Myocardial injury after noncardiac surgery: an underappreciated problem and current challenges

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Purpose of review
To review myocardial injury after noncardiac surgery (MINS), focusing on recent studies, including data on high-sensitivity troponin, which is likely to alter our understanding of MINS.

Recent findings
MINS is greatly underappreciated by clinicians, possibly because of its silent presentation. However, MINS is both common and clinically important. In total, 8% of at-risk patients will suffer a MINS, an event that is associated with death within 30 days with an odds ratio of 3.87 (95% CI 2.96–5.08). Most patients suffering MINS do not fulfill the criteria for perioperative myocardial infarction as they are asymptomatic. Consequently, postoperative troponin measurement is imperative for MINS detection. Evidence from randomized trials on how to prevent or how to treat MINS is still lacking.

Summary
Currently, we are limited to appreciating the vast extent of the MINS problem and applying recommendations based on observational data or derived from the nonoperative setting. Routine troponin measurements after noncardiac surgery and the increasing use of high-sensitivity troponins have revealed the larger underwater iceberg of perioperative myocardial injury and ischemia. Clinicians should be sensitized for this important complication and search for it using a perioperative troponin screening.

Keywords
myocardial injury after noncardiac surgery, outcomes, perioperative complications, troponin

INTRODUCTION

Cardiac death is the leading cause of postoperative death within the first 30 postoperative days [1▪] and perioperative cardiovascular events are the leading cause of mortality and morbidity in noncardiac surgery [2–5]. However, because of troponins and especially high-sensitivity troponins, we are just beginning to realize the extent of myocardial damage and its serious impact on not only long term, but especially 30-day mortality. It is estimated that of the over 200 million annual surgeries worldwide [6] approximately 100 million involve patients over 45 years of age and at-risk for myocardial infarction of injury [7▪]. Of these, we generally appreciate 1.1 million (1.1%) as patients suffering a perioperative myocardial infarction because they have ischemic symptoms, whereas another 2.2 million (2.2%) have asymptomatic myocardial infarction and 4.6 million (4.6%) have myocardial injury [1▪,4,7▪]. The 30-day mortality in these three groups is 9.7, 12.5, and 7.8%, that is, annually over 750 000 deaths within 30 days of noncardiac surgery result from myocardial ischemia [1▪,4,7▪]. Despite increasing attention in recent literature [7▪,8], the burden of myocardial injury after noncardiac surgery (MINS) is still underappreciated by clinicians.

TEXT OF REVIEW

With the advent of cardiac troponins a new age of assessing cardiac injury began. Troponin is a cardiac protein comprising three subunits (C, I, and T) and facilitates muscle contraction through the sliding of actin and myosin filaments. The cardiac isoform of the I and T subunits are specific to cardiac muscle and as such have become a mainstay in identifying

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KEY POINTS

- Clinicians greatly underappreciate the significance of MINS and its association with 30-day mortality.
- Annually there are over 750 000 deaths within 30 days of noncardiac surgery resulting from myocardial ischemia.
- The majority of MINS and asymptomatic myocardial infarction go unnoticed without routine troponin testing.
- The relative weight of mechanisms causing MINS is likely to be shifted toward myocardial oxygen supply and demand mismatch and away from coronary artery plaque rupture and thrombosis.
- Until definitive preventive measures and treatments are established, physicians should focus on reducing perioperative myocardial oxygen mismatch and ensuring optimal perioperative medication.

myocardial ischemia [9]. Furthermore, the extent of troponin concentrations correlates with the size of myocardial damage [10–12]. Figure 1 shows the temporal release profile of cardiac biomarkers following ischemic damage [13] as well as a comparison of high-sensitivity vs fourth generational troponin T [14]. Characteristics of high-sensitivity troponin assays are improved diagnostic accuracy at lower concentrations, which improve specification of the 99th percentile (the upper limit of the norm) and decrease the coefficient of variation at these concentrations (Table 1) [15–21]. Increasingly, high-sensitivity troponin assays are being used and are recommended over conventional assays [22,23]. Benefits include increased detection of both type 1 and type 2 myocardial infarction, a shortened troponin-blind interval to ischemia, as well as a higher negative predictive value for acute myocardial infarction [24▪].

