



Medical therapy for atherosclerotic cardiovascular disease in patients with myocardial injury after non-cardiac surgery

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ABSTRACT

Background: Myocardial injury after non-cardiac surgery (MINS) is a common post-operative cardiovascular complication and is associated with short and long-term mortality. The objective of this study was to describe the contemporary management of patients with and without MINS after total joint and spine orthopedic surgery at a large urban health system in the United States.

Methods: Adults admitted for total joint and major spine surgery from January 2013 through December 2015 with ≥ 1 cardiac troponin (cTn) measurement during their hospitalization were identified. MINS was defined by a peak cTn above the 99th percentile of the upper reference limit. Demographics, medical comorbidities, and admission and discharge medications were reviewed for all patients.

Results: A total of 2561 patients underwent 2798 orthopedic surgeries, and 236 cases of MINS were identified. Patients with MINS were older (71.9 ± 10.9 vs. 67.0 ± 10.0 , $p < 0.001$) and more likely to have cardiovascular risk factors, including hypertension, chronic kidney disease, prior stroke, coronary artery disease, prior MI, and a history of heart failure. Among patients with MINS, only 112 (47.5%) were discharged on a combination of aspirin and statin. Patients with MINS were more likely to be prescribed a statin (154 [65.3%] vs. 1463 [57.1%], $p = 0.018$), beta-blocker (147 [62.3%] vs. 1194 [46.6%], $p < 0.001$), and oral anticoagulation (65 [27.5%] vs. 436 [17.0%], $p < 0.001$) than patients without MINS.

Conclusions: The proportion of patients with MINS who were prescribed medical therapy for atherosclerotic cardiovascular disease was low. Additional efforts to determine optimal management of MINS are warranted.

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1. Introduction

>1.5 million total joint and/or spine surgeries are performed in the United States each year [1]. Cardiovascular complications of non-cardiac surgery are a major source of morbidity and mortality. Myocardial injury after non-cardiac surgery (MINS) is a common post-operative cardiovascular complication that is detected in 8–22% of patients and is associated with short and long-term mortality [2–7]. Perioperative acute myocardial infarction (MI), a subgroup of MINS with clinical evidence of ischemia that meets the universal definition of MI [8], only

occurs $\leq 5\%$ of elevated-risk patients undergoing non-cardiac surgery [9–11]. Since the latest American clinical practice guidelines recommend against the routine measurement of troponin in the post-operative period following non-cardiac surgery, MINS may be underdiagnosed [12].

Despite the incidence of MINS, contemporary perioperative and cardiovascular disease guidelines do not provide specific treatment recommendations for surgical patients with these syndromes [12–14]. Guideline-directed medical therapy (GDMT) for atherosclerotic cardiovascular disease (ASCVD) in patients with MINS may provide benefit but requires further investigation [15,16]. Consequently, there may be significant variability in the post-operative medical management of MINS. Given the uncertainty of diagnostic and therapeutic strategies in these high-risk patients, the objective of the study was to describe the contemporary post-operative management of MINS in patients undergoing total joint and spine orthopedic surgery at a large urban health system in the United States.

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2. Methods

2.1. Study population

We performed a retrospective cohort study of consecutive adults age ≥ 45 undergoing total joint and major spine surgery at NYU Langone Health Tisch Hospital and NYU Langone Orthopedic Hospital, 2 high-volume tertiary-care facilities within the same urban health system, between January 1, 2013 and December 31, 2015. This time period was selected based on data availability from the electronic health record. Patients were identified using International Classification of Disease, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) procedure codes for spine and total joint replacement surgeries. Patients were eligible for study inclusion if ≥ 1 cardiac troponin measurement (cTnI) was performed in the post-operative period during the surgical hospitalization. All troponin measurements were performed at the discretion of the treating clinicians. For patients who underwent multiple surgeries during a single hospital admission, only the first surgery was included in the final analysis. Among patients with multiple orthopedic surgery admissions, each surgical admission was included separately in the final analysis. All surgical patients were managed as per usual care practices at our institution, with management decisions made at the discretion of the treating clinicians.

