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Perioperative strategies to reduce risk of myocardial injury after non-cardiac surgery (MINS): A narrative review

Corina Bello, MD [a], Julian Rössler, MD [b], Peter Shehata, MD [c], Nathaniel R. Smilowitz, MD, MS [d,e], Kurt Ruetzler, MD, PhD, FAHA [b,c,*]

[a] Department of Anaesthesiology and Pain Medicine, Inselspital Bern, University Hospital, University of Bern, Switzerland
[b] Department of Outcomes Research, Anesthesiology Institute, Cleveland Clinic, Cleveland, OH, United States of America
[c] Department of General Anesthesiology, Anesthesiology Institute, Cleveland Clinic, Cleveland, OH, United States of America
[d] Division of Cardiology, Department of Medicine, NYU Grossman School of Medicine, New York, NY, United States of America
[e] Cardiology Section, Department of Medicine, VA New York Harbor Healthcare System, New York, NY, United States of America

HIGHLIGHTS

- Myocardial injury after non-cardiac surgery (MINS) is defined by troponin elevation.
- MINS is frequent, silent, and strongly associated with mortality.
- We identify modifiable precipitating factors of MINS.
- We discuss promising preventive and therapeutic options in the perioperative setting.

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ABSTRACT

Myocardial injury is a frequent complication of surgical patients after having non-cardiac surgery that is strongly associated with perioperative mortality. While intraoperative anesthesia-related deaths are exceedingly rare, about 1% of patients undergoing non-cardiac surgery die within the first 30 postoperative days. Given the number of surgeries performed annually, death following surgery is the second leading cause of death in the United States. Myocardial injury after non-cardiac surgery (MINS) is defined as an elevation in troponin concentrations within 30 days postoperatively. Although typically asymptomatic, patients with MINS suffer myocardial damage and have a 10% risk of death within 30 days after surgery and excess risks of mortality that persist during the first postoperative year. Many factors for the development of MINS are non-modifiable, such as preexistent coronary artery disease. Preventive measures, systematic approaches to surveillance and treatment standards are still lacking, however many factors are modifiable and should be considered in clinical practice: the importance of hemodynamic control, adequate oxygen supply, metabolic homeostasis, the use of perioperative medications such as statins, anti-thrombotic agents, beta-blockers, or anti-inflammatory agents, as well as some evidence regarding the choice of sedative and analgesic for anesthesia are discussed. Also, as age and complexity

Abbreviations: ACS-NSQIP, American College of Surgeons National Surgical Quality Improvement Program; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease calculator; BALANCED, Anesthetic Depth and Complications After Major Surgery; BNP/NT-proBNP, (N-terminal pro-) brain natriuretic peptide; CAD, coronary artery disease; CI, cardiac index; CPB, cardiopulmonary bypass; COP-AF, Colchicine for the Prevention of Perioperative Atrial Fibrillation in Patients Undergoing Thoracic Surgery; COPMAN, Colchicine Prevents Myocardial Injury After Non-Cardiac Surgery Pilot Study; CRIPES, Cardiac Remote Ischemic Preconditioning Prior to Elective Vascular Surgery; cTn, cardiac troponin; cTnC, cardiac troponin C; cTnI, cardiac troponin I; cTnT, cardiac troponin T; CVD, cardiovascular disease; ENIGMA, Evaluation of Nitrous Oxide in the Gas Mixture for Anesthesia; INPRESS, Intraoperative Norepinephrine to Control Arterial Pressure; FiO_2, fraction of inspired oxygen; hsTnI, high-sensitivity troponin I; hsTnT, high-sensitivity troponin T; MANAGE, Dabigatran in patients with myocardial injury after non-cardiac surgery: an international, randomized, placebo-controlled trial; MAP, mean arterial blood pressure; MI, myocardial infarction; MINS, myocardial injury after non-cardiac surgery; POISE, Perioperative Ischemic Evaluation; POPCORN, Perioperative Colchicine to Reduce Negative Events; PROTECT, Aggressive intraoperative warming versus routine thermal management during non-cardiac surgery; RCRI, revised cardiac risk index; RCT, randomized controlled trial; SAS, Surgical Apgar Score; VISION, Vascular Events in Noncardiac Surgery Cohort Evaluation.

* Corresponding author at: Department of Outcomes Research, Anesthesiology Institute, Cleveland Clinic, 9500 Euclid Avenue, L-10, Cleveland, OH, United States of America.
E-mail address: ruetzlk@ccf.org (K. Ruetzler).

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in comorbidities of the surgical patient population increase, there is an urgent need to identify patients at risk for MINS and develop prevention and treatment strategies. In this review, we provide an overview of current screening standards and promising preventive options in the perioperative setting and address knowledge gaps requiring further investigation.