EVIDENCE ON THE PROGNOSTIC IMPACT OF MYOCARDIAL INJURY AFTER NONCARDIAC SURGERY

Several studies summarized in two meta-analyses explored the association between elevated postoperative troponins and mortality. Levy and colleagues [21] examined 14 studies and 3139 patients. Troponin was associated with mortality within 1 year of surgery [odds ratio (OR) 6.7; 95% CI 4.1–10.9] as well as beyond 1 year (OR 1.8; 95% CI 1.4–2.3). Redfern and colleagues [25] examined 1873 vascular patients in eight cohorts and found isolated troponin elevation without myocardial infarction (MI) to be associated with 30-day mortality (OR 5.03; 95% CI 2.88–8.79). Within the last few years, a number of large studies on the topic have overcome the methodological issues present in the meta-analyses, for example, the use of various assays and cut-offs, and difficulties in proper multivariable adjustment.

By far the largest prospective cohort is the Vascular Events In Noncardiac Surgery Patients Cohort Evaluation Study (VISION) study [19], which explored elevated postoperative Troponin T (TnT) concentrations in the first 3 days after surgery in over 15 000 patients and found even low-level TnT concentrations to be predictive of 30-day mortality. Specifically, a concentration of 0.02 ng/ml (far below the cut-off of conventional TnT) had an adjusted hazard rate (aHR) of 2.41 (95% CI 1.33–3.77) compared with a concentration of 0.01 ng/ml or less. Higher concentrations of 0.03–0.29 ng/ml and >0.3 ng/ml had aHRs of 5.00 (95% CI 3.72 to 6.76) and 10.48 (95% CI 6.25–16.62), respectively.

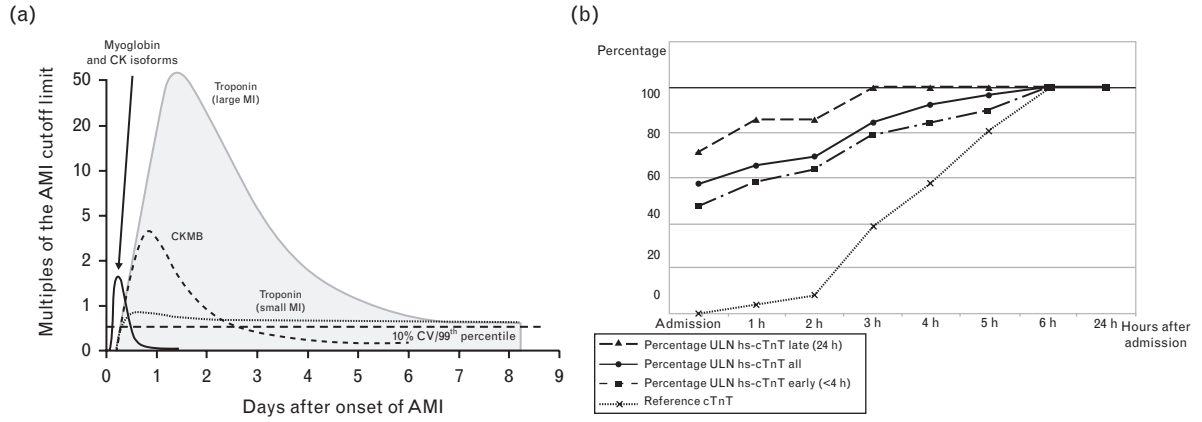

FIGURE 1. (a) Cardiac biomarker release after acute myocardial infarction [13] and (b) comparison of high-sensitivity and fourth-generational troponin T in percentage of patients above the 99th percentile of the norm (13.5 ng/l hs-cTnT; 0.03 μg/l) [14]. Reprinted with permission from the Journal of the American College of Cardiology and the American Association for Clinical Chemistry.

Table 1. Common high-sensitivity troponin assays in comparison to previous assays

Assay and troponin		LoD (ng/l) [15,20]	99th percentile (ng/l) [16,17,20]	10% CV threshold (ng/l) [16,17,20]	VISION patients [21] above cutoff
Roche, Elecsys	hs-cTnT	5	14	13	1757 (11.6%)
Roche, Elecsys	cTnT (4th generation)	10	10	35	1263 (8.3%)
Abbott, Architect	hs-cTnI	1.2	30	5.2	n/a
Abbott, Architect	cTnI	9	32	32	n/a

CV = coefficient of variation; LoD = Limit of Detection.

