Pre- and Postoperative Troponin Elevation: Effects on Postoperative Mortality

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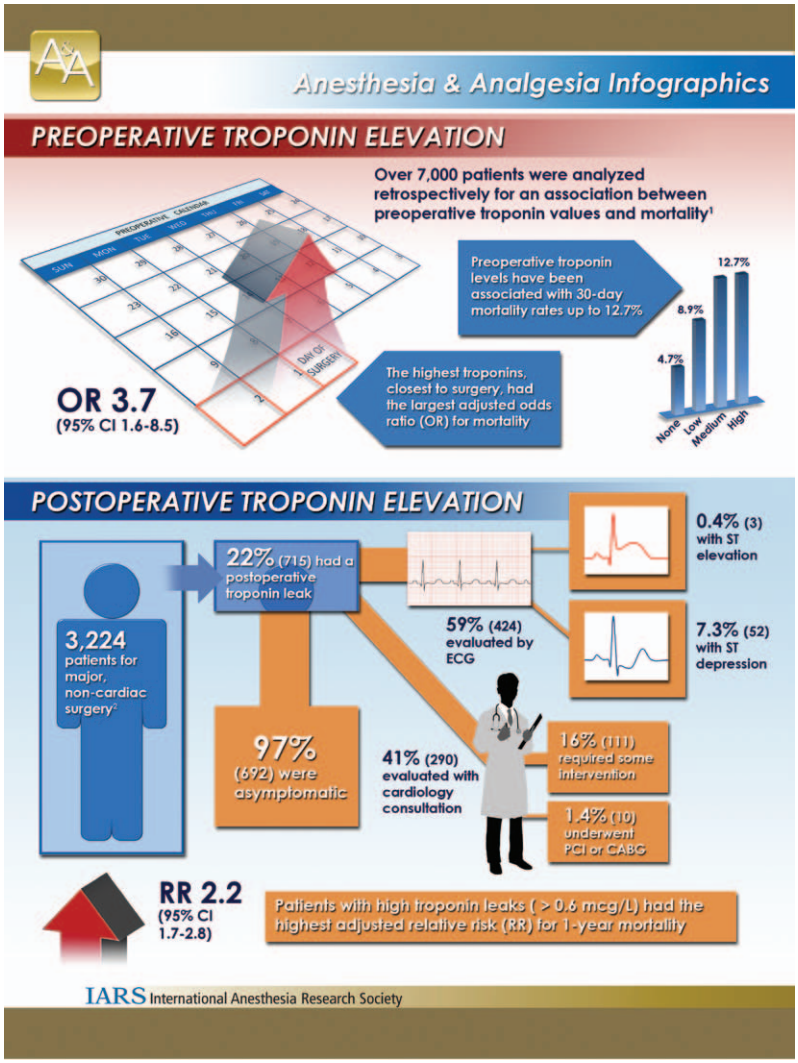
Recent analyses have demonstrated significant associations between troponin elevations in both the preoperative and postoperative settings. In this infographic, we explore the relationship between mortality and positive preoperative troponins, and the diagnostic and management pathways associated with postoperative troponin elevation.



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The Enigma of Postoperative Troponin Elevation

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Cardiac troponins are among the most intensely investigated molecules in cardiology in the past several decades and are used as the primary biomarkers for the diagnosis of myocardial infarction (MI) since the year 2000.[1] Numerous studies have documented that cardiac troponin assays are highly specific for myocardial rather than skeletal troponin I and T; cardiac troponin assays are highly sensitive to serum troponin elevations with modern assays increasingly sensitive to even minor serum troponin elevation (high-sensitivity and ultrasensitive assays), and of primary importance to clinical medicine, serum cardiac troponin elevations have strong prognostic implications in most patient subgroups encountered. In every clinical scenario and every subset of patients it has been examined, even minor serum cardiac troponin elevations strongly predicted both early and long-term complications and mortality, and higher troponins elevations predicted worse prognosis. Similar implications are accepted in high-risk patients undergoing major surgery.[2–5] This was one of the major findings reported by van Waes et al.[6] in this issue of the journal. They collected serum troponin I concentrations in 3224 patients in the first 3 days after major noncardiac surgery and found that the highest postoperative serum troponin I concentrations predicted 1-year mortality in a dose-dependent manner. However, this was not the only intriguing finding in their study. No less important was their observation that the vast majority (97%) of 715 patients with postoperative troponin I elevations were asymptomatic. A 12-lead electrocardiogram (ECG) was performed in only 59% of the patients with troponin elevations, but only 23% of those (13%) had changes suggestive of new ischemia, 3 (0.7%) with ST-elevations and 52 (12%) with new ST-segment depressions (≥1 mm). An attempt to implement a postoperative intervention protocol with a cardiology consultation in patients with troponin elevations resulted in a consultation in only 41%, and an intervention was deemed necessary in only 16% of patients with troponin elevations (38% of the patients who had cardiac consultation). The contradiction between the strong predictive value of even low-level troponin elevation and the very rare symptomatology and the limited chance to intervene and affect prognosis represents the enigma clinicians face in current practice.

