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Myocardial Injury after Non-Cardiac Surgery: A Systematic Review and Meta-analysis

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Abstract

Myocardial injury after non-cardiac surgery (MINS) is a common post-operative complication associated with adverse cardiovascular outcomes. The purpose of this systematic review was to determine the incidence, clinical features, pathogenesis, management, and outcomes of MINS. We searched PubMed, Embase, Central and Web of Science databases for studies reporting the incidence, clinical features, and prognosis of MINS. Data analysis was performed with a mixed-methods approach, with quantitative analysis of meta-analytic methods for incidence, management, and outcomes, and a qualitative synthesis of the literature to determine associated pre-operative factors and MINS pathogenesis. A total of 195 studies met study inclusion criteria. Among 169 studies reporting outcomes of 530,867 surgeries, the pooled incidence of MINS was 17.9% (95% CI 16.2%-19.6%). Patients with MINS were older, more frequently men, and more likely to have cardiovascular risk factors and known coronary artery disease. Post-operative mortality was higher among patients with MINS than those without MINS, both in-hospital (8.1%, 95% CI 4.4%-12.7% versus 0.4%, 95% CI 0.2%-0.7%; relative risk 8.3, 95% CI 4.2 - 16.6, $p<0.001$) and at 1-year after surgery (20.6%, 95% CI 15.9%-25.7% versus 5.1%, 95% CI 3.2%-7.4%; relative risk 4.1, 95% CI 3.0 - 5.6, $p<0.001$). Few studies reported mechanisms of MINS or the medical treatment provided. In conclusion, MINS occurs frequently in clinical practice, is most common in patients with cardiovascular disease and its risk factors, and is associated with increased short- and long-term mortality. Additional investigation is needed to define strategies to prevent MINS and treat patients with this diagnosis.

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Keywords

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Non-cardiac surgery is an essential therapeutic modality and more than 300 million non-cardiac surgeries are performed worldwide each year.[1] Although non-cardiac surgery confers substantial clinical benefits, adverse cardiovascular events remain a major source of morbidity and mortality in the perioperative period.[2] Myocardial injury after non-cardiac surgery (MINS) is commonly defined as a rise and fall of cardiac biomarkers within 30-days following non-cardiac surgery that may occur with or without the clinical criteria necessary to fulfill the universal definition of myocardial infarction (MI).[3] Myocardial injury is the most common cardiovascular complication following non-cardiac surgery, approximately 30-fold more common than post-operative MI among patients at increased cardiovascular risk.[4] MINS is commonly detected with perioperative measurement of cardiac troponin I (cTnI) or cardiac troponin T (cTnT), key myocardial regulatory proteins that are sensitive and specific biomarkers indicative of myocardial damage, and defined when troponin values exceed the 99th percentile of the reference distribution for the assay in healthy individuals.[5, 6] Older cardiac biomarkers, such as the MB fraction of creatine kinase (CK-MB), may also be used to identify myocardial injury, but interpretation of CK-MB is complicated by the significant rise in total creatine kinase after surgery.[7–10] Although MINS is a common and increasingly recognized post-operative phenomenon, its incidence, risk factors, pathogenesis and clinical implications have not been adequately defined.[11] We performed a mixed methods systematic review of the literature to define the epidemiology, clinical features, management, and outcomes of MINS.

METHODS

A comprehensive, structured, systematic review of the literature was performed to identify studies reporting the results of post-operative cardiac biomarker measurements in patients undergoing major non-cardiac surgery. In collaboration with an experienced systematic review librarian, we searched PubMed/MEDLINE, Ovid EMBASE, Ovid Cochrane CENTRAL, and Web of Science databases through November 11, 2017. We created a search strategy using keywords and appropriate subject headings for our three main concepts: myocardial injury, non-cardiac surgeries, and post-operative care. No additional limits were used in the search. Full search strategies can be found in Appendix 1.

Eligibility Criteria & Study Selection

Studies were eligible for inclusion if the published full-text manuscript included original data on any of the following: incidence of MINS, clinical features, pathogenesis, management of MINS, and short- and long-term outcomes. We excluded published abstracts from scientific conferences, articles that did not report the proportion of patients with abnormal cardiac biomarkers based on a clearly defined threshold value, editorials, letters to journal editors, and errata, small studies with fewer than 50 participants undergoing surgery, reviews, systematic reviews, and meta-analyses, non-English language publications, and

articles that included participants undergoing cardiac surgery. After an initial search retrieval of 6,241 results, we **eliminated** duplicate records electronically, with the remaining 3,771 results included in the initial screening. Screening was conducted in two stages. An initial title/abstract screening was independently conducted by two reviewers that excluded 3,346 irrelevant studies. A full-text review of the remaining 425 studies by two independent reviewers excluded an additional 231 studies that did not meet study eligibility criteria One additional study was identified by expert review (Figure 1). All conflicts were resolved through discussion or adjudication by a third reviewer.

