

A review of the epidemiology, prevention, prognosis and treatment of a “silent killer”

Prevention, epidemiology, and prognosis of perioperative myocardial injury

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Summary

Annually over 200 million adults undergo noncardiac surgery worldwide. Myocardial ischaemia is a frequent cause of perioperative cardiac morbidity and mortality. Approximately 8 million patients will suffer a myocardial injury after noncardiac surgery (MINS) each year. MINS is defined as a prognostically important myocardial injury due to ischaemia that occurs during, or within 30 days after, noncardiac surgery. The diagnostic criterion for MINS is an elevated troponin measurement resulting from myocardial ischaemia. MINS is a strong, independent predictor of 30-day and 1-year mortality. The majority of patients suffering MINS would go undetected without troponin monitoring since >80% of these patients do not experience ischaemic symptoms. Intensification of pharmacotherapy may reduce 30-day mortality in patients who have experienced MINS. This paper will review the epidemiology, prevention, prognosis and treatment of MINS.

Key words: perioperative medicine; cardiovascular events; myocardial ischaemia; myocardial infarction; troponin elevation; myocardial injury after noncardiac surgery; noncardiac surgery; epidemiology; prevention; prognosis; treatment; perioperative management; perioperative care

Epidemiology

Worldwide over 200 million adults undergo noncardiac surgery annually [1, 2]. Conservative estimates suggest that at least 100 million adults undergoing noncardiac surgery are in an at-risk age group for major perioperative vascular events [3]. Approximately 8 million of these patients will suffer a myocardial injury after noncardiac surgery (MINS) [4] and, as a result, over 1 million adults will die within 30 days of noncardiac surgery worldwide annually [1, 2]. The magnitude of this problem is predicted to increase owing in part to an aging population, a rise in the incidence of cardiovascular related problems, and a trend toward surgical intervention in elderly patients.

Myocardial infarction (MI) is defined in the Third Universal Definition of Myocardial Infarction, an expert

consensus document by the global Myocardial Infarction Task Force [5] (table 1). While MI is the cardiac endpoint in many perioperative studies, it is important to differentiate MINS from MI as a multitude of factors limit the ability to diagnose an MI in the perioperative period (table 1).

Typically, postoperative patients receive some form of analgesia. This is often an opioid or similar agent, which can effectively mask chest pain from myocardial ischaemia [6]. Furthermore, patients who are sedated or intubated postoperatively are unable to effectively communicate and thus perioperative ischaemia may be overlooked. The majority of troponin measurements and ECGs are ordered on the basis of ischaemic symptoms [7], therefore acute perioperative MI or MINS may be missed in patients receiving analgesia or in patients whose communication is impaired.

Based on the VISION Study (a prospective, international, cohort study involving 40 000 patients, ≥45 years of age having noncardiac surgery), the majority of patients (87%) with MINS experienced the ischaemic

Table 1: Definition of myocardial infarction (MI) and myocardial injury after noncardiac surgery (MINS).

MI	Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and with at least one of the following: <ul style="list-style-type: none"> – Symptoms of ischaemia – New or presumed new significant ST-segment–T wave changes or new left bundle-branch block – Development of pathological Q waves in the ECG – Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality – Identification of an intracoronary thrombus by angiography or autopsy [5].
MINS	A prognostically relevant myocardial injury due to ischaemia. <ul style="list-style-type: none"> – The diagnostic criterion for MINS is troponin T ≥0.03 ng/ml due to an ischaemic aetiology within 30 days of noncardiac surgery. – Ischaemic ECG changes are not required. – Ischaemic cardiac symptoms are not required [4].

Based on a lecture at the Congress of the Swiss Society of Cardiology 2015.

injury within the first 3 days after surgery [4]. A mere 15.8% of patients who developed MINS experienced ischaemic cardiac symptoms [4]. Therefore, without postoperative troponin monitoring, 84.2% of MINS events would go undetected [4]. Furthermore, in VISION, all patients with an elevated troponin measurement had an ECG. Only 34.9% of patients had ischaemic ECG changes and a minority (41.8%) of patients suffering MINS fulfilled the universal definition of MI (fig. 1) [4].

