliminating false negatives. In terms of perioperative troponin surveillance, the increased sensitivity added complexity to the interpretation thereof. The VISION study utilised the previous 4th generation cTnT test.[4] Various statistical models were tested, but MINS was finally defined as an isolated 4th generation cTnT of 30 ng/L (0.03 μg/mL) or more that was due to myocardial ischaemia.[5] Troponin elevation predicted 30-day mortality independently. Correlations between the 4th- and 5th generation cTnT test do exist. While a 4th generation cTnT level of 30 ng/L correlates with a 5th generation cTnT (hs-cTnT) level of approximately 53 ng/L, another study suggests that the 95th percentile of perioperative patients were 33 ng/L (95% CI: 26–49) for hs-cTnT.[13,14] The latter study was a sub-study from the VISION Bio-Bank. The cumulative proportion of patients with a 4th generation cTnT above 30 ng/L were 9%, while those with a hs-cTnT > 33 ng/L matched that of the 4th generation cTnT (7 – 10%).

Troponin elevation can also be caused by non-ischaemic causes. Carbon monoxide poisoning, renal failure, heart failure, acute pericarditis, acute exacerbation of chronic obstructive airway disease, chemotherapy-related myocardial damage, pulmonary arterial hypertension, pulmonary embolism, sepsis, stroke and subarachnoid haemorrhage can all result in cTnT elevations.[15–26] Not all of these elevations appear to impact prognosis consistently, especially in non-surgical patients. In the perioperative milieu, however, cTnT elevation appears to be much more robust at predicting outcome, and is independently associated with both vascular and non-vascular causes of mortality.[5,27] Pre-operative hs-cTnT elevation, as well as an absolute rise of greater than 9 ng/L hs-cTnT had significant short- and long term effect on perioperative mortality.[28]

In terms of MINS, investigators in South Africa have only published data on a single vascular surgical cohort.[29–31] These reports also concluded that locally derived prognostic markers would probably be more appropriate in risk stratifying the South African surgical population. Since the prevalence of MINS in the non-cardiac, elective, elevated risk surgical population has not yet been established, it could provide a unique insight into South African surgical patients and their potential postoperative outcomes.

Hypothesis

The prevalence of MINS in elective, non-cardiac, elevated risk surgical patients is not well established in South Africa. Because of the different patient characteristics and risk profiles, extrapolation of the prevalence of MINS in South African surgical patients from international data is undesirable, and is the principle indication for this study. The null hypothesis for this study was that the prevalence of MINS would be similar in our South African study population to other peer-reviewed international publications.

The primary objective of this study was to determine the prevalence of myocardial injury after non-cardiac surgery in the elective, elevated risk surgical population.

Methods

Study Design

This was a prospective, single centre, observational study investigating the prevalence of myocardial injury after non-cardiac surgery at Groote Schuur Hospital. After approval from the Human Research Ethics Committee of the University of Cape Town, data collection followed informed patient consent, and convenience sampling from 2014 to 2016. To conform to international standards, a Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was followed and completed.[32]

Statistical analysis was done using Minitab 17 Statistical Software.[33] Continuous variables were described using sample mean and standard deviation (SD) and categorical variables using sample median and interquartile range (IQR). Where statistical comparisons were made between continuous variables, the unpaired t-test was used, while categorical data were compared using the X^2 test, or the X^2 test with Yates's correction, as appropriate.

Patient Population

Patients ≥ 45 years of age, presenting for elective, elevated risk, non-cardiac surgery were eligible. Elevated risk surgery was defined as all surgery with a predicted risk of MACE of greater than 1%.[2] These include all intra-abdominal-, non-cardiac thoracic-, joint replacement-, major orthopaedic- and vascular surgery.

Investigation

Enrolled patients were investigated for myocardial injury after non-cardiac surgery (MINS), defined by an elevated post-operative high sensitivity cardiac troponin T suspected to be due to myocardial ischaemia, and no other known non-ischaemic causes of troponin elevation.