Study Quality

All studies were evaluated using the Newcastle-Ottawa Quality Assessment Scale, an instrument recommended for the assessment of quality of nonrandomized observational studies by the Cochrane Collaborative Group (Appendix 2).[12] Assessment of quality is determined based on selection (4 criteria), study-control group comparability (1 criterion), and outcome assessment (3 criteria), and observational studies meeting ≥5 criteria are considered to be of high quality.

Data Collection, Extraction, and Analysis

The incidence of MINS, clinical characteristics of patients with MINS, the management of MINS at hospital discharge, and short- and long-term outcomes were identified by review of full-text records. Data for these endpoints were pooled and analyzed using random effects meta-analysis models; relative risks (RR) and 95% confidence intervals (CIs) were reported. Heterogeneity in the study estimates were assessed using I-squared statistics, with larger values indicating increasing heterogeneity between studies. Additional study endpoints, including pre-operative factors associated with MINS, the results of in-hospital cardiovascular diagnostic testing, and the reported underlying mechanism of MINS, were analyzed by qualitative synthesis of the literature. All analyses were performed using STATA (version 15, College Station, TX, USA) and SPSS (version 23, IBM, Armonk, NY, USA). All data used were publicly available and were not identifiable, making the study exempt from institutional board review.

RESULTS

A total of 195 studies that met the study inclusion criteria were identified via systematic review (Figure 1). The complete list of studies that met eligibility criteria are listed in Appendix 2. We extracted data from all 195 studies meeting our inclusion criteria. Of those 195 studies, 169 unique studies reported MINS incidence, 72 reported demographics and clinical characteristics of MINS, and 62 reported outcomes by MINS status.

MINS Incidence

A total of 169 unique studies reported outcomes of 530,867 non-cardiac surgeries and provided data on post-operative cardiac biomarkers. Among these, 139 studies reported the results of systematic cardiac biomarker measurement in the perioperative period of all subjects undergoing surgery, while 30 studies reported results of clinically-indicated cardiac biomarker testing. Overall, the incidence of MINS was calculated to be 17.9% (95% CI

16.2%−19.6%; I^2 99.5%) based on random effects analysis (Figure 2; Supplemental Figure 1). Among the 139 studies that systematically measured cardiac biomarkers in all surgical patients, MINS occurred in 19.6% of patients (95% CI 17.8%−21.4%; I^2 = 98.2%). Among the 30 studies that did not systematically perform cardiac biomarker screening, the incidence of MINS was 9.9% (95% CI 8.4%−11.5%). Among high quality, prospective studies with systematic measurement of troponin in ≥250 surgeries (n=44), the incidence of MINS was 19.5% (95% CI 17.8%−21.3%; I^2 = 98.2%, Supplemental Figure 2).

The incidence of MINS varied based on the cardiac biomarker assay employed in the perioperative period. Routine post-operative measurement of high sensitivity cTnT identified MINS in the post-operative period of 24.7% (95% CI 19.7%−29.9%) of surgeries (n=10), cTnI identified MINS in 20.1% (95% CI 16.8%−23.6%) of surgeries (n=79), cTnT identified MINS in 17.4% (95% CI 14.9%−20.0%) of surgeries (n=40), and studies with combinations of either cTnI or cTnT measurement identified MINS in 12.2% (95% CI 6.3%−19.6 %) of surgeries (n=10).

MINS occurred more frequently in urgent or emergent procedures. Based on 17 studies that included data from 107,164 surgeries, MINS occurred in 32.7% (95% CI 26.1 – 39.6%) of urgent surgeries and 16.6% (95% CI 12.2% - 21.5%) of non-urgent surgeries (RR 1.74, 95% CI 1.35 – 2.25). MINS also varied by non-cardiac surgical subtype. Among 68 studies of patients undergoing vascular surgery with systematic measurement of post-operative troponin, MINS was identified in 20.1% (95% CI 17.8%−22.5%). Of the 17 studies of patients undergoing orthopedic surgery, MINS was identified in 18.0% (95% CI 12.1% −24.7%). In the 8 studies that included patients undergoing general surgery with systematic post-operative troponin measurement, MINS was identified in 25.9% (95% CI 15.1% −38.4%) of cases. Full data are shown in Appendix 3.

MINS Demographics

Patients with MINS were older than those without MINS undergoing non-cardiac surgery (70.4 years vs. 62.2 years, standardized mean difference 0.40, 95% CI 0.28 – 0.51; p<0.001), based on data from 49 studies. Sex differences in the incidence of MINS were reported in 45 studies. Overall, 35.2% of patients with MINS were women. The incidence of MINS was higher in men (17.7%, 95% CI 14.3%−21.3%) than women (16.2%, 95% CI 13.3%−19.2%) undergoing non-cardiac surgery (pooled RR 1.34, 95% CI 1.12 – 1.61, p=0.002).

Clinical Risk Factors

A total of 63 studies reported the prevalence of cardiovascular disease or at least 1 cardiovascular risk factor among subjects undergoing non-cardiac surgery. Patients with MINS were significantly more likely to have hypertension, coronary artery disease (CAD), prior MI, heart failure, and kidney disease compared with patients without MINS. Clinical characteristics of patients with and without MINS are shown in Table 1 **and** Figure 3.