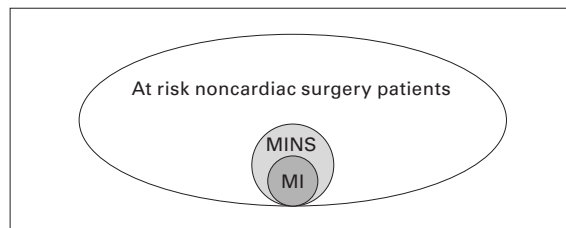


Figure 1: At least 100 million patients undergoing noncardiac surgery are at risk for perioperative vascular complications annually. Nearly 10% will suffer from MINS. Of patients with MINS, only 41.8% fulfill the diagnostic criteria for MI [4]. MINS: myocardial injury after noncardiac surgery; MI: myocardial infarction. Adapted from [7], reprint with permission.

In the POISE Trial (an international β -blocker trial of 8351 patients who underwent noncardiac surgery), only 34.7% of patients with perioperative MI experienced symptoms of ischaemia [8]. Therefore, the absence of reported ischaemic cardiac symptoms and imperfect timing of the ECG (e.g., ECG performed in response to a detected elevated troponin on routine screening but after the acute ischaemic event) may result in a missed diagnosis of perioperative MI or MINS [7].

Historical perspective

In 1967, JAMA published the VA Hypertension Trial in which US veterans with diastolic blood pressure of

115–129 mm Hg were randomised to antihypertensive drugs or placebo [9]. The follow-up period was 18 months. At the time, many experts believed that hypertension was essential for brain perfusion. The primary outcome included death, dissecting/ruptured aortic aneurysm, cerebral haemorrhage / disabling stroke, MI, congestive heart failure (CHF), retinal haemorrhage, papilloedema and rapidly progressive renal failure [9]. Thirty-nine percent of the placebo group versus three percent of the antihypertensive group experienced the primary outcome. The relative risk reduction for antihypertensive drugs was 93%, $p = 0.00000003$ [9].

Historically, physicians did not believe that non-valvular atrial fibrillation was a risk factor for stroke, but rather simply a nuisance for patients who experienced palpitations [10, 11]. Currently, it is recognised that both valvular and nonvalvular atrial fibrillation carry a significant risk of embolic stroke.

This historical perspective suggests that physicians can overlook important diagnoses. Evidence suggests that MINS is prognostically important and overlooked by most physicians. This is primarily due to a lack of perioperative troponin monitoring. In addition, the fragmented nature of perioperative follow-up likely facilitates physicians' underappreciation of the impact of MINS.

Prognosis

VISION demonstrated that MINS is not a benign entity and it independently predicts major vascular events and mortality at 30 days (table 2) [4, 12]. Levy et al. performed a systematic review and meta-analysis evaluating the intermediate and long-term prognostic value of troponin and creatinine kinase-MB measurement after noncardiac surgery. The findings demonstrate that an elevated troponin after noncardiac surgery strongly predicts mortality at 1 year [odds ratio (OR) 6.7, 95% confidence interval (CI) 4.1–10.9] [13]. Based on its high prevalence, asymptomatic nature and substantial influence on perioperative mortality, MINS has been classified as a “silent killer” [14].

MINS is associated with an adjusted hazard ratio (HR) of 3.87 (95% CI 2.96–5.08) for 30-day mortality and MINS has the highest population-attributable risk (PAR) (34%) compared with other postoperative complications that predict death at 30 days after surgery (table 3) [4]. The PAR represents the proportion of all deaths potentially attributable to the relevant risk factor (e.g., MINS) if causality was proven [12].

Higher levels of postoperative troponin T elevation correlate with increased risk of mortality. In VISION,

Table 2: Thirty-day risk of major vascular events after suffering a MINS.

Outcomes	Patients without MINS, % (95% CI)	Patients who suffered MINS, % (95% CI)
Nonfatal cardiac arrest	0.06 (0.03–0.12)	0.80 (0.46–1.54)
CHF	1.00 (0.84–1.17)	9.40 (7.85–11.20)
Stroke	0.40 (0.33–0.54)	1.90 (1.29–2.88)
Mortality	1.10 (1.06–1.24)	9.80 (8.24–11.62)
Composite major outcomes*	2.40 (2.11–2.62)	18.80 (16.65–21.07)

CHF: congestive heart failure, CI: confidence intervals, MINS: myocardial injury after noncardiac surgery.