It is first important to understand that cardiologists' approach to a troponin elevation is different from ours as anesthesiologists. Cardiologists are trained to treat patients by signs and symptoms. Patients with no clinical signs or symptoms with certain notable exceptions (e.g., diabetes mellitus) are generally not felt to require treatment. Moreover, MI is defined by an increase and decrease in serum troponin in the setting of myocardial ischemia, that is either typical chest pain or new ECG changes suggestive of acute ischemia.[1] Hence, troponin elevation without clear signs or symptoms of ischemia is not considered MI. Thus, there is an inherent problem with postoperative troponin elevation (PTE). These are usually clinically silent because patients are often sedated and treated with analgesics or they are mechanically ventilated due to sepsis or hemodynamic instability. Moreover, routine postoperative ECG monitoring with 3, or even 5 leads, is not sensitive enough to record and detect all ischemic ECG changes, let alone a randomly acquired, single 12-lead ECG once daily as is often reported in studies. We previously reported that symptoms attributable to MI occurred in a minority (18%) of patients undergoing vascular surgery with minor PTE. Ischemia longer than 15 minutes was detected in less than one-third of these patients on continuous, online 12-lead ECG monitoring, although the incidence of symptoms and ischemia on 12-lead ECG monitoring was more frequent in patients with higher levels of troponin.[2] Similar results were obtained by others.[5,7] Because serum troponin elevations in the first 3 days after surgery predict both early (30-day) and late mortality, regardless of symptomatology, researchers have tried to seize on this biomarker as an opportunity to treat and improve patients' outcomes. However, the report by van Waes et al. highlights some open questions regarding PTE.

WHAT IS THE MECHANISM OF PTE?

In the report by van Waes et al.,[6] <0.7% of the patients with PTEs had ST-elevation myocardial infarction (STEMI) on ECG. This conforms to prior studies using continuous perioperative 12-lead ECG monitoring in patients undergoing major vascular surgery, which showed the very rare occurrence of ST-elevation–type ischemia as opposed to the common postoperative ST-depression–type ischemia associated with troponin elevations.[2,8] ST-segment elevation is the hallmark of acute coronary occlusion, mostly because of acute plaque rupture and coronary thrombosis. It is remarkable

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that many patients with significant coronary artery disease, and vulnerable coronary plaques, undergo major surgery accompanied by physiologic and emotional stresses and yet very few develop STEMI. STEMI is usually a clinically symptomatic event, especially after surgery, and requires immediate coronary intervention by either thrombolysis or percutaneous coronary intervention. In contrast, postoperative non–ST-elevation–type ischemia and subsequent troponin elevation are common and often asymptomatic. This led us to postulate in 2003 that prolonged, stress-induced ST-depression–type ischemia in patients with significant yet stable coronary artery disease is the main mechanism of postoperative MI (PMI).[9] In 2007, the Universal Definition of MI[10] was published categorizing, for the first time, the existence of 2 types of MI: type I is "spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion, rupture, fissuring, or dissection," whereas type II is "MI secondary to ischemia due to imbalance between myocardial oxygen supply and demand." PMI is driven mainly by increased heart rates as a predominant mechanism.[11] Anemia, hypoxemia, increased myocardial oxygen demand, ventricular over-/underload, systolic/diastolic dysfunction, and neuroendocrine responses to stresses of surgery all may contribute to the decreased ischemic threshold early after surgery. Pegg et al.[12] reported (albeit in patients undergoing coronary artery bypass graft surgery) that postoperative serum troponin concentrations strongly correlated with the mass of new myocyte necrosis as assessed by delayed enhancement on cardiac magnetic resonance imaging. Hence, if we accept the notion that PMI is mostly type II MI, then asymptomatic PTE without clear evidence of ischemia is a subclinical type II MI or simply myocardial injury attributable to a prolonged imbalance between myocardial oxygen supply and demand.