Mortality rates for 0.01, 0.02, 0.03–0.29 ng/ml, and >0.3 ng/ml were 1.0, 4.0, 9.3, and 16.9% [19]. Higher peak TnT concentrations exhibited shorter median time to death and nearly 75% of deaths were in-hospital [19].

A nearly concurrently published retrospective study examining administrative data of 51 701 inpatient, noncardiac surgery cases [26] found postoperative TnI to be associated with increasing mortality [TnI: 0.2–0.7 ng/ml (OR 2.6, 95% CI 2.1–3.3); 0.7–7 ng/ml (OR 4.6, 95% CI 3.7–5.6); and >7 ng/ml (OR 7.8, 95% CI 5.7–10.7)]. Additionally, routine testing showed a three-fold higher detection rate of troponin elevation than testing triggered by clinical suspicion. However, TnI screening was not useful in the lowest risk category with one death in almost 19 000 patients.

In a prospective cohort study of 2232 elevated-risk surgery patients aged at least 60 years, van Waes and colleagues [27] also found higher (≥0.6 μg/l) and lower TnI elevations (0.06–0.59 μg/l) to be associated with higher relative risks (RR) than nonelevated troponin [RR 2.4, (95% CI 1.3–4.2) and RR 4.2 (95% CI 2.1–8.6), respectively].

In a secondary analysis of the above mentioned VISION cohort, Botto and colleagues [1▪] sought to determine the diagnostic criteria of MINS. MINS was defined as the prognostically relevant myocardial injury occurring within 30 days, presumably because of ischemia, and with correction for confounding by other perioperative complications. Eight percent of patients suffered MINS and mortality was more common in patients with MINS (9.8%) than without MINS (1.1%; $P < 0.001$). The aHR for 30-day mortality was 3.87 (95% CI 2.96–5.08) and the population-attributable risk was 34.0% (95% CI 26.6–41.5). As previously reported, only a minority of MINS patients (41.8%) fulfilled the criteria for myocardial infarction [1▪]. Of the 1263 patients with troponin T more than 0.03ng/ml, the vast majority suffered MINS (1200, 95%), and 87% did so within the first 2 postoperative days. Additionally, patients suffering MINS were at higher risk of nonfatal cardiac arrest, congestive heart failure, stroke, and also nonvascular causes of death.

Defining MINS has been a topic of debate and has involved a break with traditional biomarker cut-offs, which generally implement the 99th percentile of a reference population together with a coefficient of variation of 10% or less [9]. However, this cut-off is arbitrary and does not find the point at which risk increases [19]. Furthermore, biomarker concentrations below the traditional cut-off may still flag at-risk patients [1▪,19].

Presumably on the basis of the studies from the VISION cohort [1▪,19], Jammer and colleagues have defined MINS as an increase in conventional, 4th generation troponin T at least 0.03 μg/l judged to be due to of myocardial ischemia [28]. Unlike perioperative myocardial infarction (PMI), which requires either ischemic symptoms or ECG changes in addition to troponin elevations and which reflects a necrosis of myocardium [29], MINS is a 'presumably ischemic troponin elevation'; as such it may cover a spectrum from reversible myocardial injury to necrosis. As a broader concept of myocardial damage than perioperative myocardial infarction, MINS has been proposed to be a more applicable term for surgical patients [30]. PMI, with an incidence of 2–3% and a mortality of 30%, has classically dominated adverse cardiac outcomes after surgery, but appears to be only the tip of the ischemic complications iceberg. PMI is only one manifestation of myocardial ischemia, which in the absence of systematic troponin measurements greatly underestimates the extent of myocardial damage after noncardiac surgery (see chapter detection of MINS, below) [1▪,19,26,27].

MECHANISM OF MYOCARDIAL INJURY AFTER NONCARDIAC SURGERY

The mechanism of MINS remains unclear, although it is likely that it is similar to PMI. Since 2007 [29], as well as in the third universal definition of myocardial infarction in 2012 [9], different types of

myocardial infarction have been identified, with type 1 and type 2 being most significant in the noncardiac perioperative setting. Type 1 MI is the classic coronary plaque rupture with subsequent acute thrombosis and is the most dominant form in the nonsurgical population.