Outcomes

In-hospital mortality was reported in 25 studies. In-hospital post-operative mortality was higher among patients with MINS than among patients without MINS (8.1% [95% CI 4.4%

- 12.7%] versus 0.4% [95% CI 0.2% - 0.7%], p<0.001). Among 24 studies reporting 30-day outcomes, death within 30-days of surgery remained substantially higher among patients with MINS in comparison to those without MINS (8.5% [95% CI 6.2% - 11.0%] versus 1.2% [95% CI 0.9% - 1.6%], p<0.001). In the 2012 Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) study, 45% of deaths within 30 days of surgery were due to vascular causes, and MINS was strongly associated with both vascular and non-vascular mortality.[13]

Long-term outcomes of MINS were reported in 18 studies. Mortality at 1 year was 20.6% (95% CI 15.9% - 25.7%) among patients with MINS and 5.1% (95% CI 3.2% - 7.4%) among patients without MINS (p<0.001). Beyond 1 year, mortality was 42.7% (95% CI 33.8% - 51.8%) among patients with MINS and 19.7% (95% CI 10.6% - 30.9%) among patients without MINS (p<0.001), based on 11 studies with follow-up ranging from 2 to 7 years. Pooled post-operative outcomes data are shown in Table 2, Figure 4, **and** Appendix 4.

PRE-OPERATIVE THERAPY TO PREVENT MINS

Aspirin Use

Few studies have addressed the relationship between perioperative aspirin use and MINS (Appendix 5). In a study of 220 patients undergoing non-cardiac surgery who were randomly assigned to perioperative aspirin or placebo, there was no significant difference in the frequency of MINS (3.7% versus 9.0%, p=0.10).[14] A retrospective observational study of orthopedic surgeries performed during two time periods reported no difference in the incidence of MINS despite a higher proportion of patients receiving perioperative aspirin in the later period.[15] In an analysis of the Coronary Artery Revascularization Prophylaxis (CARP) study, the frequency of MINS was lower in patients who received pre-operative aspirin within 48 hours of surgery.[16] However, in the majority of observational studies reporting pre-operative clinical characteristics, rates of MINS were similar with and without pre-operative aspirin use (Appendix 5). Three observational studies reported a higher frequency of MINS in patients prescribed pre-operative aspirin.[17–19] Although the Perioperative Ischemic Evaluation (POISE)-2 study evaluated the impact of perioperative aspirin in a large cohort of patients undergoing major non-cardiac surgery, the primary outcome was a composite of death or MI, and MINS was not reported as an outcome. Thus, POISE-2 was not included in this systematic review. Overall, in a pooled analysis of 24 relevant studies, aspirin use was not associated with MINS (pooled RR 1.02, 95% CI 0.88 – 1.18) (Appendix 5).

Statin Therapy

In a sub-analysis of the VISION study, pre-operative use of statins was associated with a lower risk of MINS (RR, 0.86; 95% CI, 0.73–0.98).[20] Similarly, in a prospective study of patients undergoing vascular surgery, high dose statins in the perioperative period were associated with reductions in MINS (OR 0.84, 95% CI 0.76 to 0.93).[21] Moreover, in an observational study of statin users undergoing major vascular surgery, interruption of statin therapy in the perioperative period was associated with an increased risk for MINS (HR 4.6, 95% CI 2.2 to 9.6).[22] However, in the Lowering the Risk of Operative Complications Using

Atorvastatin Loading Dose (LOAD) randomized controlled trial, the administration of high-intensity statin therapy within 18 hours prior to major non-cardiac surgery failed to significantly reduce the incidence of MINS compared with placebo (13.2% vs. 16.5%, p=0.26; HR 0.79, 95% CI 0.53–1.19).[23] Based on the available data, the benefit of statin therapy to reduce the incidence of MINS is speculative (Appendix 5). In a pooled analysis of 25 relevant studies, statin use was not associated with MINS (pooled RR 0.92, 95% CI 0.78 – 1.08).

ACE Inhibitor/ARB Use

Withholding angiotensin-converting enzyme inhibitors (ACE) or angiotensin II receptor blockers (ARB) prior to surgery has been associated with a lower incidence of MINS compared with continuation of ACE/ARB in the perioperative period (10.6% versus 11.3%, adjusted RR 0.84 (0.70−0.998), p=0.048).[24] Other studies also reported increased frequency of MINS in patients who received perioperative ACE/ARB.[17, 19] In a pooled analysis of 18 relevant studies, ACE/ARB use was associated with the incidence of MINS (pooled RR 1.23, 95% CI 1.14 – 1.32) (Appendix 5).

Beta-blocker Use

In a large observational study, the acute initiation of pre-operative beta-blocker use was associated with a higher incidence of MINS (OR 5.96; 95% CI 3.09 – 11.52; p<0.001).[25] In contrast, beta-blocker use for >1 week prior to surgery and high-dose beta-blocker use at the time of surgery have been associated with a lower incidence of MINS.[26, 27] Although the effects of beta-blockade on the incidence of MINS remain uncertain, beta-blocker use was associated with the incidence of MINS (pooled RR 1.29, 95% CI 1.11 – 1.51) in a pooled analysis of the 27 relevant studies (Appendix 5).