Sampling protocol and procedure

Theatre lists were interrogated and patients were identified with appropriate inclusion criteria. Patients were selected by means of convenience sampling. Post-operative informed consent was taken and blood samples were collected within 24 to 72 hours of surgery. The majority of patients (91%) were sampled once within 24 hours. In some patients a second sample was taken within 72 hours. In patients with two samples, the highest troponin elevation was recorded. Specimens were analysed using *Troponin T hs (high sensitive)* immunoassay from Roche Diagnostics (Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim, Germany).

Exclusion Criteria

Exclusion criteria included emergency surgery, recent myocardial infarction or pulmonary embolism, renal dysfunction and sepsis as judged by the attending anaesthetist and pre-existing hypotension. Low risk surgery, such as ophthalmic- and superficial plastic surgery were also excluded. As sampling only commenced after surgery, we could not exclude pre-existing cTnT elevation. Therefore, myocardial infarction, pulmonary embolism, sepsis and renal dysfunction were exclusions because of their direct or indirect influence on measured postoperative cTnT. Renal impairment was defined using international guidelines.[34,35]

Outcomes

The primary outcome was the prevalence of MINS, defined as an elevated high sensitivity cTnT of above 33 ng/L.

Secondary outcomes were to investigate risk factors such as patient demographics, surgical categories and co-morbidities associated with MINS.

Sample Size

Based on previous studies, a prevalence of MINS of 10% to 15% was estimated for the study population in question. Statistical calculation revealed a required sample size of 219 to 266 for a narrow confidence interval width of 10%. A sample size of 300 was targeted.

Results

Approximately 1100 patients were screened of which 301 were eligible. After exclusions, 244 patients were included in the study. The flow diagram of patient recruitment is shown in figure 1.

Insert figure 1

The patient characteristics, surgical categories and comorbidities are shown in tables 1 to 3. The majority of patients were in the younger age category, from the ages of 45 to 65 years. General- and gynaecological surgery were the most common surgeries performed, which might explain the increased proportion of female participants. Hypertension and malignancy were the most frequently recorded comorbidities.

Insert table 1

Insert table 2

Insert table 3

The hs-cTnT results are reported in table 4.

Insert table 4

The prevalence of the primary outcome was 4.9% (95% CI 2.2 – 7.6). Because of the relative small sample size of the study and the lower than expected event rate, a multivariate regression analysis could not be performed to investigate associations between patient- or surgical risk factors and MINS.

Discussion

The majority of our patients were in the younger age category of 45 to 64 years with significantly reduced proportions in the older categories as opposed to VISION that had 50% of patients in the >=65-year category. Although hypertension and malignancy were also the most prevalent co-morbidities, a larger proportion of patients suffered from ischaemic heart disease in the VISION cohort (X^2 with Yate's correction comparison p=0.026). Gynaecological surgery was significantly more common in our study (X^2 with Yate's correction comparison p<0.001).

The main finding of this study was that the prevalence of MINS in the elective, elevated risk surgical population in South Africa was comparable to reports from large, international studies.

Three different event rates are reported (Table 4). A 4th generation cTnT of equal to or greater than 0.03 ng/mL defines MINS.[5] Debate around specific correlating values between the 4th- and newer 5th generation cTnT test, have led to this study regarding elevations of greater than 33 ng/L of hs-cTnT being diagnostic of MINS. The primary outcome of the prevalence of MINS was therefore 4.9% (95% CI 2.2 – 7.6). VISION found a prevalence of MINS of 8.0% (95% CI, 7.5–8.4), which is not statistically different from our findings (X^2 with Yate's correction comparison p=0.078). VISION included more than 15000 patients. This is an important finding, as when compared to VISION, as we only included elective surgical patients with a lower cardiovascular risk profile, yet the prevalence of MINS in our cohort is similar to that in VISION. This has important public health implications for South Africa, because of the major morbidity and mortality associated with MINS.

Furthermore, our findings suggest that the current international cardiovascular risk prediction models may be inappropriate for South African patients, and/ or they may be incorrectly calibrated, resulting in an underestimation of cardiovascular risk in South African surgical patients. Indeed, recent literature suggests that utilising the revised cardiac risk index (RCRI) in South African patients may be inappropriate, especially in vascular surgery.[31] Another confounder might be the human immunodeficiency virus (HIV) epidemic in Southern Africa, where HIV-positive patients had less traditional cardiovascular risk factors, but a similar perioperative morbidity and mortality when compared to HIV-negative patients undergoing vascular surgery.[29] The development of an appropriate (and well calibrated) perioperative cardiovascular risk prediction model is necessary in South Africa.