The evidence for the pathophysiology of PMI is limited. Histological data from small studies of patients suffering fatal PMI have demonstrated the existence of an intracoronary thrombus in approximately one-third of patients and signs of plaque rupture in nearly half of patients [31,32]. Preoperative angiographic data from a cohort of 1242 vascular patients showed that in patients suffering in-hospital death or PMI ($n = 21$), the preoperative coronary angiography failed to show a culprit stenosis for the site of myocardial infarction in seven cases. In the remaining 14 cases, no high-grade stenosis (70–99%) could be found and in eight of 14 cases, inadequate collateral vessels were identified as the most common apparent cause of infarction [33]. Postoperative angiographic data from 66 patients suffering PMI or unstable angina after noncardiac surgery showed 26% of patients to have a thrombotic etiology, 20% nonobstructive coronary disease without a culprit lesion, and 55% obstructive coronary disease suggesting a mismatch (type 2) [34]. The above studies are all potentially biased on account of either involving fatal PMI or symptomatic PMI. Troponin measurements seem not to be helpful in differentiating between type 1 and type 2 MI [35]. Expert opinion estimates that type 1 and type 2 myocardial infarctions each account for approximately 50% of PMIs in noncardiac surgery [36–38].

In terms of the cause of death after MINS, it has recently been re-emphasized that high-level postoperative troponin elevations predominantly correlate with vascular deaths, whereas low-level concentrations predominantly correlate with nonvascular deaths [37,39▪]. This was also found in a sensitivity analysis of the VISION study, in which a troponin T of 0.02 ng/ml was independently associated with mortality in patients dying of nonvascular causes (aHR 3.25, 95% CI 1.78–5.94), but not of vascular causes (aHR 1.65, 95% CI 0.74–3.67) [19]. This association of low-level troponins and short-term nonvascular mortality may potentially be explained by two subsidiary mechanisms: minor myocardial ischemia may lead nonvascular complications, manifesting at a later time point (e.g., myocardial ischemia may predispose to subsequent pneumonia [19]) or noncardiac complications lead to increased oxygen requirements, placing greater strain on marginally compensated myocardium [37]. It is worth emphasizing, that regardless of whether patients die a vascular or nonvascular death, MINS as a response to the stress test of surgery may be a red flag for a fatal secondary event in the near future.

PREVENTION OF MYOCARDIAL INJURY AFTER NONCARDIAC SURGERY

Preoperative measures

A first step for preventive measures is the identification of risk and its classification. Factors likely to facilitate perioperative type 1 myocardial ischemia are physiological and emotional stress [2], the procoagulatory response to surgery [40–43], as well as perioperative episodes of tachycardia and hypertension, both of which increase shearing forces with the associated risk of plaque rupture [2,44]. Type 2 ischemia is secondary to an oxygen supply and demand mismatch and appears to be more prominent in the perioperative setting [37,45], especially with the advent of more sensitive troponins [46]. Several perioperative factors may lead to an oxygen supply and demand mismatch [2,7▪]. Intraoperative factors include tachycardia [47,48], sympathetic stimulation [49], hypercoagulability [40–43], bleeding [50], hypotension [51▪,52▪,53], and hypothermia [54,55]. Additional postoperative factors include pain and prolonged hypoxia [56].

Beginning with the cardiac risk index [57], a number of indices have been developed, of which two – namely the revised cardiac risk index [5] and the NSQIP MICA risk-prediction rule [58] – are endorsed by current guidelines [59,60]. The independent predictive value of cardiac biomarkers in noncardiac surgery has repeatedly been shown [21,61,62]. Recently, a prospective study examining the incremental value of preoperative coronary computed tomographic angiography in 955 patients at risk of vascular disease showed that this method improved prediction of cardiovascular death or nonfatal myocardial infarction at 30 days for patients with events, but was over five times more likely to inappropriately overestimate events in patient without events [63▪]. Furthermore, routine preoperative revascularization of coronary stenosis has not proven to be of value [64]. When patients are seen weeks in advance, preoperative optimization of medical therapy may be beneficial [65▪]. However, patients are generally seen the day prior to surgery and postponing may not always be an option.