WHAT IS THE ROLE OF ROUTINE SURVEILLANCE AND INTERVENTION FOR PTE?

The strong prognostic value of PTE has led various authors to advocate routine postoperative troponin measurements in high-risk patients undergoing major surgery, first for the purpose of postoperative risk stratification and also to minimize associated risks by an intervention.[3,4,13] The potential cost-effectiveness of routine postoperative troponin surveillance and intervention using postoperative aspirin and statins[14] or tight postoperative heart rate control with β-blockers[15] has been investigated. Nevertheless, the question remains whether this added risk identified by PTE is modifiable. The answer to this question is still unclear. Data from one retrospective study in patients undergoing major vascular surgery suggest that patients with PTE in whom medical therapy (antiplatelet agent, β-blocker, angiotensin-converting enzyme inhibitor, or statin) was intensified postoperatively had better 1-year event-free survival compared with those without medical therapy intensification.[16] One trial is currently still recruiting patients with PTE in an attempt to test whether the new oral anticoagulant dabigatran (in combination with omeprazole) reduces postoperative mortality.[17] What van Waes and her colleagues discovered in their prospective study was that although surveillance for PTE is easy, an intervention in patients with significant PTE is difficult, let alone detecting the benefit from such an intervention, particularly in the absence of specific clinical guidelines. Cardiac consultation was obtained in only 41% of 715 patients with PTE, and only 111 (16%) had subsequent intervention that included any, even minor, change in cardiac, antihypertensive, or antiplatelet medications. In 23 (3.2%) patients with PTE, PMI was suspected in real time, 17 patients (2.3%) were transferred to the coronary care unit, 15 (2.1%) underwent coronary angiography, and 10 (1.4%) patients underwent subsequent percutaneous coronary intervention or coronary artery bypass graft surgery. What makes the intervention to improve risk in patients with PTE so difficult? First, the vast majority of patients with PTE are asymptomatic. Second, myocardial injury often is the result of concurrent serious noncardiac complication (massive bleeding, hypotension, and sepsis), and treatment must first be directed to prevent or treat the noncardiac complication.[18,19] Third, myocardial injury may have happened long (hours or days) before the clinician was called to intervene, when the horses had already left the barn and myocardial damage had possibly occurred. In addition, PTE is possibly a marker of severe yet stable coronary artery disease that heralds later cardiac complications, and cardiologists are generally reluctant to intervene in patients with stable coronary artery disease during the unstable phase of the postoperative period. van Waes et al.'s study is yet another important effort in the long trail of attempts to solve the puzzle of PTE.

RECUSE NOTE

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Preoperative Troponin in Patients Undergoing Noncardiac Surgery: Is Timing Everything?

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The 3-protein troponin complex and tropomyosin combine to form the major regulator of actin-myosin interaction in the myocardial contractile apparatus.[1] Each cardiac troponin (cTn) protein serves a distinct yet complimentary role: troponin C, identified by virtue of its calcium-binding ability; troponin I, the primary inhibitor of actin-myosin cycling when coupled with tropomyosin; and troponin T, so named because of its ability to bind the other troponin molecules and tropomyosin. Myocardial ischemia, trauma, infection, or inflammation releases cTn into the systemic circulation in proportion to the magnitude of injury.[2–5] Plasma cTn concentration is most often measured to quantify the severity of myocardial necrosis associated with acute myocardial infarction with a high degree of sensitivity and specificity for both cTnI (77% and 93%, respectively) and cTnT (80% and 90%, respectively) proteins.[6–8] As a result, plasma cTn concentration supplanted earlier serological markers, including aspartate transaminase,[9] lactate dehydrogenase,[10] and creatine kinase-myocardial band,[11] as the "gold standard" biochemical index for acute coronary syndrome in the European Society of Cardiology/American College of Cardiology definition of myocardial infarction.[12] Elevation of cTn concentration above the 99th percentile of the upper reference limit in healthy subjects (<0.01 ng/mL measured using currently available high-sensitivity cTn laboratory assays)[13] is required to establish the diagnosis of, and to predict the adverse outcome associated with, acute myocardial infarction,[12,14,15] although some controversy remains about whether this cTn upper reference limit value also applies to patients with known risk factors for coronary artery disease.[16]