1. Introduction

Anesthesia related intraoperative mortality constantly decreased over the last decades and was recently reported to be 0.00082%. [1] However, post-operative mortality is ~1% within 30 days following major non-cardiac surgery and ~ 5% at 1 year. [2] Annually, over 312 million patients undergo surgery worldwide. [3] 30-day mortality after major non-cardiac surgery is the second leading cause of death in the US. [4] Many of these deaths are due to cardiovascular complications. [5] In order to estimate the proportion of patients with a perioperative cardiovascular complication, the VISION prospective cohort study enrolled 15′133 patients age ≥ 45 years undergoing major non-cardiac surgery. Daily cardiac troponin (cTn) surveillance was mandatory for the first 3 days after surgery, regardless of clinical symptoms. Elevated cardiac Troponin T (cTnT) values above 20 ng/l occurred in approximately 12% of patients and were associated with increased 30-day-mortality. [6] Among patients with peak cTnT elevations between 30 and < 290 ng/l, mortality occurred in 9%, and among those with a cTn rose >300 ng/l, mortality was nearly 17%. [6] In a large prospective study that used a contemporary high-sensitivity troponin (hsTn) assay, MINS prevalence was even higher and it remained associated with post-operative mortality. According to a subsequent meta-analysis, the increased risk for mortality remained not only over a short-term period but also beyond 1 year after surgery. [7,8] In a secondary analysis of the VISION cohort, only 16% of patients with elevated cTn-values reported chest pain, the cardinal symptom of myocardial infarction (MI) in the non-surgical setting. [9] 58% of patients did not meet the diagnostic criteria defining MI - the presence of ischemic symptoms, ischemic ECG changes, or imaging evidence of a loss of viable myocardium - and thus, would have been missed. [9] Furthermore, without routine cTn-surveillance, many of those complications would have gone unnoticed. Consequently, a new syndrome called “Myocardial Injury after Non-cardiac Surgery – MINS” was established.

1.1. Definition of MI and MINS

Myocardial Infarction (MI) is defined as an ischemia-induced cTn-elevation with either ischemic symptoms, new ischemic changes or pathological Q waves on an electrocardiogram, new wall motion abnormalities detected by echocardiography, or a coronary thrombus by intracoronary imaging or autopsy. [10] (Table 1) MI can be classified based on pathological differences in the mechanism of ischemia that carry clinical and prognostic implications: MI due to atherothrombotic coronary artery disease (CAD) is designated as a type 1 MI. On the contrary, type 2 MI is caused by a mismatch between myocardial oxygen supply and demand in the absence of unstable atherosclerotic plaque. [10]

Myocardial injury after non-cardiac surgery (MINS), refers to a presumably ischemia-induced acute myocardial injury with or without clinical signs or symptoms, diagnosed by an elevation in cTn-levels exceeding the 99th percentile within the first 30 days postoperatively. [11] (Table 1) The pathophysiology of MINS is not well understood, although there is likely a shared pathophysiology with MI. Inflammatory activation and surgical stress responses may result in disruption of preexisting atherosclerotic plaques with subsequent thrombotic coronary occlusion and troponin release. [12,13] Alternatively, many patients with MINS have mismatch in myocardial oxygen supply-demand in the setting of stable CAD, precipitated by perioperative changes to cardiac, respiratory, hematologic, and metabolic physiology. In a subset of cases, MINS may, in fact, be non-ischemic, for example due to ventricular stretch in patients with acute decompensated heart failure in the perioperative setting.

1.2. Troponin assays and cut-off values

Troponins are cytoplasmic regulatory proteins of cardiomyocytic origin. There are three subunits (cTnC, cTnI, cTnT), of which two (cTnI, cTnT) are routinely used to identify myocardial injury in clinical practice. The high-sensitivity troponin T/I (hsTnT/I) assays currently represent the most accurate and sensitive diagnostic tools to detect myocardial injury. [14,15] CTn-levels above the 99th percentile upper reference limit (specific to the assay used, Table 1) are considered pathologic. [11] Although sensitive to detect MI, many conditions may lead to elevated cTn-concentrations, including tachycardia, hypotension, shock, sepsis, heart failure, pulmonary embolism, blunt trauma to the chest, chronic kidney disease, or acute stroke. [14] Assays are further influenced to a varying degree by multiple physiologic parameters (e.g. estimated glomerular filtration rate, low-density lipoprotein cholesterol, C-reactive protein). [16] Therefore, serial cTn-measurements are necessary to distinguish between acute and chronic elevations of cTn. [14] Although the 99th percentile upper reference limit for the cTn-assay is typically used to define myocardial injury, specific cTn-threshold values associated with prognosis are provided by the American Heart Association (AHA) Scientific Statement to define MINS: fourth generation cTnT ≥30 ng/l (Roche fourth-generation Elecsysc TnT assay), hsTnT 20 to <65 ng/l with an absolute change of ≥5 ng/l, or a hsTnT ≥65 ng/l (Roche Elecsys hsTnT assay) [11] or hs-cTnI ≥60 ng/l (Abbott Laboratories). [17].

1.3. Epidemiology

MINS is frequent and associated with mortality. According to a sub analysis of the prospective VISION cohort, 8% (1′200) of 15′065 patients

Table 1
Definitions of Myocardial Infarction and Myocardial Injury after Non-cardiac Surgery (MINS).