* Composite of major events: composite of mortality, nonfatal cardiac arrest, nonfatal stroke, and nonfatal congestive heart failure. Adapted from [4, 7].

Table 3: Postoperative variables predicting death at 30 days after surgery.

	Incidence (%)	Adjusted HR (95% CI)	PAR (95% CI)
MINS (TnT ≥0.03 ng/ml)	1200 (8.0)	3.87 (2.96–5.08)	34.0 (26.6–41.5)
Sepsis	812 (5.4)	7.18 (5.17–9.97)	30.5 (23.7–37.2)
Stroke	81 (0.5)	3.50 (2.05–5.97)	4.5 (1.3–7.8)
PE	95 (0.6)	6.11 (3.18–11.74)	3.5 (0.9–6.2)

A number of factors contribute to death at 30 days after noncardiac surgery. While sepsis and PE have higher adjusted HR compared to MINS, the PAR for MINS is higher because the incidence of MINS is substantially higher.

HR: hazard ratio, PAR: population-attributable risk, MINS: myocardial injury after noncardiac surgery, TnT: troponin T, PE: pulmonary embolism [4].

the incidence of 30-day mortality was 1.0, 4.0, 9.3 and 16.9% in patients with peak troponin T values of 0.01, 0.02, 0.03–0.29, and ≥0.30 ng/ml, respectively (fig. 2) [12].

Higher levels of postoperative troponin elevation also correlate with lower median days to death. A peak troponin T value of 0.03–0.29 ng/ml was associated with median time to death of 9.0 days [interquartile range (IQR) 3.5–16], whereas the median time to death for a peak troponin T value of ≥0.3 ng/ml was 6.5 days (IQR 1.5–15) [12]. The median time from discharge to death was 11 days (IQR 4–15 days) and 26.6% of the patients who died, did so after hospital discharge [12]. Therefore, MINS may serve as a “red flag” or foreshadowing of a more serious vascular event to follow in the next 30 days and up to 1 year after noncardiac surgery [12, 13].

Pathophysiology of perioperative MI and MINS

The precise pathophysiology of perioperative MI and MINS has not yet been clearly defined. The two predominant theories involve myocardial oxygen supply–demand mismatch [15], and coronary artery thrombosis [1, 16].

Multiple factors may increase myocardial oxygen demand perioperatively including fluid shifts, catecholamine surges, hypotension, anaemia, pain, hypothermia and hypoxia [17]. In coronary arteries with high-grade lesions, the inability to respond adequately to increased myocardial oxygen demand may lead to supply–demand mismatch resulting in myocardial ischaemia [1]. Thus, preexisting coronary artery disease (CAD) is an intuitive culprit. However, in an angiographic study involving vascular surgery patients, the majority of MINS occurred in myocardium supplied by arteries without high-grade stenosis [18]. The landmark CARP Trial (510 patients) demonstrated no reduction in perioperative MI with preoperative revascularisation for coronary stenosis ≥70% [19]. The coronary computed tomographic angiography (CTA) VISION Study performed coronary CTA on 955 patients before noncardiac surgery. This study showed that while the majority (72%) of perioperative MIs occurred in patients with obstructive or extensive-obstructive CAD, 24% and 4% of the perioperative MIs occurred in patients with nonobstructive disease or a normal preoperative CTA, respectively [20].

