

# Myocardial injury after non-cardiac surgery: Time to shed the ignorance

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Perioperative cardiovascular complications are common and place a significant burden on public healthcare systems. A large proportion of such complications are due to a new clinical entity, i.e. myocardial injury after non-cardiac surgery (MINS). It is important to understand MINS, its prognosis and management in the perioperative period. A literature review of MINS was done. MINS is defined as an elevated postoperative cardiac troponin level that was considered as resulting from myocardial ischaemia without evidence of a non-ischaemic cause for the troponin elevation. The perioperative milieu (surgical stress response, sympathetic activation, hypercoagulability, hypotension, bleeding, anaemia and pain) contributes to the pathophysiology of a relative myocardial hypoperfusion and ischaemia, which differentiates MINS from myocardial infarction in non-surgical patients. Globally, >7% of adults ≥45 years of age suffer MINS, with South African (SA) studies confirming similar event rates. More than 80% of MINS patients are asymptomatic for myocardial ischaemia, and therefore would not fulfil the universal definition of myocardial infarction, despite having a similar prognosis to those with the latter condition. Accurate diagnosis of MINS therefore relies on routine daily postoperative cardiac troponin surveillance for 48 - 72 hours postoperatively in patients with a >5% risk of major perioperative cardiovascular complications. This approach is cost-effective in SA. One in 10 patients with MINS dies within 30 days of surgery, and 1 in 5 develops major cardiovascular complications. Short- and long-term mortality could be improved by simple treatment strategies, including cardiovascular therapy intensification, and by ensuring aspirin use and statin therapy. All recommendations promote the involvement of a multidisciplinary team. MINS is a common, serious perioperative cardiovascular complication with public healthcare implications that has been underappreciated in SA. A multidisciplinary approach with simple treatment strategies should be adopted.

*S Afr Med J* 2018;108(6):464-467. DOI:10.7196/SAMJ.2018.v108i6.13346

## Case vignette

A clinical entry, after specialist referral of a patient who experienced a postoperative troponin elevation, reads as follows: 'Thank you for the referral. Reason for referral: postoperative troponin elevation following total hip replacement. According to the history, the patient was asymptomatic and comfortable in the ward. No ischaemic symptoms or electrocardiogram [ECG] changes noted. Vital signs were within normal limits. Assessment: isolated troponin elevation, expected in this patient population and not clinically significant. Recommendation: review patient for symptoms, no specific therapy required.'

After an uneventful hospital stay, the patient was discharged on the 4th postoperative day, but died 5 days later at home.

The global surgical volume has increased to >300 million procedures per annum.<sup>[1]</sup> Cardiovascular complications contribute to one-third of major perioperative morbidity and mortality, with perioperative myocardial infarction and myocardial injury after non-cardiac surgery (MINS) accounting for 39% of all deaths within 30 days of non-cardiac surgery.<sup>[2]</sup> These deaths are distributed equally between patients who sustain a postoperative myocardial infarction and MINS.<sup>[2]</sup> The burden of perioperative cardiovascular complications, therefore, has a major public health importance. The paucity of clinicians with an appreciation of the importance of perioperative myocardial injuries and the associated prognosis, and the knowledge necessary to manage this public healthcare burden, needs to be addressed.<sup>[3]</sup>

## Methods

A literature search on MINS in the perioperative period was conducted using MEDLINE and the following search terms: 'myocardial injury',

'noncardiac surgery', 'mortality', 'perioperative complications', 'treatment', 'prevention' and 'guidelines'. Additional reports were obtained by reviewing reference lists from the literature. Studies involving large cohorts with clear inclusion criteria and outcome data were reviewed. Reviews and smaller studies with local significance were also included.

## MINS

MINS occurs when myocardial ischaemia-related cellular damage occurs in the perioperative period. It has been defined as an elevated cardiac troponin T (cTnT) level that was considered as resulting from myocardial ischaemia without evidence of a non-ischaemic cause of cTnT elevation (Table 1).<sup>[4]</sup> The pathophysiology of MINS in surgical patients differs from that of myocardial infarction in medical (non-surgical) patients.<sup>[5]</sup> Surgical patients are exposed to a unique environment that includes sympathetic activation, bleeding, anaemia, pain, hypotension and hypercoagulability during the perioperative period. Another distinctive clinical feature of MINS is that it most commonly presents within the first 3 postoperative days, strengthening its association with the early postoperative pathophysiological environment, in contrast to postoperative atherosclerotic plaque rupture that tends to occur more randomly during the weeks after surgery, and more closely resembles a traditional medical (non-surgical) myocardial infarction.<sup>[5]</sup>