In terms of perioperative medication, the results have been disappointing. Despite its previous widespread use, the *de novo* perioperative administration of β-blockers has been a topic of debate for years. A recent meta-analysis showed that *de novo* β-blockade started within 1 day of surgery did decrease PMI, but

at a cost of higher rates of stroke and death [66▪]. The exclusion of controversial trials did not change this result. Sufficient data on *de novo* β blockade initiated prior to the first day was not available. In a retrospective study of 314 114 patients undergoing noncardiac surgery [67], patients with a higher cardiovascular risk score showed a decreased 30-day mortality rate if receiving perioperative β-blockade (OR, 0.63; 95% CI, 0.43–0.93), while those with no risk factors had an increased risk of death (OR, 1.19; 95% CI, 1.06–1.35). However, it was unclear when perioperatively β-blockade was begun and in approximately half of all patients it was not a *de novo* initiation. The European Society of Cardiology and the European Society of Anaesthesiology (ESC/ESA) [59] as well as the American College of Cardiology/American Heart Association (ACC/AHA) Guidelines [60] suggests the continuation of beta-blockers in patients already receiving beta-blockers (Class I, Level B). Their initiation for high-risk surgery in patients with clinical risk factors or myocardial ischemia may be considered (Class IIb, Level B), however not without preoperative titration (ESC/ESA Class III, Level B) and not on the day of surgery (ACC/AHA Class III, Level B).

Despite high-quality evidence for aspirin therapy in the nonoperative setting for primary and secondary prevention [68], a perioperative benefit of aspirin could not be found. In the PeriOperative ISchemic Evaluation-2 (POISE-2) trial, which examined over 10 000 patients, perioperative aspirin did not decrease death or nonfatal myocardial infarction (HR 0.99, 95%CI 0.86–1.15), but rather increased major bleeding (HR 1.23 95%CI 1.01–1.49) [69▪]. The ACC/AHA Guidelines state that the continuation of aspirin for nonurgent, noncardiac surgery may be reasonable in patients without prior coronary stenting, if the increased risk of cardiac events outweighs the increased risk of bleeding (class IIb, level B). The POISE-2 trial also examined the effect of clonidine to reduce sympathetic activation during surgery [70▪]. Clonidine administration did not reduce nonfatal MI (HR 1.08, 95%CI 0.93–1.26), but did increase clinically relevant hypotension (HR 1.32 95%CI 1.24–1.40) and nonfatal cardiac arrest (HR 3.20 95% CI 1.17–8.73). α-2 agonists are not recommended for the prevention of cardiac events (ACC/AHA: class III, level B).

The established effect of statins in reducing cardiovascular mortality in the nonsurgical population [71] has also been demonstrated perioperatively in decreasing major adverse cardiac events (MACE) and mortality, both in randomized trials [72,73] as well as in large observational studies [74,75,76▪]. In a recent observational study of the VISION data, patients receiving statins preoperatively were shown to have a significantly lower risk of all-cause mortality than a matched population (RR 0.58; 95% CI 0.40–0.83; an absolute risk reduction of 2.0%; 95% CI 0.5–3.2%) [76▪]. The ESC/ESA as well as the ACC/AHA Guidelines recommend continuing statins (class I, level C) and consider their initiation reasonable in both patients undergoing vascular surgery (class IIa, level B) as well as in patients with a clinical risk factor scheduled for elevated-risk procedures (ACC/AHA: class IIb, level C). The ESC/ESA recommends beginning statins 2 weeks prior to surgery.