Patient demographics and comorbidities were obtained from hospital administrative databases and retrospective review of the medical record. Cardiovascular comorbidities were defined by ICD-9 and ICD-10 diagnosis codes. American Society of Anesthesiologists (ASA) physical status classifications were prospectively determined prior to surgery by the treating anesthesiologists and recorded in the electronic medical record for all patients. MINS was defined as ≥ 1 cardiac troponin-I (cTnI) in the post-operative period with a peak level above the 99th percentile of the upper reference limit (URL) determined in a healthy population. Plasma cTnI was measured using the VITROS cTnI ES assay (Ortho Clinical Diagnostics, Rochester, NY; 99th percentile URL >0.04 ng/mL), or the ST AIA-PACK 2nd generation cTnI assay (Tosoh Bioscience, Tokyo, Japan; 99th percentile URL >0.06 ng/mL). Perioperative acute MI was defined by the presence of ≥ 1 cardiac troponin-I (cTnI) with a peak level $>99\%$ of the laboratory upper reference limit and an ICD-9 diagnosis code for acute MI. Cardiovascular medications prescribed at hospital admission (pre-operative) and at discharge (post-operative) were reviewed for all patients.

2.2. Statistical analysis

Clinical characteristics and treatments of patients with and without MINS were compared. Continuous variables were compared with the independent samples *t*-test for normally distributed variables and the Mann Whitney *U* test for non-normally distributed variables. Categorical variables are reported as percentages and compared by Chi-square and Fisher exact tests. Multivariable logistic regression models were generated to estimate odds ratios (OR) for the diagnosis of MINS. Logistic regression models were also generated to estimate the odds of cardiovascular medication prescribing at hospital discharge. Models were adjusted for demographics, baseline medical comorbidities, including hypertension, hyperlipidemia, diabetes, renal disease, coronary artery disease, prior myocardial infarction, prior percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), peripheral artery disease, prior stroke, heart failure, chronic obstructive pulmonary disease (COPD), malignancy, and when applicable, pre-operative cardiovascular medications. Statistical analyses were performed using SPSS 25 (IBM SPSS Statistics, Armonk, NY). Two-sided *p*-values < 0.05 were considered to be statistically significant. The study was approved by the New York University School of Medicine Institutional Review Board with a waiver of informed consent.

3. Results

3.1. Clinical characteristics

A total of 2561 patients underwent 2798 orthopedic surgeries, with 2185 joint replacements (78.1%) and 613 spine surgeries (22.0%). Demographics and preoperative cardiovascular risk factors and procedural characteristics are displayed in Table 1. The mean age was 67.4 ± 10.2 years and 53.0% of patients were female. The majority of participants were classified as either ASA class 2 (39.2%) or ASA class 3 (54.1%) prior to surgery.

Overall, MINS was detected in the post-operative period of 236 (8.4%) orthopedic surgeries. Patients with MINS were older, had lower BMI, and a higher frequency of cardiovascular risk factors, including hypertension, chronic kidney disease, prior stroke, coronary artery disease, prior MI, and a history of heart failure (Table 1). There were no significant differences in the frequency of MINS among patients who underwent spine surgery compared to those who underwent total joint replacement. In multivariable analyses, age (adjusted OR [aOR] 1.04 95% CI 1.02–1.05), heart failure (aOR 2.82 95% CI 1.9–4.19), renal disease (aOR 2.14 95% CI 1.36–3.35), coronary artery disease (aOR 1.74 95% CI 1.23–2.48), and prior MI (aOR 2.39 95% CI 1.32–4.33) were

Table 1
Baseline characteristics.