Elevated postoperative cTn concentrations have been shown to be powerful predictors of morbidity and mortality in patients undergoing noncardiac surgery.[17–20] The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) trial prospectively measured cTnT concentrations at selected intervals during the first 3 postoperative days in 15,133 patients.[17] The authors reported that 11.6% of the patients had elevated postoperative peak cTnT concentrations (≥0.02 ng/mL) that were highly predictive of increased 30-day mortality. Notably, the risk of death increased dramatically in proportion to the magnitude of cTnT elevation, because patients with peak cTnT concentrations exceeding 0.3 ng/mL had a 4-fold greater 30-day mortality rate versus those with peak cTnT levels of 0.02 ng/mL.[17] A reanalysis of the VISION trial verified the original findings, showing that myocardial necrosis (defined as cTnT ≥0.04 ng/mL in this study) after noncardiac surgery predicted 30-day mortality and postoperative complication rate.[18] The results also indicated that only 15.8% of patients with elevated postoperative cTnT concentrations reported classical symptoms of acute myocardial ischemia. Furthermore, the universal definition of myocardial infarction could not be definitely established in more than half of these patients.[18] These data emphasized that typical clinical and diagnostic criteria for myocardial ischemia and infarction were often inconclusive if not largely absent in this at-risk postoperative population. Beattie et al.[19] independently demonstrated a postoperative cTnI concentration-dependent association with 30-day mortality in their single-center, retrospective cohort analysis of 51,701 inpatients. Most recently, Noordzij et al.[20] conducted a prospective observational single-center study of 203 patients at risk for coronary artery disease undergoing major abdominal operations. The authors measured cTnT concentrations before and 1, 3, and 7 days after surgery and demonstrated that a 2-fold or greater increase in peak cTnT concentration above the preoperative baseline strongly predicted postoperative complications, prolonged hospital length of stay, and in-hospital mortality.[20]

It is within this context that Maile et al.[21] examined what would initially appear to be an intuitively obvious hypothesis, that is, whether elevated preoperative cTn concentration also predicts postoperative mortality in patients undergoing noncardiac surgery. The authors retrospectively examined the University of Michigan electronic medical record database to identify 7137 patients who underwent preoperative cTn testing before noncardiac surgery because of chest pain, abnormal electrocardiography, or cardiovascular instability. Patients who underwent preoperative myocardial revascularization or percutaneous coronary intervention (i.e., those in whom marked elevations in cTn could be anticipated because of these procedures) before noncardiac surgery were excluded from analysis. The experimental design

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was composed of a 3 × 3 matrix of 9 separate groups based on terciles of the magnitude of preoperative cTn elevation (≤0.23, >0.23 but <1.02, and ≥1.02 ng/mL, respectively) and the timing of its measurement before surgery (≤3.36, >3.36 but <11.59, and ≥11.59 days, respectively). A reference group of patients with undetectable preoperative cTn (<0.01 ng/mL) served as the study's control. This approach allowed the authors not only to ascertain the prognostic significance of progressive elevations in preoperative cTn concentration but also to determine whether delays between cTn measurement and subsequent surgery were associated with postoperative mortality. The study's results provide new insight into the significance of elevated preoperative cTn levels and the timing of their measurement. Not surprisingly, the authors found that an increase in preoperative cTn concentration above the limit of detection was associated with greater postoperative 30-day mortality. These data confirm and extend previous findings, suggesting that preoperative high-sensitivity cTnT concentrations were associated with postoperative myocardial infarction and long-term mortality after noncardiac surgery.[22] The current authors further demonstrated a direct relationship between the magnitude of preoperative cTn level and the subsequent postoperative mortality rate (11.4%, 14.6%, and 15.7% for the 3 cTn tercile cohorts versus 6.9% for control patients [indicating that the enrolled subjects represent a relatively high-risk cohort]), similar to the findings of previous investigations correlating with postoperative cTn concentration and mortality after noncardiac surgery.[17–20] As expected, the unadjusted risk of 30-day mortality was highest in patients who had the greatest degree of myocardial injury and the shortest duration between cTn measurement and surgery (odds ratio of 3.080). A longer delay between cTn measurement and subsequent surgery was associated with a decrease in mortality, but such delays were only effective at reducing risk in patients with relatively minor elevations in preoperative cTn levels (the ≤0.23 ng/mL tercile). This latter observation is particularly important because delays before noncardiac surgery in patients with more pronounced elevations in preoperative cTn concentrations did not meaningfully reduce the incidence of postoperative mortality.