Intraoperative and postoperative measures

There are no intraoperative and/or postoperative measures known to reduce the incidence of MINS. Although initially promising in coronary artery bypass graft surgery [77] and recommended by earlier guidelines for noncardiac surgery [78], the use of volatile anesthetics has not reduced myocardial ischemia, major adverse cardiac events, troponin, or B-Type Natriuretic Peptide concentrations [79,80]. Blood pressure optimization may be beneficial. An association between intraoperative hypotension and mortality has been discussed in a number of recent observational studies [51▪,53]. van Waes and colleagues [52▪] examined almost 900 vascular patients and showed that a 40% decrease of preinduction mean arterial pressure over more than 30 cumulative minutes was associated with postoperative myocardial injury (RR 1.8; 99% CI, 1.2–2.6, $P < 0.001$), while shorter durations were not. Other recent studies have shown increased myocardial injury [53] and 30-day mortality [51▪] for shorter periods of intraoperative hypotension. Finally, higher transfusion thresholds for red blood cells have not been shown to affect mortality in the short [81] or long term [82].

The majority of MINS occur within two postoperative days [1▪]. Postoperative strategies proposed to prevent MINS include more frequent or continuous vital sign monitoring, avoidance of hypoxemia, correction of potentially contributing factors, and intravascular volume optimization [21]. Despite its compelling logic, high-quality data showing an improvement in hard outcomes through monitoring (including rapid response teams) is inconclusive at best [83–85].

DETECTION AND TREATMENT OF MYOCARDIAL INJURY AFTER NONCARDIAC SURGERY

The complexity of perioperative mechanisms contributing to myocardial injury makes the treatment of MINS and PMI challenging. Furthermore, some of

the treatment options established for the nonoperative setting, for example, antiplatelet agents, are burdened by the non-negligible risk of postoperative bleeding [69▪]. Data from randomized clinical trials on the treatment of MINS and PMI is scarce.

It is evident from a number of cohort studies, that MI will only be detected reliably if troponin is measured. Ideally, troponin measurements should flag at-risk patients, be validated in prospective studies examining hard outcomes, exhibit incremental value, be of clinical utility, and improve clinical outcomes [86]. The last point has yet to be shown in the treatment of MINS. This uncertainty with regard to modification of clinical outcomes has resulted in a debate on the utility of routine perioperative screening. Some expert groups advocate measuring troponin in high-risk patients both before and 48–72 h after major surgery (class IIb, level B) [9,59]. The ACC/AHA Guidelines state that the usefulness of postoperative troponin screening in patients without signs or symptoms of ischemia is uncertain as defined management strategy are lacking (class IIb, level B), and only recommend measuring troponin when signs or symptoms suggestive of ischemia or infarction are present [60]. This approach has been criticized as it suggests that the utility of troponin screening is only established in symptomatic patients [30].

Observational data from the POISE trial has shown suboptimal medical therapy for patients suffering PMI [87]. At discharge, only 64.8% of patients suffering PMI received aspirin [17.8% clopidogrel or ticlopidine, 52.0% statins, and 55.4% angiotensin-converting enzyme inhibitors or Angiotensin II receptor blockers] [4]. In a prospective, matched study examining 667 patients undergoing major vascular surgery, patients suffering PMI without postoperative medical intensification according to 2007 ACC/AHA Guidelines on the medical management of chronic stable angina ($n = 23$) exhibited a higher HR (2.80; 95% CI 1.05–24.20) than those with PMI with postoperative medical intensification ($n = 43$) [88▪]. However, a small study examining 70 patients with postoperative troponin elevation randomized to cardiology care vs standard ward care showed no difference in 1-year mortality [89]. In observational studies, patients on statins at the time of discharge have had improved long-term survival [statin OR 0.7 (0.5–0.9); statin and antiplatelet drug OR 0.5 (0.4–0.7)], despite often being more ill [65▪,75].

Examining a hypothetical hospital with 10 000 elevated-risk, in-patient surgeries/year and implementing perioperative troponin screening in patients who are either aged at least 65 or aged at least 45 with a history of coronary artery disease, peripheral vascular disease, or cerebral vascular disease would result in approximately 4000 screened patients (40%). Of these, around 320 patients will suffer MINS. If we were to measure troponin only in the case of symptomatic patients, we would only register around 44 events and, therefore, deprive some 276 patients from potentially effective treatment [1▪,4]. Assuming 66.5% of our patients are not taking statins preoperatively [4], we might be able to prevent 29 MINS by beginning preoperative statin therapy well in advance [76▪]. As this is not always feasible, let us assume that we only conduct an intensification of postoperative medical treatment. By this measure we might be able to increase MACE-free survival at 12 months from 43 to 77% [88▪] or from 138 to 246 of our 320 patients with detected MI by routine testing vs 19 to 34 of our 44 patients with symptomatic events. This would be a real net improvement of 108–15 or 93 patients. By comparison, cervical cancer has an adjusted annual incidence of 6.6/100.000 and screening is recommended every 3 years in women aged 21–65 [90]. Assuming a sensitivity of 100%, and ignoring the stress caused by false positives, screening 10 000 women in a hypothetical hospital could successfully identify one woman with cervical cancer.