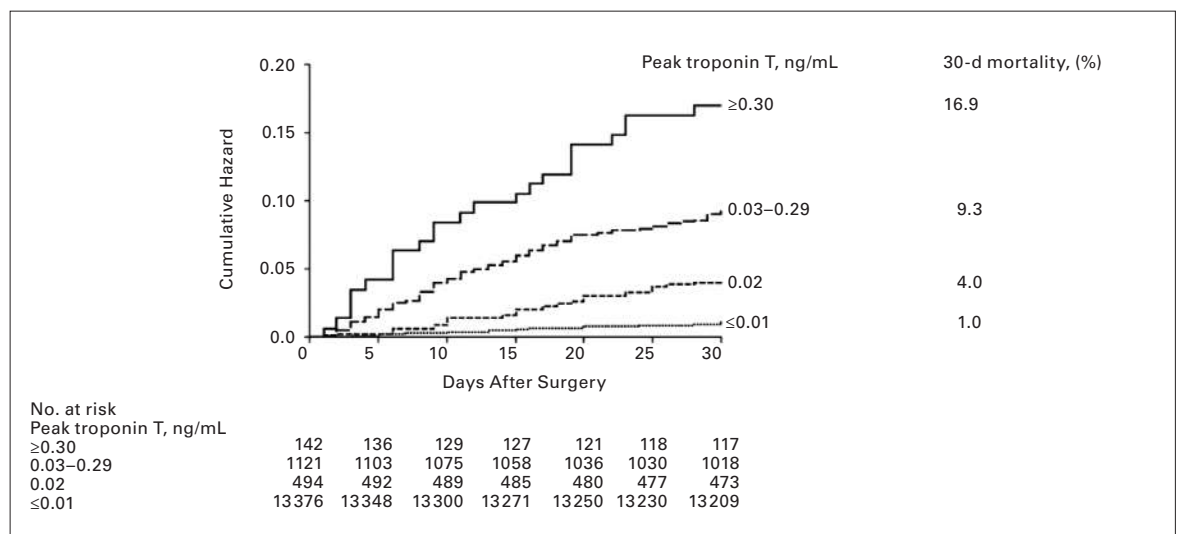


Figure 2: Kaplan-Meier estimates of 30-day mortality based on peak troponin T values. Copyright © 2012 American Medical Association. All rights reserved. Adapted and reprinted, with permission, from : Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators, Devereaux PJ, Chan MT, Alonso-Coello P, Walsh M, Berwanger O, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. JAMA. 2012;307(21):2295–304.

In contrast to CARP, a recent trial randomised 426 patients to preoperative coronary angiography followed by selective percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) versus no preoperative coronary angiogram or revascularisation before elective carotid endarterectomy [21]. This trial demonstrated a reduction in the risk of MI in the group allocated to preoperative coronary angiography ($p = 0.01$). Although this represents encouraging data, there were only six perioperative MIs and thus the results require cautious interpretation because of the fragility of this finding [22].

Evidence also supports coronary artery thrombus as a potential culprit for perioperative MI. Sympathetic activation in the perioperative period promotes a hypercoagulable state by up-regulating platelets and down-grading fibrosis [23–25]. This hypercoagulable state, coupled with increased shear wall stress, may lead to plaque fracture and subsequent thrombus formation [1, 16]. Small autopsy studies in <70 patients who suffered a fatal perioperative MI found intracoronary thrombus in one third of patients [26]. However, given the late timing of autopsy relative to the MI, it is possible that resolution of additional intracoronary thrombus occurred prior to the time of examination [26].

More recently, a study evaluated 120 consecutive patients who suffered a perioperative acute coronary syndrome (PACS) after noncardiac surgery and subsequently underwent coronary angiography [16]. The angiography results of the PACS patients were compared with the angiographic results of a group of 120 patients who suffered a nonoperative ACS (recruited from the emergency room on randomly selected days) and 240 patients with stable CAD (who were recruited prior to angiography on randomly selected days). Angiography in the PACS group showed that 45% of patients had Ambrose's type II lesions (i.e., findings strongly associated with a disrupted plaque) versus 56.7% in the nonoperative ACS group and 16.4% in the stable CAD group ($p < 0.001$) [16]. Both PACS and nonoperative ACS patients had more complex lesions (i.e., intraluminal filling defect, plaque ulceration, plaque irregularity/haziness, or TIMI flow <3) than patients in the stable CAD group (56.7 vs 79.2 vs 31.8%, respectively; $p < 0.001$) [16]. These results suggest that a substantial proportion of patients suffering MINS have angiographic evidence that it was due to a thrombotic event, and that the frequency of these findings is similar to that in patients suffering a nonoperative MI.