Variable	Total cohort (n = 2798)	No MINS (n = 2562)	MINS (n = 236)	p-Value
Age, mean (SD) (year)	67.4 \pm 10.2	67.0 \pm 10.0	71.9 \pm 10.9	<0.001
Female sex	1482 (53.0)	1352 (52.8)	130 (55.1)	0.54
Race				0.004
White	1940 (69.3)	1754 (68.5)	186 (78.8)	–
African American	390 (13.9)	369 (14.4)	21 (8.9)	–
Other	468 (16.7)	439 (17.1)	29 (12.3)	–
Ethnicity				0.09
Hispanic	205 (7.9)	195 (7.6)	10 (3.7)	–
Non-Hispanic	2463 (88.0)	2245 (87.0)	218 (93.1)	–
Unknown	130 (4.0)	122 (4.8)	8 (3.2)	–
Body Mass Index, median (IQR) (kg/m ²)	30.0 (26.4–34.5)	30.1 (26.5–34.6)	28.6 (25.2–32.9)	0.001
Hypertension	1635 (58.4)	1485 (58.0)	150 (63.6)	0.10
Hyperlipidemia	1064 (38.0)	976 (38.1)	88 (37.3)	0.81
Diabetes mellitus	626 (22.4)	564 (26.3)	62 (26.3)	0.13
Chronic kidney disease	169 (6.0)	135 (5.3)	34 (14.4)	<0.001
Coronary artery disease	941 (33.6)	833 (32.5)	108 (45.8)	<0.001
Prior PCI	389 (13.9)	360 (14.1)	29 (12.3)	0.52
Prior CABG	59 (2.1)	50 (2.0)	9 (3.8)	0.10
Prior myocardial infarction	81 (2.9)	62 (2.4)	19 (8.1)	<0.001
Prior stroke	127 (4.5)	106 (4.1)	21 (8.9)	0.001
Heart failure	188 (6.7)	141 (5.5)	47 (19.9)	<0.001
Cancer	265 (9.5)	244 (9.5)	21 (8.9)	0.84
COPD	187 (6.7)	171 (6.7)	16 (6.8)	1.00
Peripheral artery disease	115 (4.1)	103 (4.0)	12 (5.1)	0.54

COPD: chronic obstructive pulmonary disease; SD: standard deviation.

independently associated with the development of MINS (Table 2). Among patients with MINS, the median peak post-operative troponin was 0.22 ng/mL (IQR 0.09–0.60 ng/mL) and in 42 cases (17.8%) the peak troponin was >1.0 ng/mL. The median peak troponin was 0.27 ng/mL (IQR 0.10–0.79 ng/mL) when MINS was detected by the ST AIA-PACK 2nd generation cTnI assay (n = 176) and was 0.12 ng/mL (IQR 0.05–0.45 ng/mL) when MINS was detected by the VITROS cTnI ES assay (n = 60).

3.2. Preoperative medical therapy

Guideline directed medical therapy for ASCVD prescribed preoperatively and at discharge are shown in Table 3. At hospital admission prior to surgery, patients were prescribed aspirin in 43.1% of cases, a P2Y12

Table 2
Multivariable predictors of myocardial injury after non-cardiac surgery.

Variable	Adjusted OR (95% CI)
Age	1.04 (1.02–1.05)
female sex	1.17 (0.88–1.57)
Race	
White	Reference
Black	0.57 (0.35–0.93)
Other/unknown	0.65 (0.43–1)
Hypertension	1.07 (0.78–1.46)
Hyperlipidemia	0.72 (0.52–0.99)
Diabetes mellitus	1.19 (0.85–1.66)
Chronic kidney disease	2.14 (1.36–3.35)
Prior myocardial infarction	2.39 (1.32–4.33)
Coronary artery disease	1.74 (1.23–2.48)
Prior PCI	0.5 (0.31–0.81)
Prior CABG	0.93 (0.42–2.07)
Prior stroke	1.24 (0.49–3.16)
Heart failure	2.82 (1.9–4.19)
Cancer	0.73 (0.45–1.18)
COPD	0.74 (0.42–1.3)
Peripheral artery disease	0.72 (0.37–1.4)

CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; OR: odds ratio; PAD: peripheral artery disease; PCI: percutaneous coronary intervention.