## Incidence of MINS

International data estimate that >100 million adults ≥45 years of age undergo non-cardiac surgery per annum.<sup>[2]</sup> In the recent Vascular Events In Non-cardiac Surgery Patients Cohort Evaluation (VISION)

study non-cardiac surgical patients were studied for perioperative complications.<sup>[6]</sup> More than 40 000 patients were enrolled, of whom 7% experienced MINS.<sup>[4,7]</sup> MINS is therefore a common perioperative complication, especially when one considers the non-selective nature of the VISION study's inclusion criteria:  $\geq 45$  years of age and the need to spend a night in hospital following surgery, thereby providing a representative sample of perioperative outcomes in unselected surgical patients. Therefore, about 1 in 14 in-hospital patients  $\geq 45$  years old, who undergo non-cardiac surgery, will experience MINS as a perioperative complication. Factors that increase the risk for experiencing MINS occur commonly in our surgical population. These include increasing age, patients with known cardiovascular disease or known risk factors for cardiovascular disease, and operations associated with an elevated risk (typically intermediate and major surgical severity, and all non-elective surgery) (Table 2).<sup>[4]</sup>

### Clinical presentation of MINS in the postoperative period

To diagnose medical (non-surgical) myocardial infarction, the diagnostic criteria require documented elevated cardiac biomarkers and features of ischaemia (clinical, electrocardiographic or imaging).<sup>[8]</sup> Current studies employ cTnT, as it is universally standardised.<sup>[9]</sup> In contrast to medical myocardial infarction, clinical features of ischaemia are notoriously absent in surgical patients. Therefore, the diagnosis of MINS hinges on perioperative troponin elevation, and the exclusion of known non-ischaemic causes of perioperative troponin elevation, e.g. sepsis and pulmonary embolism.<sup>[4]</sup> More than 93% of patients who experienced MINS, did not fulfil the diagnostic criteria for the

universal definition of myocardial infarction; only 7% presented with ischaemic symptoms and 15% had nonspecific ECG changes.<sup>[4,7]</sup>

The majority of troponin elevations occur within 48 hours of surgery, and the patient's prognosis is positively correlated with the peak troponin level.<sup>[4,7]</sup> Studies of the high-sensitivity cTnT (hs-cTnT) test found that a small absolute increase in hs-cTnT from the preoperative to the postoperative period has prognostic use (Table 1).<sup>[7]</sup> Furthermore, observational data have shown that ~50% of patients demonstrate an early 24-hour postoperative window, where the troponin levels remain low before a subsequent rise in these levels, highlighting the need for serial troponin surveillance in the postoperative period.<sup>[10]</sup> As most of the prognostically significant troponin elevations occur asymptotically, it is inappropriate to depend on ECG changes or ischaemic symptomatology to alert a clinician to MINS, as this will result in the majority (>80%) of diagnoses being missed.<sup>[4]</sup>

### Cardiac troponin T thresholds should be considered according to clinical context

The diagnostic troponin thresholds for MINS differ from those used to diagnose medical patients with myocardial infarction.<sup>[4,7,8]</sup> Before cardiac biomarkers are used in clinical practice, their diagnostic thresholds need to be determined by investigating specific reference populations.<sup>[8]</sup> The clinical environment of surgical and medical patients differs, which influences the sensitivity and specificity of these tests for specific outcomes and therefore requires population-specific investigation.<sup>[9]</sup> The literature investigating different troponin assays in perioperative patients has provided assay-specific troponin levels that are of prognostic relevance in the surgical patient (i.e. independently associated with 30-day mortality),<sup>[4,7]</sup> but may not be typically associated with an adverse prognosis in the non-surgical patient (Table 1).

### Prognosis of surgical patients with MINS

MINS has a 30-day mortality of 10%.<sup>[4]</sup> One in 10 patients with MINS dies, and 1 in 5 patients suffers a major cardiovascular complication (congestive cardiac failure, non-fatal cardiac arrest and stroke) within 30 days of surgery.<sup>[4]</sup> Various investigators have reported similar outcomes, as demonstrated by two meta-analyses independently associating postoperative troponin elevation with long- and short-term mortality.<sup>[3]</sup> A recent study found that the incidence of MINS in a South African (SA) patient population was comparable with those of large international cohorts.<sup>[11]</sup> The 1 500 SA patients included in the VISION cohort also suggested findings that could be compared with those of other international cohorts, and showed no evidence of differences between clusters.<sup>[6,7]</sup> It is therefore reasonable to assume that the SA patient population has a similar risk for MINS and outcomes after MINS to that in the literature.