Myocardial Infarction	Myocardial Injury after Non-cardiac Surgery (MINS)
rise and/or fall of cTn-concentration with at least one value above the 99th percentile	at least one post-operative cTn-concentration that exceeds the 99th percentile *
and	with or without
any clinical symptoms like	any clinical symptom
✓ chest pain ✓ shortness of breath ✓ New ST elevations or Q-waves in ECG ✓ regional wall motion abnormalities	within 30 days after surgery
4th Universal Definition of Myocardial Infarction [10]	Diagnosis and Management of Patients With Myocardial Injury After Non-cardiac Surgery: A Scientific Statement From the American Heart Association [11]

* Fourth generation cTnT ≥30 ng/l (Roche fourth-generation Elecsysc TnT assay), hsTnT 20 to <65 ng/L with an absolute change of ≥5 ng/L, or a hsTnT ≥65 ng/L (Roche Elecsys hsTnT assay) [11] or or hs-cTnI ≥60 ng/L (Abbott Laboratories). [17].

undergoing non-cardiac surgery fulfilled the diagnostic criteria for MINS. [9] Other studies suggest, that the incidence is even higher and reaches almost 20% of patients undergoing major surgery. [7] 84% of patients with MINS remained without clinical signs or symptoms. [9] 30-day-mortality, 1-year mortality as well as overall mortality were increased in patients developing MINS. [9,18] Multiple patient-related factors such as age, renal function or sex, the presence of cardiovascular disease (CVD), diabetes, obstructive sleep apnea or congestive heart failure as well as the surgical setting (emergency or planned) and surgical specialty (liver or kidney transplantations [19]) may alter the incidence of MINS according to population-based differences. [11]

1.4. Screening and predictive tools

The American Heart Association (AHA), European Society of Cardiology and the Canadian Cardiovascular Society suggest screening for perioperative myocardial ischemia by cTn-screening in high-risk patients. [11,15,20] (Table 2) About 94% of cTn-elevations are detected within the first 2 postoperative days. [11] Since MINS is common, significantly alters medical outcome, is efficiently measurable (highly sensitive and specific as well as cost-efficient assays are available) [21] and manageable by changes in clinical practice, it is recommended to monitor cTn in the first 2 to 3 postoperative days. [11]

Some preoperative biomarkers, including BNP and NT-proBNP [22], lipoprotein-associated phospholipase A2 [23], serum alpha-hydroxybutyrate dehydrogenase levels [24] or copeptin [25], are promising to predict the risk of developing MINS and mortality. Scoring systems such as the revised cardiac risk index (RCRI) correlate with the risk of MINS in certain populations. [26] Still, as many as 1 in 12 patients >45 years of age developing MINS were missed using such scores. [27]

Table 2
Guidance from the American Heart Association (AHA), European Society of Cardiology and the Canadian Cardiovascular Society regarding cardiac troponin (cTn)-monitoring in the perioperative setting (major differences are highlighted in bold letters). BNP (brain-natriuretic peptide), CVD (cardiovascular disease), RCRI (Revised Cardiac Risk Index Score).

	American Heart Association Scientific Statement (AHA) [11]	European Society of Cardiology [20]	Canadian Cardiovascular Society [15]
Recommendation / Guidance	Suggestion to measure cTn within the first 48 to 72 h postoperatively in high-risk patients	Consideration of **preoperative** and postoperative hsTn-measurements for 48 to 72 h as well as BNP-measurements in high-risk patients undergoing high- or intermediate-risk non-cardiac surgery	Strong recommendation of postoperative cTn-measurements **daily** for 48 to 72 h in elevated-risk patients
Definition of patients at elevated-risk	- age ≥ 65 years or - age ≥ 45 years with established coronary or peripheral atherosclerotic cardiovascular disease	- existence of cardiovascular risk factors (eg. age ≥ 65 years) - known CVD - presence of symptoms suggesting CVD	- Elevation in preoperative BNP-testing or - Revised Cardiac Risk Index score (RCRI) ≥1 or - age ≥ 65 years or - age of 45 to 64 years with significant cardiovascular disease

Combinations of data from multiple specialties such as by the Surgical Apgar Score (SAS) (intraoperative heart rate, lowest MAP and estimated blood loss) [28,29] or even by integrating laboratory values, clinical signs and biomarkers might be promising tools for optimal individualized prediction and treatment decisions in the near future.

2. Management strategies

Myocardial ischemia is per definition the underlying mechanisms of MINS (e.g. caused by an oxygen supply-demand mismatch or atherothrombosis). [30,31] Apart from patient- or surgery-related factors (Table 3), multiple physiologic changes may contribute to postoperative cTn-elevations. [32] In the perioperative setting, which refers to the pre-, intra- and early postoperative course, inflammation, hemodynamic changes, such as blood pressure fluctuations or tachycardia, a hypercoagulable state or anemia might lead to an increased risk of cardiac adverse events. [33] Many of those are modifiable risk factors and may serve as clinical targets to prevent MINS (See Fig. 1):