Table 3
Preoperative and postoperative medical therapy in patients with and without MINS.

	Total cohort (n = 2798)		No MINS (n = 2562)		MINS (n = 236)					
	Pre-operative	Discharge	Pre-operative	Discharge	Pre-operative	Discharge	P1	P2	P3	P4
Medication										
Aspirin	1206 (43.1)	1733 (61.9)	1104 (43.1)	1582 (61.7)	102 (43.2)	151 (64.0)	0.99	0.54	<0.001	<0.001
P2Y ₁₂ inhibitor	257 (9.2)	260 (9.3)	234 (9.1)	232 (9.1)	23 (9.7)	28 (11.9)	0.85	0.19	1.0	0.55
Oral anticoagulation	231 (8.3)	501 (17.9)	213 (8.3)	436 (17.0)	18 (7.6)	65 (27.5)	0.81	<0.001	<0.001	<0.001
Statin	1575 (56.3)	1617 (57.8)	1442 (56.3)	1463 (57.1)	133 (56.4)	154 (65.3)	0.99	0.018	0.57	0.06
Beta blockers	1234 (44.1)	1341 (47.9)	1107 (43.2)	1194 (46.6)	127 (53.8)	147 (62.3)	0.002	<0.001	0.016	0.08
ACEi/ARBs	1304 (46.6)	1283 (45.9)	1202 (46.9)	1179 (46.0)	102 (43.2)	104 (44.1)	0.31	0.61	0.54	0.92
Combinations										
No aspirin or statin	908 (32.5)	598 (21.4)	831 (32.4)	555 (21.7)	77 (32.6)	43 (18.2)	0.99	0.25	<0.001	<0.001
Aspirin only	315 (11.3)	583 (20.8)	289 (11.3)	544 (21.2)	26 (11.0)	39 (16.5)	0.99	0.11	<0.001	0.11
Statin only	684 (24.4)	467 (16.7)	627 (24.5)	425 (16.6)	57 (24.2)	42 (17.8)	0.98	0.70	<0.001	0.11
Aspirin + statin	891 (31.8)	1150 (41.1)	815 (31.8)	1038 (40.5)	76 (32.2)	112 (47.5)	0.96	0.045	<0.001	<0.001
DAPT	206 (7.4)	229 (8.2)	187 (7.3)	204 (8.0)	19 (8.1)	25 (10.6)	0.77	0.20	0.40	0.43
DAPT + statin	181 (6.5)	208 (7.4)	167 (6.5)	186 (7.3)	14 (5.9)	22 (9.3)	0.83	0.31	0.32	0.23

P1: comparison of pre-operative medical therapy in patients with MINS versus without MINS.

P2: comparison of post-operative (discharge) medical therapy in patients with MINS versus without MINS.

P3: comparison of pre-operative versus post-operative (discharge) medical therapy in patients without MINS.

P4: comparison of pre-operative versus post-operative (discharge) medical therapy in patients with MINS.

ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; DAPT: dual anti-platelet therapy (aspirin + P2Y₁₂ inhibitor).

inhibitor in 9.2%, warfarin in 6.1%, a statin in 56.3%, a beta-blocker in 44.1%, and an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) in 46.6% of cases. Patients who developed MINS were more likely to have received a beta-blocker prior to surgery than patients who did not develop MINS (53.8% vs. 43.2%, $p = 0.002$), but beta-blocker use was not a significant predictor of MINS after multivariable adjustment. No other differences in pre-operative medical therapy between patients with and without MINS were observed.