Remote Ischemic Preconditioning

Remote ischemic preconditioning is the application of brief episodes of transient ischemia at a remote tissue prior to a planned ischemic insult of the myocardium. In theory, remote ischemic preconditioning may provide protection against myocardial ischemia-reperfusion injury during non-cardiac surgery, although studies evaluating this concept have reached discordant conclusions (Appendix 5). In a study of patients undergoing elective open abdominal aortic aneurysm repair who were randomly assigned to remote ischemic preconditioning versus usual care, remote ischemic preconditioning was associated with a reduced incidence of MINS (OR: 0.22, 95% CI: 0.07 to 0.6).[28] In contrast, in the prospective, randomized Cardiac Remote Ischemic Preconditioning Prior to Elective Vascular Surgery (CRIPES) study, there was no significant difference in the frequency of MINS among patients assigned to remote ischemic preconditioning compared with usual care (22.2% vs. 24.7%; p=0.67).[29] Thus, the available evidence does not support the use of remote ischemic preconditioning to reduce the incidence of MINS. In a pooled analysis of 3 studies, remote ischemic preconditioning was not associated with the incidence of MINS (pooled RR 0.71, 95% CI 0.43 – 1.18).

INTRAOPERATIVE RISK FACTORS

Patients with MINS were significantly more likely to undergo urgent or emergent surgery, open surgery (versus endovascular surgery), receive intraoperative transfusions, have prolonged intraoperative time with a mean arterial pressure <65 mmHg, a maximum intra-operative heart rate of >110 beats per minute, and receive perioperative vasopressors than patients without MINS.[16, 30–35] The relationship between anesthesia type and MINS remains uncertain. Although sevoflurane was associated with lower rates of MINS than propofol (11.7% vs 29.0% $P = 0.018$) in one study,[36] four others failed to show any benefit of volatile anesthetics with respect to MINS.[37–40]

MECHANISMS OF MINS

Five studies reported mechanisms of MINS. In a large cohort of 1,023 patients with MINS who were referred for coronary angiography within 7 days of surgery, obstructive CAD was present in 46.1% of cases, and revascularization was performed in 32%.[41] In a study of patients undergoing vascular surgery, 732 patients with MINS were systematically classified by the presumed mechanism of myocardial injury. A baseline elevation in troponin was identified in 66% of patients, intraluminal thrombosis (type 1 MI) was reported in 12%, and a mismatch in myocardial oxygen-demand in the setting of stable or non-obstructive CAD (type 2 MI) was identified in 22% of patients.[42] In a prospective cohort study of 46 patients with MINS who were referred for coronary computed tomography angiography, obstructive CAD was identified in 50% of cases, and pulmonary embolism was present in 33% of patients with MINS.[43]

The mechanism of MINS may also be classified based on the predisposing or provoking cardiac and non-cardiac conditions present at the time of the event. In 290 patients with MINS who were evaluated by a cardiology consultant, anemia, hypertension, sinus tachycardia, hypotension, sepsis and volume overload were reported as the most common extrinsic provoking conditions. Tachyarrhythmia (supraventricular or ventricular tachycardia), pre-existing CAD, cardiomyopathy, and left ventricular hypertrophy were the most common intrinsic cardiac conditions provoking MINS. No specific etiology was identified in 43% of patients.[17] In other larger series, non-ischemic mechanisms of MINS were reported in only 11%, with chronic elevations in 64.2%, troponin elevations attributed to sepsis in 11%, atrial fibrillation in 9%, and pulmonary embolism in 3%.[44]

POST-OPERATIVE MANAGEMENT OF MINS

Cardiovascular medications are inconsistently prescribed at discharge in patients with MINS. Based on data from 5 studies, aspirin was prescribed in 58.6% (95% CI 31.0% −83.7%) of patients with MINS, beta-blockers were prescribed in 57.2% (95% CI 34.7% −78.3%), statins were prescribed in 49.1% (95% CI 31.3%−67.0%), and ACE inhibitors were prescribed in 37.0% (95% CI 17.0%−59.5%). The Management of Myocardial Injury After Noncardiac Surgery (MANAGE) trial of dabigatran versus placebo in patients with MINS is the first study to prospectively evaluate treatment strategies in a large cohort of patients with MINS.[45] Dabigatran was associated with a 28% reduction in a composite

endpoint of vascular mortality, MI, non-hemorrhagic stroke, peripheral arterial thrombosis, amputation, and symptomatic venous thromboembolism.[46] This provides evidence that patients with MINS may benefit from intensive antithrombotic therapies to reduce major adverse cardiovascular events.