2.1. Hemodynamic management

2.1.1. Hypotension

Intraoperative systemic hypotension reduces organ perfusion and is independently associated with postoperative organ injuries, MINS and mortality. [34–41] Even short episodes of systemic hypotension can have tremendous effects. For example, MINS is associated with a relative negative change of 30% from baseline or mean arterial pressure (MAP) of <65 mmHg. [37] This effect is aggravated when accounting for the duration of hypotension, where even few minutes with a MAP of 55 mmHg may compromise cardiac supply [35,41] in both, healthy patients and those suffering from chronic hypertension. [42] Currently, there is no consensus on a generalizable blood pressure threshold, as results from 3 randomized controlled trials (RCT) are challenging to interpret. The INPRESS trial studied 298 high-risk patients and reported a roughly 25% risk reduction if systolic pressure was maintained >80 mmHg vs. ± 10% from baseline. [43] Wanner et al. randomized 458 high-risk patients to a MAP ≥60 mmHg vs. MAP ≥75 mmHg, and POISE-3 randomized 7500 patients in a hypotension-avoidance (target MAP ≥80 mmHg) versus hypertension-avoidance (target MAP ≥60 mmHg) intraoperative strategy, but each trial reported no benefit from tight blood pressure control. [44] Interpretation of the results ofboth studies are complicated by lack of reported detail with respect to extent of

Table 3
Risk factors for developing MINS adapted by the AHA Scientific Statement on Diagnosis and Management of Patients with Myocardial Injury After Non-cardiac Surgery. [11].

Risk Factors for the development of MINS
Patient-related risk factors
Demographics: increased age [9,22,110], sex (male) [9]
Cardiovascular risk factors: smoking [111], dyslipidaemia [9]
Cardiovascular comorbidities: hypertension [9], diabetes [9], coronary/peripheral artery disease [9,86,112], cerebrovascular disease [9]
Other cardiovascular disease: atrial fibrillation [9], heart failure [9]
Other comorbidities: untreated severe obstructive sleep apnoea [113], chronic renal insufficiency (eGFR <60 ml·min^{-1}·1.73 m^{-2}) [9]
Relevant Risk indices and Preoperative test results:
Revised Cardiac Risk index score [22]
STOP-Bang risk score [113]
Random blood glucose concentration [114], Natriuretic peptide concentration [22], Neutrophil-lymphocyte ratio > 4 [115], Reticulated platelet concentration [116]
Postexercise Heart Rate Recovery [117,118], Reversibility on Myocardial perfusion testing [112,119]
Functional Capacity: Duke Activity Status Index score [120,121]
Surgical procedure-related risk factors
Emergency major surgery [9]
Peripheral vascular or aortic and major vascular surgery [9]
Procedures of long duration with large fluid shifts or blood transfusions [72]

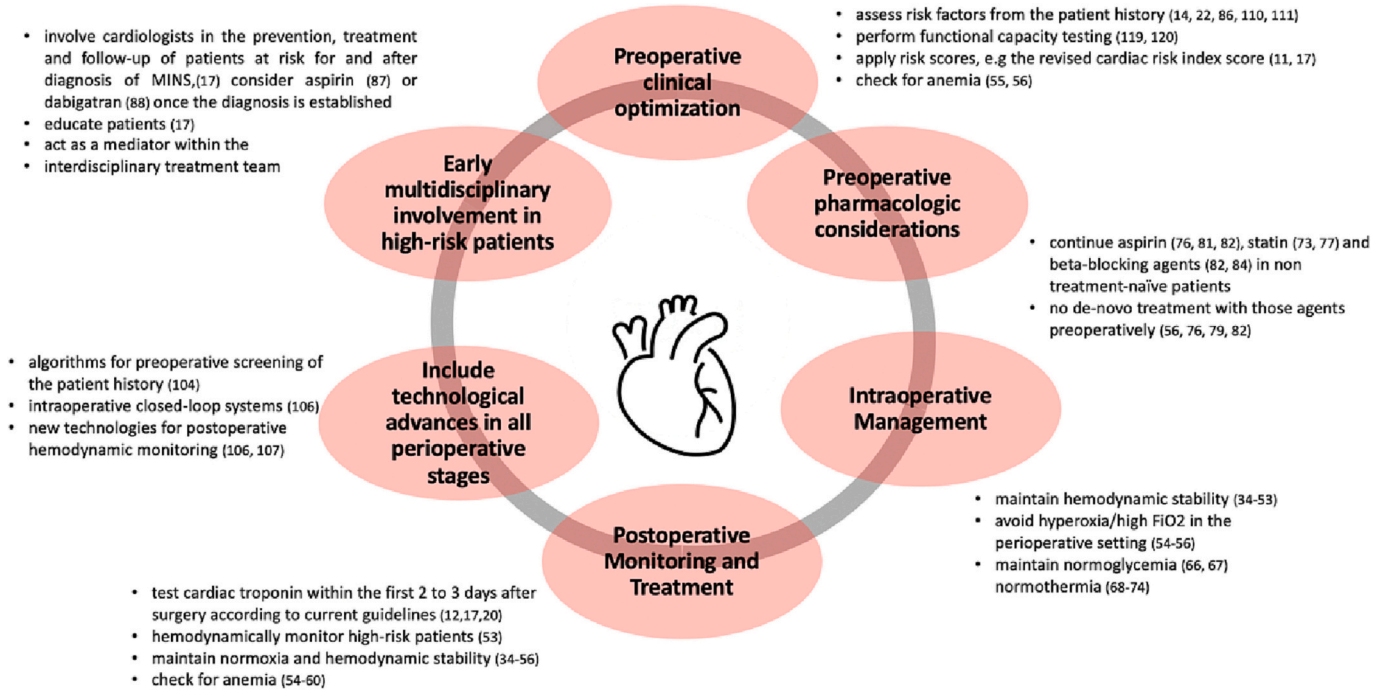

Fig. 1. Current evidence-based perioperative considerations to manage patients at risk for MINS.