3.3. Post-operative medical therapy

Overall, a total of 2558 patients (99.9%) survived to hospital discharge. At the time of hospital discharge after surgery, aspirin was prescribed in 61.9% of cases, a P2Y₁₂ inhibitor in 9.3% of cases, warfarin in 12% of cases, a statin in 57.8% of cases, a beta-blocker in 47.9% of cases, and an ACE inhibitor or ARB in 45.9% of cases overall (Table 3). Among patients with MINS, 64.0% received aspirin at discharge, 11.9% received a P2Y₁₂ inhibitor, 20.3% received warfarin, 65.3% received a statin, and 62.3% received a beta-blocker (Table 3). Only 47.5% were discharged on a combination of aspirin and statin. In univariate analyses, patients with MINS were more likely to be prescribed a statin (65.3% vs. 57.1%, $p = 0.018$), a beta-blocker (62.3% vs. 46.6%, $p < 0.001$), and oral anticoagulation (27.5% vs. 17.0%, $p < 0.001$) at discharge than patients without MINS. There were no differences in the prescribing frequency of other medication classes (Table 3).

3.4. Associations between MINS and changes in medical therapy

Overall, aspirin was added at discharge in 37.1% of cases when it had not been prescribed pre-operatively, P2Y₁₂ inhibitor was added in 1.9% of cases, a statin was added in 4.4% of cases, and a beta-blocker was added in 8.6% of cases. Patients with MINS were more likely to be prescribed ≥ 1 new cardiovascular medication at hospital discharge in comparison to patients without MINS. Specifically, MINS patients were more likely to be discharged with a new prescription for oral anticoagulation (22.5% vs. 9.9%, $p < 0.001$), a statin (23.3% vs. 2.3%, $p < 0.001$), a beta-blocker (22.9% vs. 7.5%, $p < 0.001$), and the combination of aspirin and statin (26.3% vs. 14.7%, $p < 0.001$) compared with patients without MINS (Table 4).

4. Discussion

In this retrospective cohort study, MINS was identified after 8.4% of major non-cardiac joint and spine surgeries with ≥ 1 postoperative troponin measurement. Patients with MINS were older and had a greater burden of cardiovascular risk factors than patients without MINS. Detection of MINS was associated with greater intensification of medical therapy at hospital discharge in comparison to patients without MINS. Even so, few patients with MINS were discharged on GDMT for ASCVD.

Perioperative cardiovascular events are an important cause of mortality and morbidity in non-cardiac surgery [9,11,17]. Myocardial injury after non-cardiac surgery, the most common cardiovascular complication, remains a challenging clinical problem. In the large Vascular Events In Non-cardiac Surgery Patients Cohort Evaluation (VISION) study of patients ≥ 45 years of age undergoing non-cardiac surgery, low-level elevations in troponin and high-sensitivity troponin were significant predictors of 30-day mortality [2,5]. Other studies of MINS have also reported associations between MINS and short and long-term outcomes [4,18,19].

Mechanisms of MINS remain unknown, contributing to provider uncertainty and the variability in post-operative medical management of this condition. Conventional GDMT for ASCVD, such as antiplatelet therapy, carry risks of postoperative bleeding [20]. However, in a recent retrospective observational study of high-risk patients undergoing major

Table 4

Proportion of patients with and without MINS receiving guideline directed medical therapy for atherosclerotic disease at discharge among those not previously prescribed therapy.

	All patients	No MINS	MINS	p-Value
Change in medical therapy				
Aspirin added (%)	37.1	36.6	43.3	0.15
P2Y ₁₂ inhibitor added (%)	1.9	1.8	3.3	0.21
Oral anticoagulation added (%)	11.0	9.9	22.5	<0.001
Statin added (%)	4.4	2.3	23.3	<0.001
Beta-blocker added (%)	8.6	7.5	22.9	<0.001
Change in medication combinations				
Aspirin + statin added (%)	15.7	14.7	26.3	<0.001
DAPT only added (%)	2.2	2.1	3.2	0.38
DAPT + statin added (%)	2.2	2.0	4.1	0.08

ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; DAPT: dual anti-platelet therapy (aspirin + P2Y₁₂ inhibitor).

orthopedic surgery, the use of antiplatelet therapy throughout the perioperative period appeared to be safe [21]. Lipid-lowering therapy with statins reduces the risk of cardiovascular events in non-surgical populations for primary and secondary prevention [22,23], but declines in perioperative cardiovascular events due to statin use remain somewhat speculative [23–27]. In large observational studies, preoperative statin use was associated with significantly reduced risk of MINS, cardiovascular complications, and all-cause mortality [23,27]. However, a 2013 Cochrane review of randomized controlled trials of statins in non-cardiac surgery identified insufficient evidence to conclude that statins reduce perioperative cardiovascular events [28]. Thus, current ESC/ESA and ACC/AHA clinical practice guidelines recommend the continuation of statins in the perioperative period, and consider the initiation of statins reasonable in patients undergoing vascular surgery or with clinical risk factors and undergoing elevated-risk procedures [12,29]. GDMT for ASCVD is likely beneficial in patients with MINS, and recent clinical trials have tested novel approaches to management of this high-risk condition. In the MANAGE trial, patients age ≥ 45 years with MINS who were randomly assigned to receive low dose dabigatran 110 mg twice daily within 35 days of surgery had a significantly lower incidence of the composite endpoint of all-cause mortality, arterial and venous events at 2 years compared with patients who received placebo [30]. Based on these findings, MINS patients appear to derive benefit from intensification of antithrombotic therapy, and it is plausible that they may benefit from other cardiovascular medical therapy for secondary prevention of MI as well.

There are several limitations of the present study. First, patients without post-operative troponin measurements were not included in this analysis, and troponin measurements were performed at the discretion of the treating providers. As such, troponin measurements were limited to patients with the greatest cardiovascular risk factors and a higher pretest probability of perioperative myocardial injury. In prior studies of patients undergoing orthopedic surgery, patients with any clinically indicated troponin measurement, including those with a result within the normal reference range, had less favorable long-term outcomes in comparison to patients for whom troponin was not measured [4]. Despite this selection bias, the study population represents a real-world cohort of orthopedic surgery patients with clinically indicated post-operative troponin measurements. Second, initiation, continuation, and discontinuation of medical therapy were performed at the discretion of the clinical providers. Standardized clinical risk assessments were not employed. The clinical rationale for the choice of therapy was not available from available documentation. Third, this study was conducted at a single high-volume urban health system, which may affect the generalizability of the study findings to smaller centers. Still, this represents the largest cohort of patients undergoing major orthopedic surgery with perioperative troponin measurements and data on changes in medical therapy for ASCVD before and after surgery.

In conclusion, in a large retrospective cohort study of patients undergoing major non-cardiac orthopedic surgery, 8.4% of patients developed MINS. Patients with MINS were more likely to have intensification of medical therapy for ASCVD in comparison to patients without MINS. However, the proportion of MINS patients prescribed GDMT for ASCVD remained low. Additional efforts to determine optimal management of MINS are warranted.

Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
ASA	American Society of Anesthesiologists
ACE	Angiotensin Converting Enzyme
ARB	Inhibitor, Angiotensin Receptor Blocker
ASCVD	Atherosclerotic Cardiovascular Disease
BMI	Body Mass Index
cTnI	Cardiac Troponin Measurement

COPD	Chronic Obstructive Pulmonary Disease
CABG	Coronary Artery Bypass Grafting
ESA	European Society of Anaesthesiology
ESC	European Society of Cardiology
GDMT	Guideline-directed medical therapy
ICD	International Classification of Disease
MI	Myocardial Infarction
MINS	Myocardial Injury after Non-cardiac Surgery
PCI	Percutaneous coronary intervention
VISION	Vascular Events In Non-cardiac Surgery Patients Cohort Evaluation

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Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

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