Study Strengths and Weaknesses

A strength of this study is the prospective screening of a specific population group (non-cardiac surgery patients) for whom previously there was no published data of the prevalence of MINS. Since the South African population still lacks population-specific prognostic values for cTnT, this study could form an initial contribution to future, larger studies, and provides important data necessary to power these studies.

Despite screening over 1100 patients, the sample size of this study remains relatively small, with wide confidence intervals. This is a potential weakness, however, this was to ensure that

through the exclusion criteria, this study attempted to reduce the number of confounders of postoperative cTnT elevation (which may not have been secondary to myocardial ischaemia). We believe the estimate of the prevalence of MINS in this study is therefore robust. Since the prevalence of MINS was only 5%, the current study appears to be underpowered. However, it is possible that the prevalence may even be higher than reported here as we excluded some patients at high risk of cardiovascular complications, because they had comorbidities which may be associated with non-ischaemic cTnT release and we would not be able to confidently ascribe troponin elevation to MINS in these patients. A further limitation was the lack of a preoperative cTnT screen. It is possible that some of the patients may have been troponin positive preoperatively. The fact that the majority of patients were only subject to a single cTnT investigation also introduced another limitation. Most of the international studies provides more than 2 days of postoperative troponin surveillance.[4,28] Since troponin elevation occurs within the first 3 days following surgery, this limitation could also have reduced our event rate further, and result in our reduced perceived prevalence.[6]

Conclusion

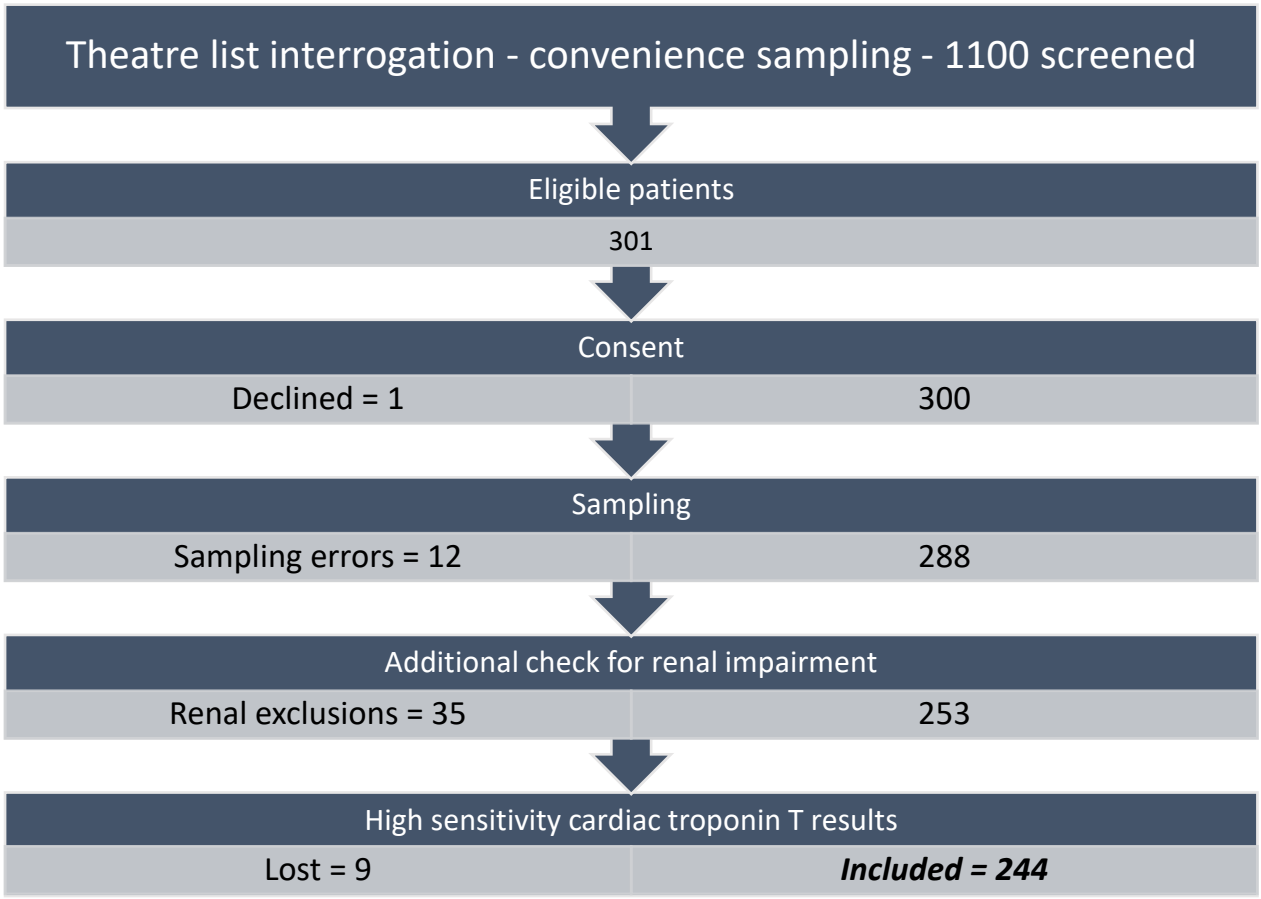
Since the prevalence of MINS in South Africa appear to be similar to that found in international studies, its strong association with perioperative mortality and major morbidity suggests significant implications for public health outcomes in South Africa. Furthermore, elective surgery has been associated with a higher mortality in South Africa compared to international cohorts, despite similar risk profiles. Therefore, there is a need to address the calibration of cardiovascular risk models in South Africa, and/or the development of South African cardiovascular risk prediction models, so patients at risk can be identified early for both primary and secondary prevention. International guidelines promote the utility of troponin surveillance, and a recent study found troponin surveillance to be financially viable in South Africa.[36] Our data suggest that postoperative troponin surveillance is necessary in elevated-risk non-cardiac surgical patients.