hypotension, especially in the potentially harmful MAP range of 55–70 mmHg. There is thus currently little trial evidence supporting any particular harm threshold. The threshold of harm in observational analyses appears to be roughly a MAP <65 mmHg or a systolic pressure < 90 mmHg maintained for about 15 min. [37,45]

About a third of all hypotensive events occur in the time between induction of anesthesia and surgical incision [46] highlighting the importance of the careful choice of a suitable anesthetic induction agent and mindful dosing for the individual patient as well as tight and continuous blood pressure monitoring in this period. [47,48] Postoperative hypotension is common and difficult to detect. Especially in ambulatory surgery but also on the general ward, blood pressure monitoring is scarce. [49] Almost a quarter of surgical ward patients experience undetected hypotensive episodes with MAP <70 mmHg for a duration of about half an hour. [50] With the highest risk incidence of MINS within the first 48 h after surgery, the early postoperative period is an important time where optimization of monitoring is needed. Stable blood pressure management along the whole perioperative pathway is an important target for outcome optimization in anesthesiology. [43]

2.1.2. Tachycardia

Tachycardia reduces the diastolic filling of the coronaries and thus myocardial perfusion, which potentially causes myocardial oxygen supply-demand mismatch, the most likely pathologic basis of MINS. [51] Several studies reported the importance of both the severity and duration of tachycardia as a critical risk factor for MINS and mortality especially when hypotension is present in parallel. [6,52] Conflicting data from large cohort studies assessing the association of MINS and mortality with a combined severity and duration of intraoperative tachycardia score (by the use of area above heart rate) [51] have led to a lack of a clear recommendation regarding heart rate control for intraoperative use. In the postoperative period, prolonged tachycardic intervals may foster the development of MINS. [53]. This risk can for example be mitigated through a comprehensive pain management strategy along the whole perioperative pathway. [53]

Take home messages

- *The threshold of harm regarding blood pressure management appears to be roughly a MAP < 65 mmHg or a systolic pressure < 90 mmHg maintained for about 15* min.
- *One third of all hypotension episodes occur between induction of anesthesia and surgical incision.*
- *Tachycardia may raise the risk for the development of MINS and should be avoided in patients at cardiac risk, although the threshold of harm remains unknown.*

2.2. Oxygen supply

2.2.1. Perioperative anemia

The oxygen carrying capacity of the blood critically depends on hemoglobin levels, the main oxygen transport medium. [54] In anemic patients, there is a depleted amount of healthy red blood cells, thus an impaired oxygen supply that may lead to MI. [55] A preoperative hemoglobin level of below 12.2 g/dl has been recently reported to be associated with elevated risk of MINS, while moderate-to-severe anemia (hemoglobin <11 g/dl) was more significantly associated with MINS compared to mild anemia with an incidence of 18.6% for mild and 28.6% for moderate-to-severe compromise. [55] An association of anemia and the incidence of MINS was also reported in the postoperative setting, where hemoglobin values <11 g/dl were associated with a higher incidence of MINS. [56] Another study including patients from the POISE-2-, ENIGMA-II-, VISION- and BALANCED-studies reports an incidence as high as 9% for patients with a minimum postoperative hemoglobin of 8 g/dl. [57,58] At a hemoglobin value of <11 g/dl, every 1 g/dl decrease in hemoglobin accounts for a 1.46 (95% confidence interval: 1.37–1.56; $P < 0.001$) fold increase of the odds developing myocardial infarction, unstable angina or death. [57] However, comparisons of more restrictive vs. a liberal transfusion strategy remain controversial [59,60] and large scale prospective trials are needed as transfusions may after all negatively impact cardiac function. [56]

2.2.2. Intraoperative hyperoxia

Increased fraction of inspired oxygen (FiO_2) increases cellular oxygen concentration, which is believed to mediate oxidative killing by neutrophils via a “respiratory burst” during phagocytosis and therefore

reduces the incidence of surgical site infections by a small fraction. [61] However, a retrospective analysis including 1386 patients reported an association between hyperoxia and increased risk of MI, acute coronary syndrome, and death. [62] In 2 RCT's including 260 and 600 surgical patients, respectively, hyperoxia was not associated with increased risk of myocardial injury or NT-proBNP-release within 3 days after surgery. [63,64] A subsequent retrospective analysis including 1617 surgical patients also reported no association between hyperoxia and MINS. [65] In summary, despite conflicting data, hyperoxia is unlikely to significantly increase the risk of MINS.