The authors' findings suggest that routine preoperative measurement of cTn in patients undergoing noncardiac surgery, especially those scheduled for higher risk procedures (e.g., major abdominal, thoracic, vascular), may be warranted and that a delay of elective surgery, perhaps in combination with intensive cardiovascular therapy,[23] may be justified when cTn values are elevated. The results are provocative and also raise a number of intriguing questions, many of which will require future prospective studies to answer. Whether patients with elevated preoperative cTn levels should be referred for additional evaluation and treatment before elective surgery is not clear based on the current data. The precise nature and timing of such treatment and its relative impact on the outcomes of patients with elevated preoperative cTn concentrations also remain to be characterized. The current data also do not define the optimal duration of time that elective noncardiac surgery should be postponed when more pronounced elevations in preoperative cTn concentration are identified. The authors[21] suggest that waiting between 1 and 3 months for cTn concentration to return to normal may be sufficient, but unfortunately, their study was not designed to confirm or refute this hypothesis. It is also unclear how the perioperative management of patients with preoperative cTn elevation requiring urgent or emergent noncardiac operations should be tailored to minimize postoperative risk of major adverse cardiac events. The most recent American College of Cardiology/American Heart Association guidelines on preoperative evaluation and management of patients undergoing noncardiac surgery[24] suggest that such treatment should most likely follow current recommendations for the management of patients with stable ischemic heart disease,[23,25] but the guidelines do not specifically address patients with elevated preoperative cTn concentration. Thus, as is the hallmark of any high-quality study, this investigation raises more questions than it answers, motivating us to perform more prospective research for the benefit of our patients.

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Timing of Preoperative Troponin Elevations and Postoperative Mortality After Noncardiac Surgery

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BACKGROUND: Even small elevations in preoperative troponin levels have been shown to be associated with adverse outcomes. However, there are currently limited data on the relationship between troponin increase and timing of surgery.
METHODS: We performed a single-institution, retrospective cohort study of 6030 individuals with a troponin measurement made during the 30 days preceding a noncardiac surgical procedure. Subjects with detectable troponin levels were separated into terciles based on both the magnitude of the value and the time elapsed between this value and the surgery. For those undergoing nonemergent procedures, these 9 cohorts were compared with the group of individuals with undetectable preoperative troponin levels using bivariable and multivariable logistic regression.
RESULTS: Thirty-day mortality was 4.7% in the group with undetectable troponin levels and increased with higher concentrations, with rates of 8.9%, 12.7%, and 12.7% in the low, medium, and high tercile groups, respectively. Unadjusted risk of 30-day mortality was highest in those with the highest troponin levels and shortest duration between the measurement and surgery (odds ratio, 4.497; 95% confidence interval, 2.058–9.825). After adjusting for subject characteristics, troponin remained associated with 30-day mortality in several groups, including individuals with troponin levels in the normal range.
CONCLUSIONS: Higher levels of preoperative cardiac troponin I were associated with higher postoperative mortality, and longer time to surgery appeared to reduce this risk for individuals with mild preoperative troponin elevations. Prospective studies are needed to determine whether delaying surgery in patients with elevated preoperative troponin levels improves postoperative outcomes. (Anesth Analg 2016;123:135–40)

Inadequate coronary perfusion can lead to cellular damage with subsequent release of intracellular components into the circulation. Some of these proteins, such as cardiac troponin (cTn), have isoforms that differ from those found in other muscles.[1] Because of this specificity, cTn is a cornerstone in the diagnosis of acute coronary syndrome (ACS).[2] Furthermore, the magnitude of cTn elevation in ACS is correlated with the risk of short-term mortality.[3] Given the importance of early diagnosis and treatment, cTn concentrations are measured liberally in at-risk patients.