DISCUSSION AND CONCLUSION

This systematic review provides a comprehensive overview of the incidence, management and outcomes of MINS. We demonstrate that MINS occurs in 19.5% (1 in 5) of non-cardiac surgeries, but is only detected in 9.8% of cases (1 in 10) when selective, clinically indicated post-operative biomarker screening is employed. This is due to the fact that myocardial injury is often clinically silent in the post-operative period following the administration of anesthesia and analgesia, and only 15.8% of patients with MINS have ischemic symptoms in large series.[30] Therefore, a post-operative troponin measurement may be due to clinical evidence of ischemia, or simply a high index of suspicion based on estimated cardiovascular risk. Regardless, routine postoperative measurement of cardiac biomarkers detects up to three-fold more individuals with MINS in comparison to clinically–driven troponin measurements. [47] Consequently, the routine measurement of troponin may be reasonable among patients undergoing non-cardiac surgery who are at an increased risk for cardiovascular events.

The incidence of MINS may vary based on the timing of troponin measurement after surgery. Among patients diagnosed with MINS, 51% have an abnormal serum troponin-I within the first 24 hours following surgery, with 78% of MINS detected by 48 hours.[4] Longer periods of troponin monitoring may increase MINS incidence, but may also capture cardiovascular events that were not precipitated by surgery. Unfortunately, no standardized approach to the duration of troponin screening to detect MINS has been established. The choice of cardiac biomarker assay also affects the MINS incidence, with the highest incidence associated with high-sensitivity troponin assays. This is likely due to the use of lower absolute thresholds for MINS with more sensitive assays. As the degree of troponin elevation is thought to reflect a continuum of risk, more sensitive assays may identify greater numbers of low risk patients. This has serious implications to clinical care, as the risk-benefit profile of therapies to treat MINS may differ according to the baseline cardiovascular risk of the treated population. Careful consideration must be given to the implications of diagnosis and treatment, particularly if next-generation high sensitivity troponins are used. In general, patients at the highest risk for MINS should be considered for post-operative troponin measurement.

Older age, male sex, and cardiovascular risk factors were associated with the development of MINS. Patients who developed MINS were significantly more likely to have hypertension, CAD, prior MI, heart failure, and kidney disease. Diabetes and peripheral arterial disease were also associated with MINS in some studies.[30] Patients without MINS also had a substantial burden of cardiovascular risk factors in the studies analyzed. This reflects the selective inclusion of high-risk surgical candidates in the studies that report the incidence of MINS.

Few studies reported mechanisms of MINS, likely due to the diagnostic challenges in this complex patient population. In many cases, MINS may represent a mismatch in myocardial oxygen supply-demand that leads to an ischemic imbalance in the setting of stable obstructive CAD or microvascular CAD. When the appropriate clinical features are present, episodes of MINS may meet the criteria for type 2 MI. Alternative etiologies may include acute coronary syndromes due to unstable atherosclerotic plaques (type 1 MI), stress-induced cardiomyopathy, or cardiomyocyte stretch associated with increased intravascular volume in patients with underlying myocardial abnormalities. Secondary causes, including inflammation related to sepsis and myocardial strain related to pulmonary embolism, may also play a role. However, further investigation is necessary to appropriately subtype patients based on the mechanism of myocardial injury. Additionally, the clinical significance of the distinction between MINS and perioperative MI, as defined by the Universal Definition, remains uncertain.[3] Recent series report a similar prognosis associated with MINS and perioperative MI.[48] This may be due to unreliable symptom ascertainment or diagnostic limitations in the perioperative setting, leading to misclassification of patients with MINS who have unrecognized MI.

MINS is associated with significant short- and long-term increases in post-operative mortality, irrespective of the presence of an ischemic feature and the diagnosis of MI.[30, 47, 49] Although the relative risk of mortality associated with MINS declined over time, patients with MINS were more than twice as likely to die than patients without MINS even after 2–7 years of post-operative follow-up. As a consequence, MINS has been proposed as a surrogate endpoint for perioperative quality improvement.[50]

Despite interest in MINS, the optimal management of this condition remains uncertain. Anticoagulation with dabigatran was associated with a significant reduction in a composite of cardiovascular outcomes in a large randomized controlled trial.[46] This provides evidence that MINS treatment should include intensive antithrombotic therapy. Further investigation and confirmation of this finding is necessary. Currently, patients with MINS are infrequently prescribed medical therapy for atherosclerotic cardiovascular disease.[51] Empiric initiation and intensification of guideline-directed medical therapy for ischemic heart disease should be considered for all patients with MINS unless there are contraindications. After recovery from surgery, cardiovascular risk stratification with stress testing or coronary angiography may also be considered for patients diagnosed with MINS, although the benefit of routine cardiovascular testing in this population remains unknown.