2.3. Metabolic management

2.3.1. Temperature

Adrenergic and metabolic responses to hypothermia may upset the balance between myocardial oxygen supply and demand, leading to myocardial ischemia. Thus, a 1997 trial randomizing patients to additional intraoperative warming or no warming found a reduced incidence of cardiac arrest, MI or unstable angina when normothermia was maintained intraoperatively. [66] More recently, the PROTECT (Aggressive intraoperative warming versus routine thermal management during non-cardiac surgery) trial found that aggressive warming to a target core temperature of 37 °C did not increase the incidence of a composite of non-fatal cardiac arrest, myocardial injury or mortality, compared to maintaining routine thermal management to a target of 35.5 °C. [67] Consequently, maintaining a body core temperature above 35.5 °C during surgery is sufficient.

2.3.2. Glycemic control

Perioperative hyperglycemia may lead to inflammatory physiological changes and increased cardiovascular morbidity. [68,69] Increased blood sugar levels to >180 mg/dl have been shown to be associated with MINS. [70,71] Control of glucose levels, for example by preoperative treatments with glucose-insulin-potassium, [72] is protective regarding the development of postoperative MI in a cardiac surgical patient population. In patients with CAD and exercise-inducible ischemic symptoms, improvements of echocardiographically displayed severity of ischemia, regarding the reversibility of myocardial underperfusion, thus optimizing reperfusion recovery period, and exercise tolerance could be found by the administration of glucose-insulin-potassium before exercise testing. [73] This cardioprotective effect might be beneficial in patients at risk for MINS undergoing non-cardiac surgery. Studies assessing such effects in non-diabetic patients are lacking up to today and urgently needed.

2.3.3. Remote ischemic preconditioning

In remote ischemic preconditioning, short episodes of ischemia are applied at a peripheral tissue (e.g. the arm) prior to an expected ischemic insult of the myocardium. In theory, it may protect against myocardial ischemia-reperfusion in MINS by an assumed humoral response. Although animal models were promising, two trials randomly assigning humans to remote ischemic preconditioning versus usual care yielded mixed results. [74,75] The larger of the two, the Cardiac Remote Ischemic Preconditioning Prior to Elective Vascular Surgery (CRIPES) study with 201 patients, showed no difference between the groups. [75] With current available evidence we do not recommend remote ischemic preconditioning to reduce the incidence of MINS.

Take home messages:

- *Pre-operative and postoperative anemia are associated with a higher incidence of MINS with a graded-pattern for hemoglobin values < 11 g/dl. Therefore, preoperative treatment of anemia in patients at elevated cardiac risk is encouraged.*
- *Supplemental oxygen does decrease the risk of surgical site infection by a small fraction but does not increase the risk of cardiovascular complications including MINS.*
- *Normothermia (core body temperature > 35.5 °C) and normoglycemia (blood glucose ≤ 180 mg/dl) should be maintained through the perioperative period.*

2.4. Medications

2.4.1. Lipid lowering agents: statins

Statins have been suggested as beneficial for patients with, or at risk for, MINS, given the strong associations between MINS and atherosclerotic cardiovascular disease. [9] However, in 2016 in a trial enrolling 648 statin-naïve patients who were randomly assigned to receive a loading dose of atorvastatin within 18 h of surgery, statins failed to demonstrate a cardioprotective benefit to reduce MINS or MI, although numerically fewer participants developed MI or MINS. [76] It is conceivable that loading doses of statin administered with a longer time interval before surgery might confer a greater benefit. Similarly, given the common pathophysiological pathway with MI – where secondary prevention with statins is a cornerstone of optimal medical therapy – postoperative initiation of statins in patients with MINS could reduce further complications. According to one observational study in patients with diagnosed MINS, statin prescription at hospital discharge was associated with a reduction in one-year mortality. [77] Albeit, the study was at risk for potential unmeasured confounding: Most patients with post-discharge statins were already taking statins preoperatively, and the reduction of mortality in the statin group was mostly due to non-cardiovascular deaths – rendering the observed effect likely due to better overall medical therapy. [77] Large multicenter trials of statins in the surgical setting are still lacking. Consequently, despite a number of potential benefits of statins in the perioperative period, we lack evidence to support a pre-operative statin load to protect patients from MINS.

2.4.2. Antithrombotic agents: dabigatran and aspirin

In the large POISE-2 RCT, preoperative aspirin followed by a 30-day postoperative course of treatment did not reduce the risk of developing MI but increased rates of bleeding. [78] However, in a POISE-2 subgroup analysis of patients with CAD and prior coronary stents, aspirin was associated with a significant reduction in cardiovascular events. [79] In an observational study of patients with CAD and a history of aspirin use undergoing knee, hip or spine surgery, aspirin continuation in the perioperative period was associated with a decreased incidence of postoperative cardiovascular adverse events (myocardial injury in 13.5% under aspirin and 19.3% without treatment, $R = 0.05$) alongside with a stable safety profile regarding the risk of bleeding (red blood cell transfusion in 37.2% under aspirin and 44.2% without treatment $P < 0.001$). [80] Based on the available evidence, aspirin is not recommended as a de-novo therapy for the primary prevention of MINS in the perioperative setting [79] but can be continued in high-risk patients [81] and should be considered for the treatment of patients with a confirmed diagnosis of MINS. [82]

Once the diagnosis of MINS is established, dabigatran is the only antithrombotic agent studied to reduce long-term vascular events. [83] Dabigatran 110 mg twice a day decreased cardiovascular complications with a small increased risk of bleeding. [83] However, MANAGE was terminated early, relied on a complex composite endpoint, dabigatran is not routinely used in contemporary clinical practice, and this finding has yet to be confirmed in a second RCT.