With improvements in the sensitivity of clinically used assays, it is increasingly recognized that many patients have low, but detectable, levels of serum cTn outside the setting of ACS.[4] Elevations of cTn indicative of cardiac strain or injury, but not associated with coronary atherosclerosis, include such diverse causes as perimyocarditis, endocarditis, takotsubo cardiomyopathy, radiofrequency catheter ablation, cardiac contusion, strenuous exercise, and sympathomimetic drugs.[2,4] Although sometimes trivialized as only a troponin leak, several studies have demonstrated that, although not produced by myocardial ischemia or ACS, these elevations are associated with adverse outcomes.[5–7] Although preoperative myocardial infarction is an established risk factor for adverse events,[8] less is known about patients with preoperative cTn elevation not related to ACS. This creates a precarious situation for clinicians, given that not only are optimal management strategies undefined, but also the risk of proceeding to surgery is poorly quantified. For example, although a preoperative cTnT level >14 ng/L was associated with increased postoperative mortality,[9] we do not know whether the postoperative mortality risk is proportional to the magnitude of cTn elevation, if there is a risk for smaller elevations, or if this risk decreases with longer time between peak cTn measurement and time of surgery.

To answer these questions we conducted a retrospective cohort study of patients undergoing noncardiac surgery who underwent cTnI testing before surgery. In addition to analyzing the effect of concentration, the time between peak cTnI levels and surgery was also examined. We hypothesized that both high cTnI levels and short duration between the peak level and surgery were associated with increased risk of postoperative mortality.

METHODS

Study Population

This retrospective study was approved by the IRB, which waived informed consent because it only involved deidentified, previously collected data. Patients at least 18 years old who had a cTnI measurement made within 30 days before a noncardiac surgical procedure at the University of Michigan

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were included (Fig. 1). Current procedural terminology codes were used to identify the individuals who had undergone a preoperative percutaneous coronary intervention, and this group was excluded from the analysis. The time period included was March 1, 2006 to June 5, 2013. The start date was chosen as the first date all data were reliably available in our electronic medical record and the last date was chosen as the last date before submission to the IRB. Given the retrospective nature of this research, measurement of preoperative cTnI concentration was at the discretion of the managing service and was based on clinical reasons. Typical indications include chest pain, hemodynamic instability, and electrocardiographic abnormalities. At our institution, cTnI (Troponin I Ultra assay; Siemens Healthcare Diagnostics, Deerfield, IL) is measured and values as low as 0.10 ng/mL are reported. The upper limit for normal, or reference range, is <0.30 ng/mL and was constant throughout the study period. Of note, although this assay can detect lower troponin levels, the hospital laboratory does not report them. Instead, they are reported as undetected.

Subjects with detected cTnI concentrations were divided into 9 cohorts using terciles of cTnI levels and terciles of time between this measurement and surgery. Patients with undetected cTnI levels served as controls. Emergent surgical procedures were removed from the analysis and patients who underwent a nonemergent, noncardiac surgical procedure and had their preoperative troponin level measured during the 30 preceding days were included in the analysis. The following subject characteristics were also collected: age, sex, ASA physical status, surgical duration, and several laboratory values (bicarbonate, creatinine, total bilirubin, lactate, and brain natriuretic peptide). Missing data were present for laboratory values and body mass index. These were imputed, with 10 iterations per imputation, using IVEware version 2.0 (Institute for Social Research, University of Michigan, Ann Arbor, MI) and SAS software, Version 9.3 for Windows (SAS Institute, Cary, NC).