There are a number of limitations of the present analysis. First, this systematic review and meta-analysis is based on the available published literature and is limited by publication and selection biases. Many of the studies included patients undergoing vascular surgery, which may limit the generalizability of the findings to other surgical subtypes. Second, studies included in this analysis used a variety of troponin assays with varying thresholds for MINS and variable timing of troponin measurement in relation to surgery. We identified significant heterogeneity between the included studies, although random effects models were used for the primary analysis to account for this limitation. Studies that relied on the delta troponin without an absolute threshold to identify MINS were not included. Third, given the limited data from studies reporting potential mechanisms of MINS, we were unable to perform a

robust meta-analysis and instead relied on qualitative evaluation of the literature. Fourth, observational associations between pre-operative cardiovascular medication use and the incidence of MINS are subject to confounding by indication and should be interpreted with caution. Fifth, we included potentially controversial studies authored by Dr. Poldermanns, who published extensively on the cardiovascular risks of non-cardiac surgery but was accused of ethical lapses and falsification of data (Appendix 2).[52] Sixth, the cause of death after MINS was not frequently reported and could not be reliably assessed in this meta-analysis.

In conclusion, MINS is common and is associated with adverse short- and long-term outcomes. The incidence of MINS depends on the demographics and comorbidities of the surgical population, and the approach and timing of troponin measurement. The diagnosis of MINS may provide opportunities for implementing strategies to reduce cardiovascular risk, but the optimal therapies in this setting remain uncertain. Until guideline recommendations are available, screening for and treating MINS will require thoughtful and individualized assessment of the patient and surgery-specific cardiovascular risks.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Dr. Smilowitz affirms that the manuscript is an honest, accurate, and transparent account of the study being reported.

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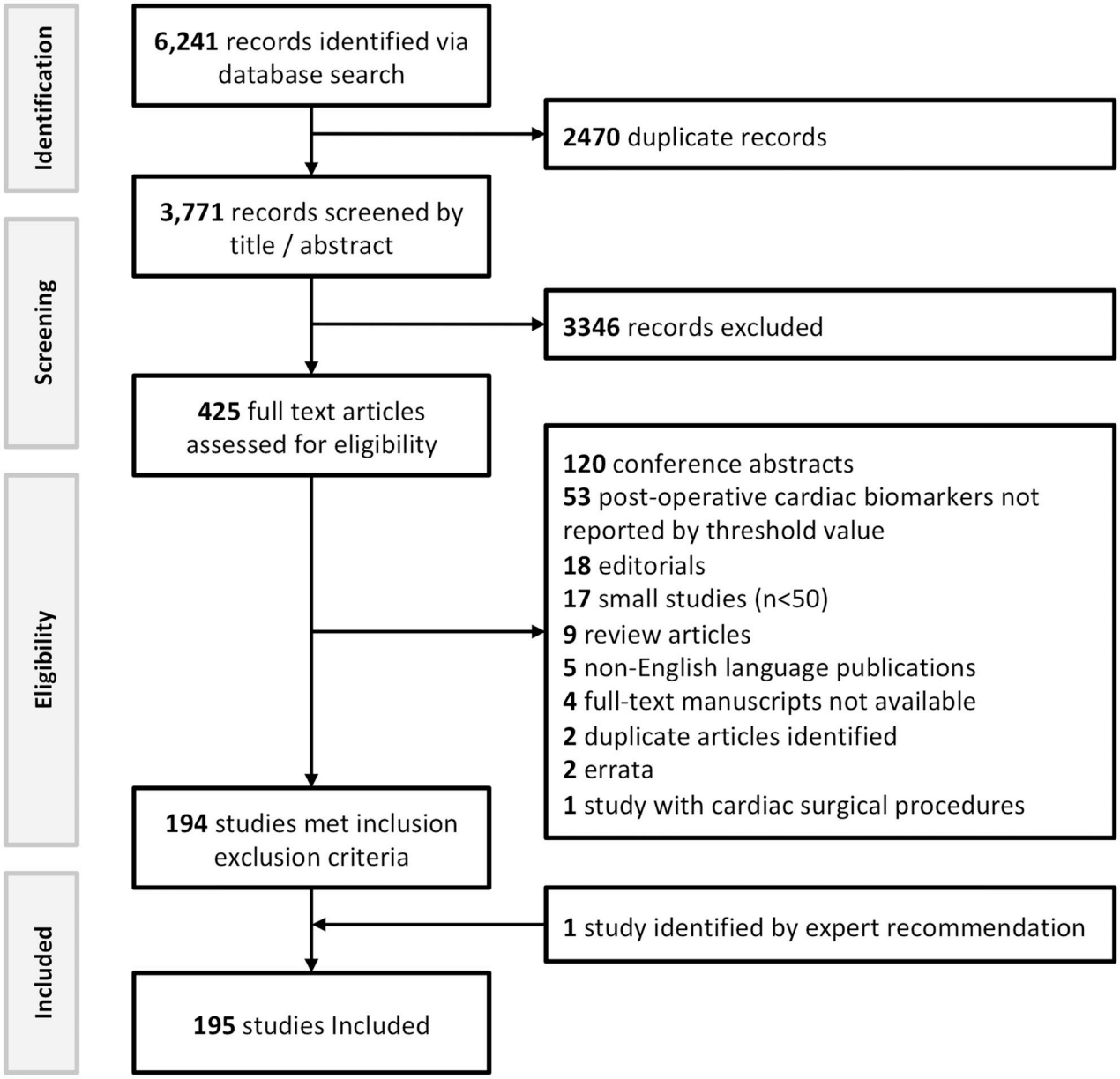

Figure 1.
Flow diagram of study selection process.