It seems probable that both intrinsic and extrinsic factors influence patients' risk of adverse cardiovascular events. It is possible that the underlying mechanism

for MINS may vary among patients with different risk factors. The perioperative period is fraught with a multitude of stressors including increased sympathetic stimulation, hypercoagulability, bleeding, inflammation, hypotension, tachycardia, hypothermia, hypoxia and pain [1, 8]. These stressors, superimposed on preexisting chronic conditions such as renal insufficiency, CAD, peripheral vascular disease, cerebrovascular disease, diabetes, CHF, atrial fibrillation, hypertension, advanced age, male sex [4] and severe aortic stenosis [27], may lead to increased susceptibility to cardiovascular complications. Patients with recent high-risk CAD [4, 28, 29], recent coronary artery stent [28, 29], recent stroke [29], acute trauma (e.g., hip fracture) [30] and the need for urgent or emergency surgery [4] are at particularly high risk of complications including MINS, CHF, nonfatal cardiac arrest, and cardiovascular death [4].

Perioperative prevention of MINS

Clinical risk assessment, noninvasive risk stratification and biomarkers

Accurate preoperative risk assessment serves a number of important purposes for both physicians and patients. Accurate risk estimates provide physicians with guidance for selection of surgical approach and anaesthetic techniques, as well as the location and intensity of postoperative care [31]. For patients, accurate risk assessment may assist with informed decision-making about the appropriateness or timing of the proposed surgery [31]. For example, patients may forgo an operation if they deem the risk of a major perioperative cardiac complication unacceptable, or they may opt to defer the procedure (e.g., to experience an important life event) [31]. MINS is an independent predictor of death [12], and the risk remains elevated up to a year postoperatively [13]. Therefore, in addition to immediate perioperative complications, patients and clinicians should consider the risk implications for the coming year.

Many surgical patients may have occult cardiac disease, but owing to their underlying disease states (e.g., arthritis, cancer, peripheral vascular disease), their activity level may be insufficient to exhibit symptoms [31]. Thus, for patients undergoing major noncardiac surgery, clinical cardiovascular risk assessment tools have only modest predictive power [17]. Noninvasive cardiac testing (e.g., dobutamine echocardiography, dipyridamole myocardial perfusion scan) may provide some additional predictive value beyond clinical variables [32]; however, data are limited and these investigations are costly and time-consuming. Biomarkers, spe-

cifically brain natriuretic peptide (BNP) secreted from ventricular cardiomyocytes, may offer a fast, simple and cost-effective method to enhance preoperative cardiovascular risk assessment [31].

A recent systematic review and meta-analysis of nine observational studies (3281 patients) investigated whether preoperative serum concentrations of BNP (a prohormone) or its inactive cleavage product N-terminal fragment (NT-proBNP) could serve as an independent predictor of adverse cardiovascular outcomes within 30 days of noncardiac surgery [31]. The preoperative BNP measurement was an independent predictor of perioperative cardiovascular events (death, cardiovascular death, or MI) (OR 44.2, 95% CI 7.6–257.0, I^2 51.6%) [31]. These results suggest that an elevated preoperative measurement of BNP or NT-proBNP is a powerful, independent predictor of cardiovascular events in the first 30 days after noncardiac surgery [31]. Given that NT-proBNP is more accurate, efficient and less costly than a preoperative noninvasive cardiac stress test suggests that this biomarker is the preferred preoperative cardiac test.

Evidence-based perioperative pharmacology

Increased sympathetic drive increases a patient's heart rate and hence myocardial demand, which may lead to myocardial oxygen supply–demand mismatch. Moreover, it can also induce a hypercoagulable state [23–25] and catecholamine release that increases shear stress [33]. This may trigger plaque rupture and acute coronary syndromes (ACS) perioperatively [33]. Thus, in an attempt to prevent MINS or major adverse cardiac events (MACE) in the perioperative setting, various agents including β -blockers, α_2 -adrenergic antagonists, statins and aspirin (acetylsalicylic acid, ASA) have been trialed to reduce the sympathetic response [8, 34], stabilise coronary plaque [35] or to inhibit platelet function [8, 36].