2.4.3. Heart rate modifying agents: beta-blockers

As mentioned above, tachycardia is regarded a risk factor for MINS. A study assessing the perioperative use of beta-blocking agents (metoprolol) attempted to show possible advantageous effects. [82] However, the application of extended-release oral metoprolol preoperatively and 6 h after surgery as well for the following 30 days of the postoperative course led to an increased risk of death and incidence of stroke. [82] Those risks outweigh the tachycardia-suppressing effects regarding the prevention of MINS and MI. Consequently, beta-blocking agents should

thus not be initiated as a de-novo therapy in high-risk patients. Continuing beta-blockers in the perioperative period for long-term users still remains a valid approach. [84]

2.4.4. Type of anesthesia and anesthetic agent

In most studies assessing MINS, no clear distinction between the types of anesthesia was made. Clearly, hypotension, one of the greatest risk factors for MINS, is highly associated with the type of anesthesia and the anesthetic agent used for induction and maintenance of anesthesia. [46,85] Interestingly, a higher incidence of MINS in patients having regional anesthesia was reported.(54) It remains unclear whether this finding is simply attributable to the high number of comorbid patients in the regional anesthesia group compared to patients undergoing surgery with general anesthesia. [86] Regarding general anesthesia, current research comparing the most common intravenous anesthetic agent, propofol, with inhalational sevoflurane has not detected any difference for the incidence of MINS neither in high-cardiovascular-risk patients as identified by an altered RCRI [87], for patients truly suffering from CAD [88] nor in a specific elderly (65–80 years) patient cohort suffering from CAD. [89] Therefore, despite the previously described cardio-protective effect of sevoflurane through myocardial preconditioning, [90,91] such favorable results are not scientifically validated for MINS yet. Still, the use of sevoflurane improved hemodynamic stability in a population of patients between 65 and 80 years of age receiving general anesthesia thus it might still be beneficial in certain settings. [89]

Alternatively, cardioprotective effects have been attributed to dexmedetomidine, an agent used as a sedative or co-analgesic in the intraoperative setting. Current evidence is contradictory regarding its benefits. Some studies report better hemodynamic stability and lower incidences of tachycardic episodes while shortening the hospital length of stay. [92] Others identify an increase in bradycardic and hypotensive events throughout the perioperative pathway. [93] An additional benefit of dexmedetomidine may be its assumed anti-inflammatory properties, which could help mitigate the risk of developing MINS associated to the perioperative pro-inflammatory state. [94] Overall, intraoperative dexmedetomidine use is unlikely to reduce cardiac complications, [95] myocardial infarction, [96] atrial arrhythmias, postoperative delirium or mortality. [69,96] However, some authors report slightly better outcomes (all-cause mortality, non-fatal MI and myocardial ischemia) and highlight fact that the conclusions advocating against the cardioprotective effect of dexmedetomidine are drawn from studies where dexmedetomidine was mostly used in the pre- or intraoperative setting, and not in the vulnerable postoperative phase, where prolonged tachycardia might still promote the development MINS. [93] Further research is needed to clarify the effect of different types of anesthesia and sedative and co-analgesic agents regarding MINS in general and in specific patient populations.

2.4.5. Adjuvant inhalational anesthetic agents: intraoperative N_2O

Nitrous oxide (N_2O) may serve as a respiratory and hemodynamically stable adjuvant inhalational anesthetic and analgesic. [97] It seems plausible, that intraoperative N_2O exposure increases cardiovascular short and long-term morbidity and even mortality. N_2O inactivates the methionine synthase, leading to persistent vitamin-B-deficiency and hyper-homocysteinemia for at least one week post-surgically. [98] Vitamin-B-deficiency may then lead to endothelial dysfunction. [98] The ENIGMA trial randomized 2050 surgical patients having noncardiac surgery lasting >2 h to N_2O-based or N_2O-free anesthesia. The median follow-up time was 3.5 (range (0 to 5.7) years. N_2O did not increase the risk of death [hazard ratio = 0.98 (95% confidence interval: 0.80 to 1.20; $P = 0.82$)], nor stroke [adjusted odds ratio: 1.01 (95% CI: 0.55 to 1.87; $P = 0.97$)]. However, adjusted odds ratio for myocardial infarction in patients with N_2O was mildly elevated 1.59 (95% CI: 1.01 to 2.51; $P = 0.04$).