Patients who develop MINS postoperatively, have prognostic risk factors independently associated with 30-day mortality (Table 3).<sup>[4]</sup> A point system allows for prediction of the risk of 30-day mortality:

**Table 1. MINS diagnostic criteria and hs-cTnT thresholds independently associated with 30-day mortality<sup>[7]</sup>**

MINS diagnostic criteria (only one required)		
Any peak hs-cTnT $\geq 65$ ng/L		
An absolute increase in hs-cTnT of 5 ng/L, with peak cTnT 20 - 64 ng/L		
hs-cTnT thresholds associated with 30-day mortality		
hs-cTnT, ng/L	Adjusted hazard ratio (95% CI)*	30-day mortality, %
14 - <20	9.1 (3.8 - 22.1)	1.1
20 - <65	23.6 (10.3 - 54.1)	3.0
65 - <1 000	70.3 (30.6 - 161.7)	9.1
$\geq 1$ 000	227.0 (87.4 - 589.9)	29.6

MINS = myocardial injury after non-cardiac surgery; hs-cTnT = high-sensitivity cardiac troponin T; CI = confidence interval.  
\*All  $p < 0.001$ .

**Table 2. Perioperative risk factors for the development of MINS<sup>[4]</sup>**

Risk factor
Increasing age
Current atrial fibrillation
Diabetes
Hypertension
Congestive heart failure
Coronary artery disease
Peripheral vascular disease
Stroke
Decreasing renal function
Urgent or emergency surgery

MINS = myocardial injury after non-cardiac surgery.

**Table 3. Independent predictors of 30-day mortality in patients who experience MINS<sup>[4]</sup>**

Independent predictors	Adjusted odds ratio (95% CI)*
Age $\geq 75$ years	2.06 (1.33 - 3.37)
ST elevation or new LBBB	3.96 (1.54 - 9.14)
Anterior ischaemic changes on ECG	2.33 (1.42 - 3.70)

MINS = myocardial injury after non-cardiac surgery; LBBB = left bundle branch block; ECG = electrocardiogram; CI = confidence interval.  
\*All  $p < 0.01$ .

0 points (5%), 1 point (10%), 2 points (20%), 3 points (30%) and 4 points (50%).<sup>[4]</sup> The cTnT diagnostic thresholds required for MINS, along with the 30-day prognostic impact, are shown in Table 1. The prognostically significant impact of MINS in the perioperative period is thus clear and therefore demands that clinicians understand the clinical entity of MINS and its associated diagnostic criteria, prognosis, prognostic markers and the need for active therapeutic intervention. The consultation example shown in the introduction of this article can therefore no longer be accepted.

### Proposed management of MINS

The most recently published perioperative cardiovascular guidelines propose postoperative troponin surveillance for patients who have a >5% risk of a perioperative major adverse cardiovascular event. The following criteria apply: (i) any patient ≥65 years of age; (ii) patients between 45 and 64 years of age with a revised cardiac risk index (RCRI) of ≥1; or (iii) any patient with an elevated preoperative natriuretic peptide (including brain natriuretic peptide or N-terminal probrain natriuretic peptide).<sup>[12]</sup> The recent Canadian guidelines on cTnT surveillance and RCRI score are summarised in Table 4. As complications are common in the first week after MINS, we would advocate early intervention.<sup>[13]</sup> Evidence from randomised controlled trials is lacking, but we expect this to change over the next few years.<sup>[3]</sup> The Management of Myocardial Injury After Noncardiac Surgery Trial (MANAGE) (clinicaltrials.gov/ct2/show/NCT01661101) results are currently in press, but initial reports indicate improved primary endpoints. MANAGE evaluated the impact of anticoagulation on perioperative vascular complications after MINS. The final results will provide more insight into therapeutic options.

Current observational data suggest that simple therapeutic measures could improve outcomes once MINS occurs. The literature supports the use of postoperative aspirin administration and statin therapy to reduce 30-day mortality after MINS.<sup>[14]</sup> Furthermore, intensification of therapy (defined as introducing or increasing any of the following cardiovascular drug groups: antiplatelet agents, beta-blockers, statins or angiotensin converting enzyme inhibitors) during the postoperative period has been shown to be associated with an improved 1-year survival.<sup>[15]</sup> However, deciding on a specific therapy should be part of a multidisciplinary approach. The potential benefits of therapies should be

weighed against potential risks on an individual basis. After initiation of treatment intensification, surveillance for additional prognostic information should continue (Table 3).<sup>[4]</sup> Increased postoperative monitoring (i.e. continuous invasive haemodynamic monitoring and a high-care facility) and optimised myocardial oxygen balance (i.e. haemodynamic support, correction of anaemia and electrolyte disturbances) could be of additional benefit, but is currently only supported by recommendations.<sup>[13]</sup> A pharmacoeconomic study showed that troponin surveillance in the SA context should be cost-effective for all patients ≥45 years of age who undergo non-cardiac surgery, but only when combined with active intervention once MINS is diagnosed.<sup>[16]</sup>

An adapted proposed algorithm for MINS management is depicted in Fig. 1.