Beta-blockers

Beta-blockers were proposed as a potential cardioprotective agent in the perioperative period [37]. A small trial in the 1990s found that β -blockers had a large effect in preventing perioperative MI; however, it had methodological limitations including not performing an intent-to-treat analysis [37]. Two later trials of moderate size with fewer limitations did not show a benefit of perioperative β -blocker use [38, 39]. POISE, a large international randomised controlled trial (RCT), compared metoprolol with placebo initiated on the day of surgery [8]. The results showed decreased MI (HR 0.73, 95% CI 0.60–0.90, $p = 0.002$) but a significantly higher risk of stroke (HR 2.17, 95% CI 1.26–3.74, $p = 0.005$) and

death (HR 1.33, 95% CI 1.03–1.74, $p = 0.002$) [8]. More patients in the metoprolol group experienced clinically important hypotension (HR 1.55, 95% CI 1.38–1.74). Subsequently, a meta-analysis of high-quality trials found that beta-blockade resulted in a 27% relative risk (RR) (95% CI 1.01–1.60, $p = 0.04$) increase in 30-day mortality, increased stroke risk (RR 1.73, 95% CI 1.00–2.99, $p = 0.05$) and hypotension (RR 1.51, 95% CI 1.37–1.67, $p < 0.00001$) [40]. Given the association with increased mortality and stroke, current guidelines no longer recommend initiation of β -blocker therapy in the perioperative period [8, 40–42].

Aspirin

Noncardiac surgery is associated with platelet activation [43]. ASA inhibits thrombus formation and observational data had suggested that discontinuation of ASA prior to surgery would result in increased thrombotic risk [44, 45]. A systematic review and two small RCTs showed mixed results but with a potential decreased risk of vascular events in patients on ASA in the perioperative period [46–48]. In contrast, the PEP trial, involving 13 356 patients undergoing hip surgery, demonstrated more cardiac ischaemic events (death due to ischaemic heart disease or nonfatal MI) in patients randomised to ASA versus placebo (HR 1.33, 95% CI 1.00–1.78) [49]. There was also an increased risk of bleeding (6 per 1000 patients) [49].

In 2014, POISE 2 (an international, multicentre RCT of 10 010 patients) found a significant increase in major bleeding risk for patients randomised to ASA [36]. ASA-naïve patients were randomised to initiation of ASA or placebo, starting on the morning of surgery and continued for 30 days; patients on chronic ASA therapy were randomised to restart ASA or to placebo on the day of surgery and for 30 days thereafter [36]. Patients who had been taking ASA chronically on average stopped it 7 days before surgery. ASA had no significant effect on the primary outcome of death or MI at 30 days (7% in ASA group vs 7.1% in placebo group; HR 0.99, 95% CI 0.86–1.15, $p = 0.92$). Major bleeding, however, was more common in the ASA group than with placebo (4.6% vs 3.8%; HR 1.23, 95% CI 1.01–1.49, $p = 0.04$). Major bleeding was defined as a significant drop in haemoglobin requiring red blood cell transfusion or intervention (i.e., embolization, superficial vascular repair, nasal packing); or bleeding in a high risk location (i.e., intraspinal). The authors theorised that while ASA may have prevented some MIs due to coronary artery thrombus, it may have contributed to MI via supply–demand mismatch from bleeding and hypotension, giving rise to an overall neutral MI signal [36]. In summary, the largest trial in this area, with the power to

detect changes in outcome, shows that continuing ASA in the perioperative period causes more harm than benefit [36].

Statins

There is overwhelming evidence for the benefit of statin use in secondary prevention for patients who have suffered an MI. Statins may also prevent perioperative complications through pleiotropic mechanisms like plaque stabilisation, anti-inflammatory effects and improved endothelial function [1, 35]. A Cochrane review of three vascular surgery RCTs (178 patients) found a nonsignificant decrease of death and MI at 30 days [50]; two recent systematic reviews, predominantly in vascular noncardiac surgery, found a decrease in MI and all-cause mortality in patients taking statins [35, 51]. However, because of the limited number of cardiac events in dedicated RCTs, there remains uncertainty as to the degree of support for recommendations for perioperative statin use [35, 41, 42, 50].