Interestingly, cTnT surveillance 6–12 h after surgery and on the first 3 postoperative days did not provide any evidence for short-term myocardial injury. Therefore, there is currently no evidence suggesting a deteriorating effect of N_2O on the development of MINS [98] but its use is limited by other anesthesia-related deleterious effects such as an increased risk for postoperative nausea and vomiting. [97]

2.4.6. Anti-inflammatory agents (vitamin C, N-acetylcystein, colchicine)

Many alternative prophylactic and therapeutic options for MINS are currently under investigation: the preoperative application of the anti-inflammatory agents vitamin C and *N*-acetylcysteine did not affect cardiovascular risk in patients undergoing major non-cardiac surgery. [63] It should not be used as a preventive agent for MINS. Alternatively, colchicine, a drug mostly used in the treatment and prevention of gout flares, is known for its anti-inflammatory properties [99], and has been used in patients with pericarditis and CAD. [100] Among surgical patients, colchicine has mainly been studied in the perioperative period of cardiac surgery. There is some evidence suggesting a reduction in hsTnT and CK-MB by a perioperative course of colchicine administration in patients undergoing on-pump coronary artery bypass grafting [101] and a significantly lower increase in hsTnI-levels in patients undergoing percutaneous coronary intervention after preoperative colchicine treatment compared to patients without such a preoperative treatment course. [102] Although colchicine is conceptually appealing for patients undergoing non-cardiac surgery, there is currently insufficient data to recommend its use to prevent MINS. Results of further ongoing RCTs such as COP-AF (Colchicine for the Prevention of Perioperative Atrial Fibrillation in Patients Undergoing Thoracic Surgery; NCT03310125), COPMAN (Colchicine Prevents Myocardial Injury After Non-Cardiac Surgery Pilot Study; NCT04139655), and POPCORN (Perioperative Colchicine to Reduce Negative Events; NCT NCT05618353) should guide decision-making regarding the perioperative use of colchicine in the near future.

Take home messages:

- *Currently, there is no evidence for a beneficial effect of preoperative statin-loading, the novel use of antithrombotic medication, anticoagulation or beta-blocking drugs, the choice of a certain type of anesthesia or anesthetic agent, the application of intraoperative N_2O or anti-inflammatory agents to reduce the risk of MINS.*
- *Aspirin should be continued in the preoperative period in high-risk patients.*
- *Beta-blocking agents should be continued preoperatively in patients under long-term treatment.*
- *Neither beta-blockers nor aspirin should be initiated de-novo to prevent perioperative MINS.*
- *Sevoflurane provides improved hemodynamic stability and might still be considered for the especially vulnerable elderly population.*
- *Once the diagnosis of MINS is made, aspirin and dabigatran should be considered, while keeping in mind that the observed reduction of long-term vascular events through the use of dabigatran still needs validation in future RCT's.*

3. Future perspectives and the role of anesthesia practitioners

In the near future, more individualized predictive scores based on large data sets integrating clinical function, demographics and biomarkers may set a milestone in optimal screening and high-end treatment. [103] Modern technology may be used to streamline the preoperative information acquisition process and identify risk factors automatically and early in the perioperative course. [104] Risk stratification models may also help proactively approach patients at risk for developing MINS. Still, personalized intraoperative and postoperative treatment plans are of special importance regarding the management of MINS [105]: In the intraoperative setting, technological advances may support clinicians predict hypotensive events or provide optimal hemodynamic control during anesthesia. [106] Postoperative safety should be improved by closer monitoring through the use of innovative

technology, such as mobile alert systems for general ward patients or modern technologies to more readily track hemodynamic changes [107,108] and systematically planned follow-ups for optimal secondary prevention. Given limited data on the optimal management of MINS, perioperative cTn-surveillance is not widely practiced. [109] To change practice, novel medical therapies to prevent and treat MINS are necessary. The development of treatment guidelines and promotion of research should be based on interdisciplinary collaboration and include bundles of care and multidimensional approaches. [11] Anesthesia providers are perioperative specialists and should act as mediators in the multidisciplinary setting, protecting patient safety and providing high-end care.

Perioperative physicians may promote prehabilitation programs or individualized preoperative tools for screening for frailty, use advanced monitoring and technological tools to assist hemodynamic management in the intraoperative period and finally, provide high standards of care and surveillance also in the postoperative period such as by remote monitoring for the surgical wards, post-operative care units or intensive-care units.

4. Conclusion

MINS is a common cardiovascular event and is strongly associated with short and long-term mortality after non-cardiac surgery. Routine perioperative cTn-surveillance is not performed at many centers, despite the fact that it is cost-effective and recommended by several expert panels. Anesthesiologists need to be sensitized to the importance of identifying patients at risk for MINS. It is paramount to recognize non-modifiable and optimize modifiable preoperative risks, provide safe and hemodynamically stable intraoperative care and systematic post-operative follow-up with cTn-measurements at least for the first 2 to 3 days after surgery in high-risk patients, and among patients with MINS, implement cardiovascular therapies for secondary prevention, including statins and antithrombotic agents. Early interdisciplinary involvement, patient education about MINS-associated risks and a proposal for the implementation of lifestyle changes are strongly encouraged to create true impact in this deadly perioperative entity. Anesthesiologists may act as perioperative mediators within the interdisciplinary network of cardiologists, surgeons, nurses and patients alike to aim for the best outcome for all patients.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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