In consideration of limited availability of data, we would like to delineate our practice (Fig. 2). We measure high-sensitivity troponin T (hsTnT) prior to surgery and on the first 2 postoperative days in patients aged at least 65 or aged at least 45 with a history of coronary artery disease, peripheral vascular disease, or cerebral vascular disease. Patients with an increase in hsTnT at least 14 ng/l receive a cardiology consultation. Based on the suspected type of myocardial ischemia and individual patient comorbidities and bleeding risk the patients may either receive aspirin and a statin and potentially coronary angiography (suspected type 1 ischemia) or an optimization of oxygen supply and demand mismatch (correction of hypotension, tachycardia, etc.) and potentially a statin and/or the recommendation for outpatient cardiac ischemic testing (suspected type 2 ischemia). We recommend initiating aspirin as soon as possible and independent of thrombosis prophylaxis. However, this should be weighed against the risk of major bleeding in an interdisciplinary approach. In our institution, we introduced the perioperative troponin screening in close collaboration with the cardiology department with the benefit of an interdisciplinary approach to the MINS patients. Whether or not the appraisal of MINS patients and treatment intensification should be done by an anesthesiologist or a cardiologist is a matter of debate and alternative models, for example, primary assessment of patients with

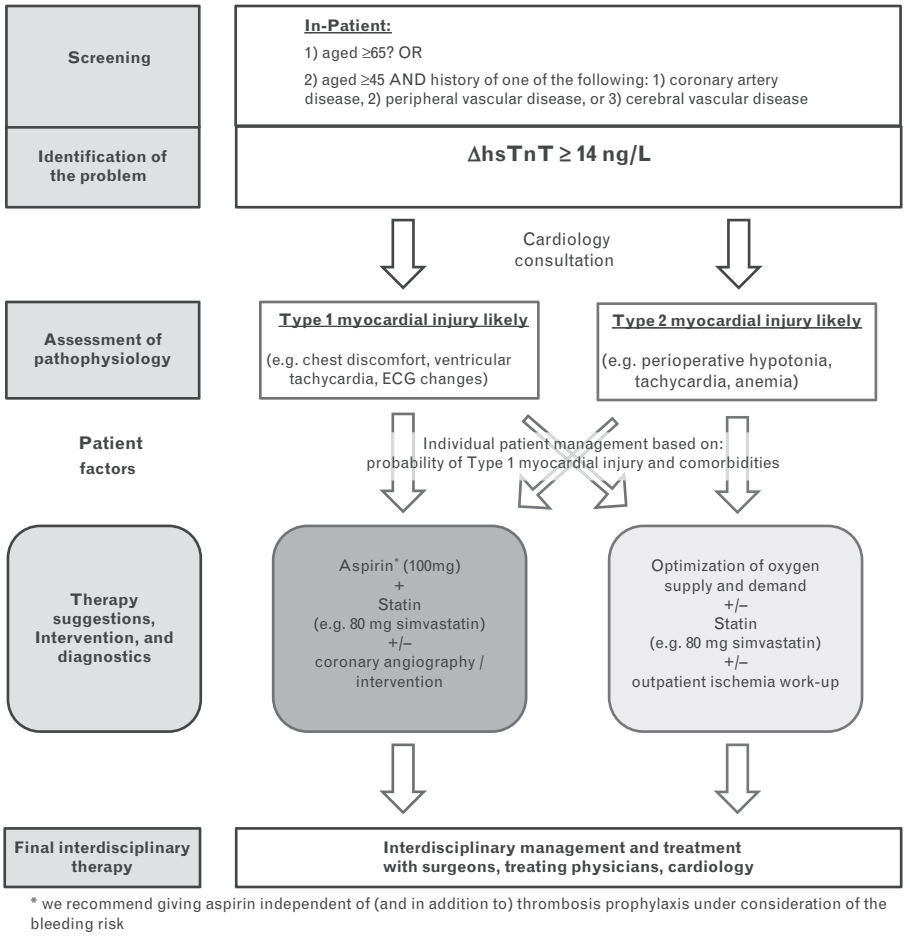

FIGURE 2. Suggested management plan of myocardial injury after noncardiac surgery.

elevated perioperative troponin by anesthesiologists or intensivists who may be better aware of bleeding risk, may be equally valid.