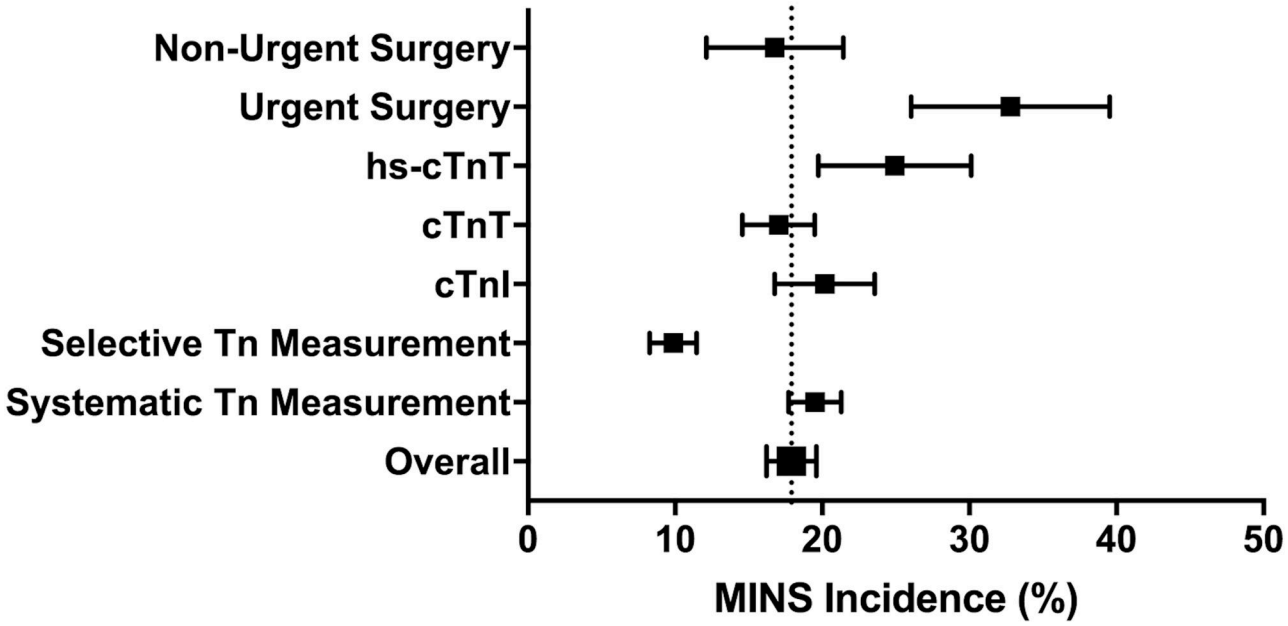

Figure 2.
Incidence of myocardial injury after non-cardiac surgery (MINS) overall and by subgroups.

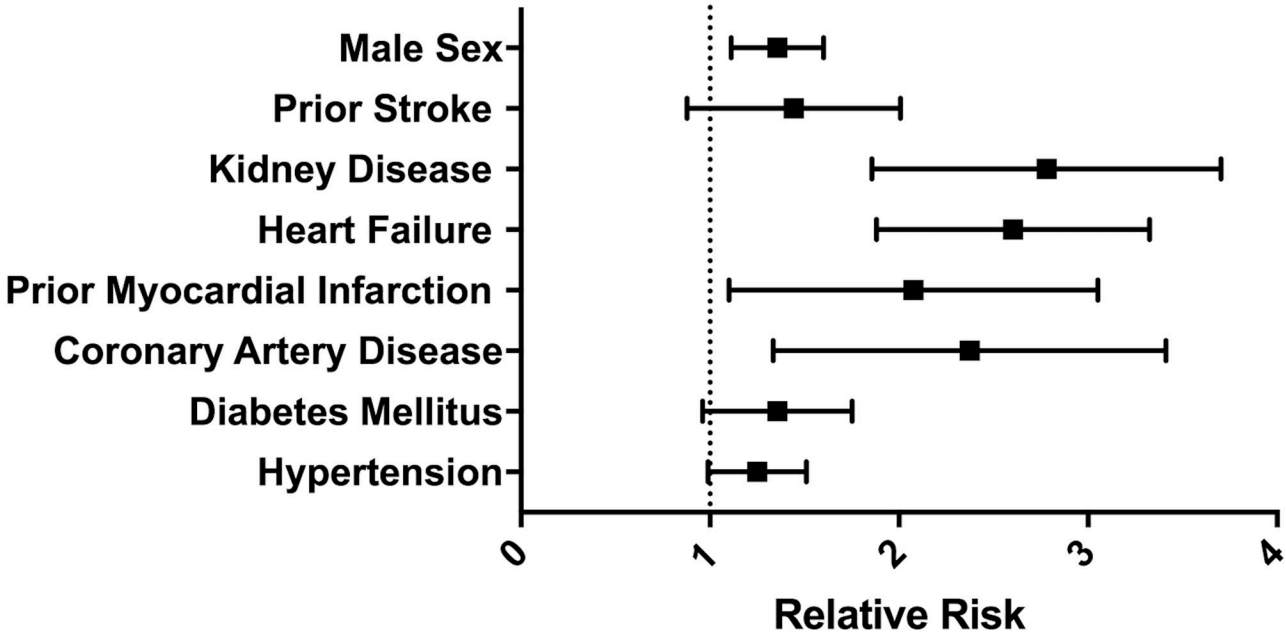

Figure 3.
Demographics and cardiovascular risk factors associated with MINS.