The VISION study compared 18.4% of patients on statin therapy with 29% of controls. Preoperative statin use was associated with a lower risk of the composite primary outcome (all-cause mortality, MINS or stroke at 30 days) (RR 0.83, 95% CI 0.73–0.95, $p = 0.007$) [52]. This was driven by a statistically significant lower risk of MINS and death [52]. This relative effect corresponded to an absolute risk reduction of 2.0% (95% CI 0.5–3.2%, $p = 0.005$). VISION is the only study to look at the association of statin use with MINS, and the results are hypothesis generating in that preoperative statin use may reduce the risk of adverse perioperative cardiac outcomes [52]. A large RCT is required to evaluate these findings further.

Alpha-2 adrenergic agonists

Results of small RCTs initially suggested that clonidine (an α_2 -adrenergic agonist) may prevent MI [53, 54] by blunting central sympathetic outflow with associated anxiolytic, and anti-inflammatory effects [54, 55]. However, these trials were small (<300 patients) with few events [53–56]. A meta-analysis of 12 RCTs looking at α_2 -adrenergic agonists in noncardiac surgery showed no difference in overall mortality or MI in the entire study population; however, a decrease in MI and death was found in the vascular surgery subgroup [57]. These findings were driven largely by a trial from 1999 that used mivazerol, an α_2 -adrenergic agonist [56, 57].

More recently, POISE 2, found that clonidine did not reduce the rate of death or nonfatal MI at 30 days (HR 1.08, 95% CI 0.93–1.26, $p = 0.29$) [34]. It did, however, increase the rate of nonfatal cardiac arrest (HR 3.20, 95% CI 1.17–8.73, $p = 0.02$) and clinically important brady-

cardia (HR 1.49, 95% CI 1.32–1.69, $p < 0.001$) and hypotension (HR 1.32, 95% CI 1.24–1.40, $p < 0.001$). While enhanced heart rate control may be protective [8], perioperative hypotension is an independent risk factor for perioperative MI [34, 58]. Thus, in the largest trial in this area, α_2 -adrenergic agonists were not protective and increased the risk of significant perioperative hypotension and bradycardia [34].

Perioperative hypotension

POISE demonstrated that clinically significant hypotension (defined as systolic blood pressure <90 mm Hg requiring intervention) had the largest PAR (37.3%) for perioperative death and the largest PAR for stroke (14.7%) [8]. In POISE 2, more patients in the clonidine group had clinically important hypotension, bradycardia and an increased risk of nonfatal cardiac arrest [34]. Prospective observational studies have suggested an association between intraoperative hypotension with myocardial injury [59, 60] and 30-day mortality [58]. A recent cohort study on perioperative hypotension assessed adults ≥ 60 years of age undergoing vascular surgery with routine troponin monitoring on postoperative days 0–3 [59]. The authors found that intraoperative hypotension (defined as decrease of 40% from preinduction mean blood pressure for >30 minutes) was associated with increased postoperative myocardial injury (RR 1.8, 95% CI 1.2–2.6, $p < 0.001$) [59]. The association of hypotension with adverse cardiac events has important implications for perioperative management of antihypertensive agents. In POISE 2, clinically important hypotension occurred more often after patients left the postanesthetic care unit (PACU). In the clonidine group, the median intraoperative period of hypotension was 15 minutes and on the first postoperative day it was 180 minutes [34]. This highlights the need for caution regarding the use of antihypertensives in the perioperative setting, including consideration of omitting some or all antihypertensive agents on the day of surgery, careful reintroduction of antihypertensives postoperatively, and close monitoring of vital signs once the patient has returned to the ward after surgery. Future studies are required to assess whether close monitoring for postoperative hypotension with rapid, protocol-driven intervention may be cardioprotective.