DIRECTION AND OUTLOOK

Two main issues are likely to influence the MINS debate in the next few years: the use of high-sensitivity assays and the modification of risk through prevention and treatment of MINS.

The use of high-sensitivity troponin has greatly expedited the diagnosis of Non-ST-Segment Elevation Myocardial Infarction and has partially obviated the need for serial testing [24▪]. A limit of detection of 3 ng/l [14] coupled with prognostically relevant concentrations below conventional assays cut-offs [91▪] are likely to influence the MINS discussion. In a study of nearly 50 000 nonsurgical patients admitted for acute coronary syndrome, high-sensitivity troponins were able to identify a large group of patients (6491 or 13.4%) previously considered to be troponin negative and able to show an association with 12-month all-cause mortality with an adjusted HR of 2.53 (95% CI: 2.00–3.21; $P < 0.001$) [91▪]. High-sensitivity troponin T concentrations were elevated above 14ng/l in 31% and 41% of patients at-risk for coronary artery disease preoperatively [92,93] and 45% postoperatively [94]. This suggests that the incidence and cut-offs of MINS with hsTnT may be challenging and may require consideration of the perioperative change (i.e., delta) [24▪,39▪,93]. Data collection of additional 25 000 patients from the VISION study with high-sensitivity troponin is expected in the early part of 2016 and may provide new insights. Additionally, being able to measure troponin at very low concentrations may enable us to differentiate between acute postoperative increases and chronic elevation in a range previously deemed to be troponin negative.

Future studies must determine whether or not the risk of mortality imposed by MINS is modifiable, and if so, by which treatment. Although no compelling data is currently available, a number of interesting trials are due to finish in the next few years.

For MINS prevention, two smaller studies seem interesting: the Prevention of Myocardial Injury in

Non-cardiac Surgery trial is set to finish in 2017, which will examine whether or not remote ischemic preconditioning can reduce the number of patients with MINS in 540 patients undergoing hip fracture repair (however given the existing data in cardiac surgery [20,95,96], it seems unlikely that remote ischemic preconditioning is likely to significantly reduce MINS) and the Biomarkers, Blood Pressure, BIS: Risk Stratification/Management of Patients at Cardiac Risk in Major Noncardiac Surgery (BBB) study, set to finish in 2019 which will randomize 458 at-risk patients to a liberal or tight blood pressure control for influencing postoperative troponin.

In terms of MINS treatment, two larger studies are due to finish in 2017 and 2018: (1) the Management of Myocardial Injury After Noncardiac Surgery Trial study, which examines the impact of dabigatran and omeprazole on vascular mortality and major adverse cardiac and cerebral events in 3200 patients suffering MINS, and (2) the Study of Ticagrelor Versus Aspirin Treatment in Patients With Myocardial Injury Post Major Non-cardiac Surgery which examines the impact of ticagrelor and aspirin on major adverse cardiovascular events at 12 months in 1000 patients suffering MINS.

CONCLUSION

MINS is an adverse condition of great magnitude and prognostic relevance affecting millions of patients and associated with approximately three-quarters of a million deaths annually. The number of affected and identified patients is likely to rise with both an aging population and the use of high-sensitivity troponins. The mechanisms of MINS are poorly understood, but are likely to be similar to type 1 and type 2 MI. Furthermore, preventive measures and treatments have not yet conclusively been identified, although trials are underway. In the meanwhile, the avoidance of intraoperative and postoperative factors potentially exacerbating myocardial ischemia and optimal, guideline-based, postoperative re-evaluation of medical therapy seem sensible.

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Conflicts of interest

There are no conflicts of interest.

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- ■■ of outstanding interest

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