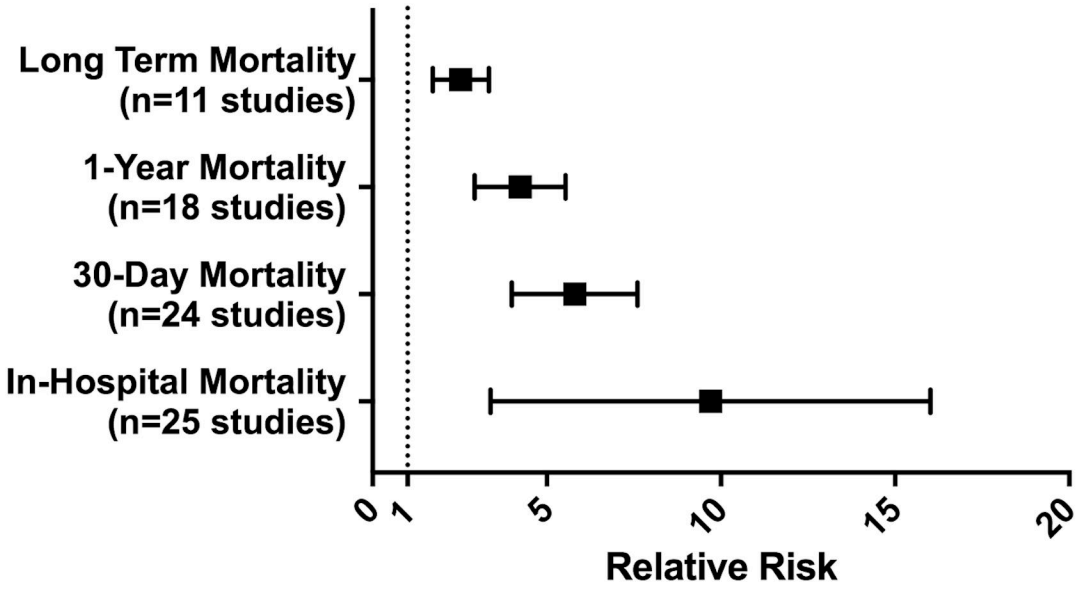

Figure 4.
Short and long-term mortality associated with MINS

Table 1.

Prevalence of pre-existing cardiovascular risk factors and disease in patients with and without MINS.

	MINS	No MINS	Relative Risk	P-value
Hypertension (n=46 studies)	63.1% (56.5% - 69.4%)	54.8% (44.0% - 65.3%)	1.23 (1.00-1.52)	0.047
Diabetes Mellitus (n=43 studies)	25.7% (22.1% - 29.5%)	21.0% (16.3% - 26.0%)	1.32 (0.98-1.77)	0.065
Coronary Artery Disease (n=38 studies)	41.3% (35.2% - 47.5%)	25.5% (18.9% - 32.7%)	2.22 (1.42-3.48)	<0.001
Prior Myocardial Infarction (n=24 studies)	25.4% (21.3% - 29.7%)	16.1% (11.1% - 21.8%)	1.92 (1.19 - 3.12)	0.008
Heart Failure (n=41 studies)	14.9% (11.3% - 18.9%)	6.7% (5.1% - 8.4%)	2.67 (1.85-3.29)	<0.001
Kidney Disease (n=30 studies)	14.0% (10.0% - 18.5%)	5.8% (4.3% - 7.3%)	2.63 (1.94 - 3.77)	<0.001
Prior Stroke (n=28 studies)	12.8% (9.8% - 16.1%)	11.7% (8.4% - 15.3%)	1.37 (0.92 - 2.04)	0.124

Table 2.

Short and long-term post-operative outcomes in patients with and without MINS.

	MINS	No MINS	Relative Risk	P-value
In-Hospital Mortality (n=25 studies)	8.1% (4.4% - 12.7%)	0.4% (0.2% - 0.7%)	8.3 (4.2 - 16.6)	<0.001
30-Day Mortality (n=24 studies)	8.5% (6.2% - 11.0%)	1.2% (0.9% - 1.6%)	5.6 (4.1 - 7.7)	<0.001
1 Year Mortality (n=18 studies)	20.6% (15.9% - 25.7%)	5.1% (3.2% - 7.4%)	4.1 (3.0 - 5.6)	<0.001
Long-Term Mortality (n=11 studies)	42.7% (33.8% - 51.8%)	19.7% (10.6% - 30.9%)	2.4 (1.8 - 3.4)	<0.001