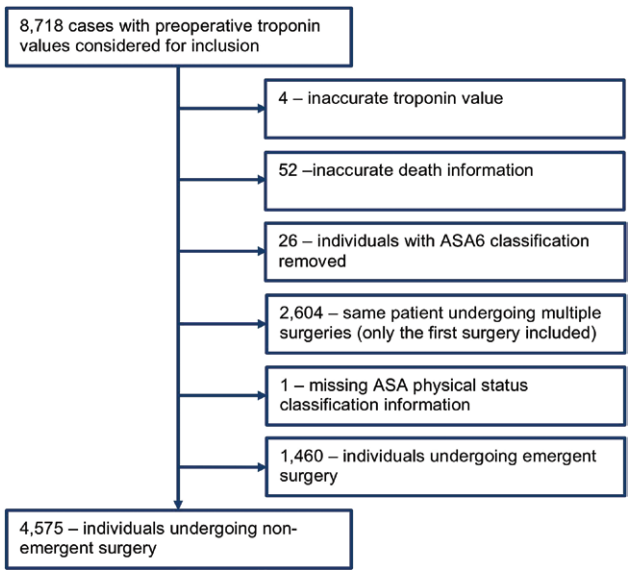

Figure 1. Diagram describing the derivation of the study population. The initial list of eligible subjects was found by searching for noncardiac surgical cases in which the individual had a troponin level measured during the 30 days preceding the operation.

Outcomes

The primary outcome of this study was 30-day postoperative mortality. These data were obtained from hospital records and the Michigan death index.

Statistics

Data were described using means and SDs for normally distributed characteristics and median and interquartile range for nonnormally distributed variables. Study cohorts were created by dividing subjects with detectable preoperative cTnI levels into 9 groups according to time terciles: short (0–2.10 days), medium (>2.10–8.86 days), and long (>8.86–30 days) and cTnI terciles: low (0.10–0.23 ng/mL), medium (0.23–0.84 ng/mL), and high (0.84–494.20 ng/mL) (Fig. 2). This method of categorization was used given the lack of data to define what represents a clinically significant preoperative troponin level. Subjects with undetectable preoperative cTnI levels comprised the tenth (reference) group.

The Cochran-Armitage trend test was used to determine whether there was a change in risk among the different cohorts. Bivariable and multivariable logistic regressions were used to compare the incidence of 30-day mortality among groups and to adjust for the differences in risk factors. All preoperative patient information (Table 1) was included in the multivariable models, regardless of their univariable association with 30-day mortality. The odds ratio (OR) and 95% confidence interval (CI) were used to describe the magnitude and precision of associations. For all statistical tests, a P value <0.05 was used to denote statistical significance. Statistical analysis was completed using R Core Team (2013) (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: http://www.R-project.org/).

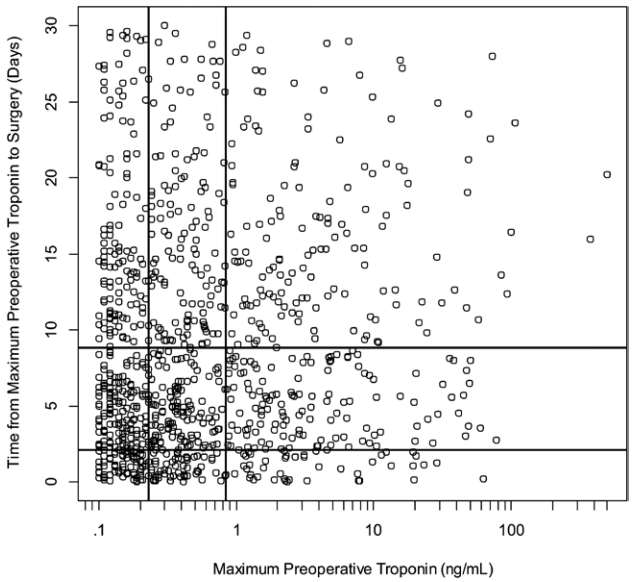

Figure 2. Scatterplot demonstrating the distribution of preoperative troponin concentrations and duration of time between the highest measured troponin value and surgery for the study population with detectable preoperative troponin levels. Lines reflect the 9 study cohorts, which were generated by dividing subjects into troponin terciles and time terciles. The study population is skewed toward low troponin concentrations that were measured in shortly before surgery.