Funding and Conflicts of Interest

No funding was required for this study and the authors declared no conflicts of interest.

Figures

Figure 1: Flow diagram of patient recruitment



Tables

Table 1. Patient demographics

Included patients (n)	244
Male (%)	43
Female (%)	57
Age (mean, years) (SD)	60.5 (9.4)
Age 45-64 (%; 95% CI)	68.9 (63.0-74.7)
Age 65-75 (%; 95% CI)	23.8 (18.4-29.1)
Age >75 (%; 95% CI)	6.6 (3.5-9.7)

SD standard deviation; CI confidence interval

Table 2. Surgical categories

General; n (%)	63 (25.8)
Gynaecological; n (%)	52 (21.3)
Orthopaedic; n (%)	40 (16.4)
Urological; n (%)	27 (11.1)
Vascular; n (%)	18 (7.4)
Otolaryngological; n (%)	16 (6.6)
Thoracic; n (%)	9 (3.7)
Neurological; n (%)	3 (1.2)

Table 3. Patient comorbidities

Median number of comorbidities (IQR)	1 (1-2)
Hypertension; n (%)	161 (66.0)
Malignancy; n (%)	78 (32.0)
Smoking; n (%)	69 (28.3)
Diabetes Mellitus; n (%)	50 (20.5)
Hypercholesterolemia; n (%)	47 (19.3)
Previous myocardial infarction; n (%)	20 (8.2)
Previous stroke; n (%)	15 (6.1)
Previous heart failure; n (%)	6 (2.5)

IQR interquartile range

Table 4. High Sensitivity Cardiac Troponin T results at Groote Schuur Hospital

cTnT undetectable; n (%)	42 (17.2)
cTnT median (IQR)	7 ng/L (4 – 14)
cTnT median >30 ng/L (IQR)	60 ng/L (37 – 83)
cTnT > 99th percentile* (number, proportion)	55, 22.5%; 95% CI 17.3 – 27.8
cTnT > 33 ng/L† (number, proportion)	12, 4.9%; 95% CI 2.2 – 7.6
cTnT > 53 ng/L (number, proportion)	7, 2.9%; 95% CI 0.8 – 5.0

* above 13 ng/L; † primary outcome definition; IQR interquartile range

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