### Conclusion

MINS commonly occurs in non-cardiac surgical patients ≥ 45 years of age. Ten percent of patients who experience MINS die within 30 days of surgery. MINS can be easily diagnosed if routine, postoperative hs-cTnT surveillance is conducted, as recommended by current international guidelines, and it is likely to be cost-effective in SA. Once MINS is diagnosed, institution of simple therapies may improve outcome. Large studies are expected to provide more therapeutic insight in the near future. Screening and treatment of MINS need to be incorporated into routine postoperative surgical management.

**Table 4. Postoperative troponin surveillance recommendations from the Canadian Cardiovascular Society Guidelines<sup>[12,17]</sup>**

Daily postoperative cTnT surveillance for 48 - 72 hours if baseline risk >5% for cardiovascular death or non-fatal myocardial infarction at 30 days after surgery, including: <sup>[12]</sup>
Elevated preoperative NT-proBNP or BNP measurement
RCRI score ≥1*
Age 45 - 64 years, with significant cardiovascular disease*
Age ≥65 years*
RCRI <sup>[17]</sup>
High-risk-type surgery (intra-abdominal, intrathoracic or supra-inguinal vascular)
Ischaemic heart disease
History of congestive heart failure
History of cerebrovascular disease
Insulin therapy for diabetes
Preoperative serum creatinine >2.0 mg/dL (177 μmol/L)
<small>RCRI = revised cardiac risk index; NT-proBNP = N-terminal probrain natriuretic peptide; BNP = brain natriuretic peptide; cTnT = cardiac troponin T; CI = confidence interval.</small>
<small>*If preoperative NT-proBNP or BNP not available.</small>

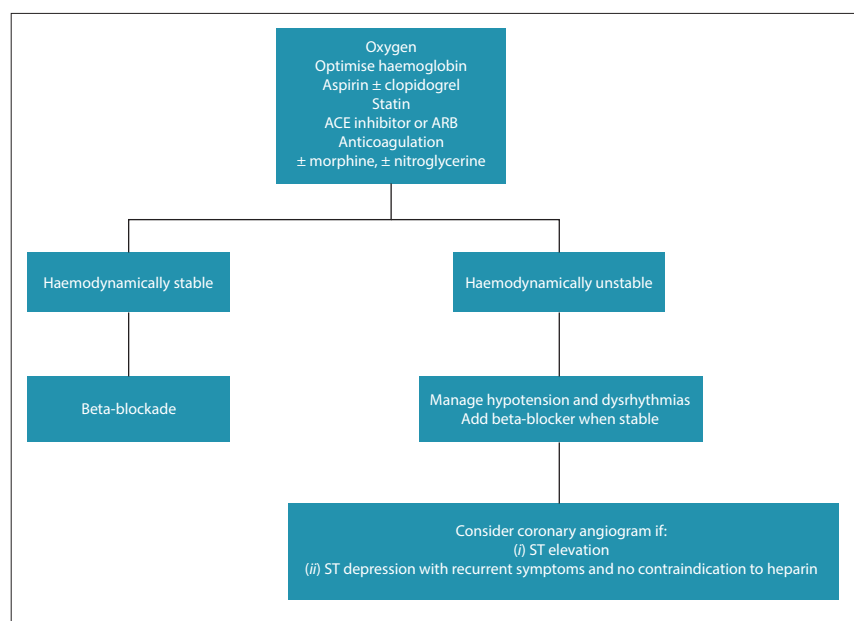


Fig. 1. Proposed algorithm for the management of patients with MINS. (Adapted from Biccari.<sup>[18]</sup> MINS = myocardial injury after non-cardiac surgery; ACE inhibitor = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker.)

**Acknowledgement.** None.

**Author contributions.** The draft article was produced by EC and all subsequent versions were edited and proofread by BMB and EC.

**Funding.** None.

**Conflicts of interest.** None.

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Accepted 3 April 2018.