Treatment options for MINS

Data that informs on the optimal treatment for MINS patients is limited; however, extrapolation from the ACS literature [61, 62] and other recent perioperative work [52, 63, 64] provides the modern day clinician

with a reasonable strategy until future RCTs provide further guidance. Examination of the placebo arms from ACS studies demonstrates that some patients survive, and may do well clinically, despite not being on the active agent [65]. However, at the time of the acute event, it is not possible to predict with precision which patients will benefit from the drug and which patient will not and thus clinicians err on the side of caution by prescribing a standard cocktail of cardiac medications to each ACS patient.

Multivariable regression analysis among patients suffering MINS from the original POISE Trial identified two drugs that were associated with reduced 30-day risk of death: ASA [adjusted odds ratio (aOR) 0.54, 95% CI 0.29–0.99] and statin (aOR 0.26, 95% CI 0.13–0.54) [8]. In a propensity-matched study on 1-year outcomes (death, MI, coronary revascularisation, or CHF requiring hospitalisation), 66 MINS patients were compared with 132 matched non-MINS patients (controls) [64]. Among the MINS patients, 43 received therapeutic intensification of ≥ 1 of four cardiac medications [ASA, statin, β -blocker, angiotensin-converting enzyme inhibitor (ACE inhibitor)], while 23 patients did not receive therapeutic intensification after MINS. MINS patients not receiving therapeutic intensification had a hazard ratio of 1.77 (95% CI 1.13–2.42) while MINS patients receiving therapeutic intensification had a hazard ratio of 0.63 (95% CI 0.1–1.19) [64]. These data suggest that secondary cardiac prevention interventions may benefit MINS patients.

MANAGE (an international, multicentre RCT) is currently evaluating the impact of an anticoagulant (dabigatran 110 mg b.i.d) versus placebo on major vascular complications in patients suffering MINS [66]. INTREPID (an open-label, randomised pilot study) is currently evaluating the impact of ticagrelor (antiplatelet agent, 90 mg bid) versus ASA (81 mg) on the rate of cardiovascular events in patients with elevated troponin levels after major, noncardiac surgery [67]. More treatment-focused RCTs are needed, but until these trials are conducted, the evidence in the available literature suggests that pharmacological intensification for MINS patients may prove beneficial and possibly even life-saving. At the very least, these patients need to be identified and referred to internal medicine or cardiology departments for close outpatient follow-up, preferably within 1 week of discharge given that the median time to death following MINS was found to be 11 days [12].

A cost-consequence study analysed the cost associated with postoperative troponin monitoring, including the assumption that every patient will have an echocardiogram and therapeutic cardiac medication inten-

sification [68]. This study demonstrated that postoperative troponin monitoring, which predicts death within 30 days, is profoundly less expensive than cancer screening which typically predicts death within several years.

Conclusion

MINS is common and is associated with poor outcomes. One in ten patients suffering from MINS will die in 30 days after noncardiac surgery [12]. Failure to monitor troponin after noncardiac surgery will miss over 80% of MINS events [12].

The current model of perioperative patient care lacks continuity of care, and it is easy to assume that patients do well postoperatively if they are not followed longitudinally. Clinicians are unlikely to attribute a MI occurring 6 weeks after surgery to a complex cascade of inflammation and hypercoagulation that was first initiated during the perioperative period. However, there is strong evidence to support the conclusion that MINS is an important and clinically relevant entity with a profound impact on perioperative mortality [4, 12, 13]. Dismissal of asymptomatic perioperative troponin elevation as “troponitis” comes at a risk to patients. Clinicians should recognise MINS as a marker of increased risk of perioperative morbidity and mortality. Furthermore, clinicians should be proactive in monitoring troponin postoperatively for patients with elevated cardiovascular risk [4, 12], offer MINS patients cardiac medications for secondary prevention (including ASA, statin, plus consideration of an ACE inhibitor and potentially a beta-blocker) [52, 63, 64] and arrange timely patient follow-up with internal medicine or cardiology departments after hospital discharge.

A shared care model that integrates anaesthesia, internal medicine, cardiology and surgery would be a step forward in helping to ensure the continuity of perioperative patient care while providing potentially life-saving risk stratification and secondary prevention.

Disclosure statement

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The full list of references is included in the online version of the article at www.cardiovascmed.ch.

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