Table 1. Preoperative Subject Characteristics

	n (%)
30-day mortality	281 (6.1)
Male	2531 (55.3)
Troponin >0.10 ng/mL	986 (21.6)
Procedure type	
General	1014 (22.2)
Neurosurgery	488 (10.7)
Obstetrics/gynecology	106 (2.3)
Oral/maxillofacial	237 (5.2)
Orthopedics	735 (16.1)
Otolaryngology	387 (8.5)
Plastics	209 (4.6)
Thoracic	341 (7.5)
Transplant	267 (5.8)
Urology	340 (7.4)
Vascular	451 (9.9)
	Median (Q1, Q3)
Age (y)	63 (52, 73)
ASA physical status	3 (3, 4)
BMI (kg/m^2)	27.6 (23.7, 32.9)
Case duration (min)	159 (108, 236)
Bicarbonate (mmol/L)	27 (25, 30)
Creatinine (mg/dL)	0.9 (0.7, 1.2)
Lactate (mmol/L)	1.1 (0.8, 1.7)
Bilirubin (mg/dL)	0.6 (0.3, 1.0)

BMI = body mass index.

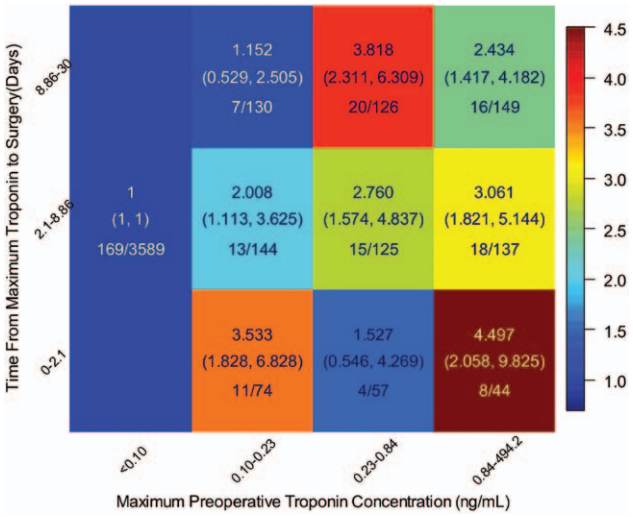

Figure 3. Heatmap summarizing the relationship between time and troponin concentration and 30-day mortality. Text in each box provides the odds ratio, 95% confidence interval, and the proportion of individuals experiencing 30-day mortality. Risk appears to remain elevated longer for those subjects who had a higher peak troponin level. Risk decreases with longer amounts of time between the peak troponin level and surgery ($P = 0.0032$).

RESULTS

During the study period, 4575 patients had cTnI levels drawn within 30 days before a noncardiac surgical procedure. They were predominantly middle aged and had a variety of comorbidities (Table 1). Of these patients, 986 (21.6%) had cTnI >0.10 ng/mL (Fig. 2) and 281 patients (6.1%) died within 30 days. The mortality for those with undetectable and detectable preoperative troponin levels was 4.7% and 11.4%, respectively. Any increase in cTnI above the reported level (0.10 ng/dL) was associated with increased 30-day mortality. This risk increased from 4.7% in the undetectable cTnI group to 12.7% in high tercile group. Compared with those with undetectable levels, the OR of 30-day mortality progressively increased from 1.98 (95% CI, 1.33–2.95) in the low cTnI tercile to 2.95 (95% CI, 2.06–4.22) in the high tercile.

For patients in the low cTnI tercile, having surgery <2.10 days or between 2.10 and 8.86 days after the cTnI measurement was associated with increased 30-day mortality. However, if surgery occurred >8.86 days after cTnI elevation, the risk was similar to patients without elevation (Fig. 3). For patients who had more extensive cTnI elevations (>0.23 ng/mL), the unadjusted OR of 30-day mortality was higher than in the control group, except for the medium-troponin/short-time group, which had an OR similar to the control group (OR = 1.53; 95% CI, 0.55–4.27) (Fig. 3). Examination of this risk across time terciles revealed a trend between lower mortality and longer time between the peak cTnI concentration and surgery for the low cTnI cohort ($P = 0.0238$) but not the medium ($P = 0.09$) or high ($P = 0.20$) cohorts.

After using multivariable logistic regression to adjust for surgical specialty, demographics, comorbidities, and other laboratory values, preoperative cTnI values remained associated with 30-day mortality for 3 of the 9 groups (Table 2 and Fig. 4). To assess interactions between the troponin/time categories and other significant variables, additional logistic regression models were developed with these interaction terms as a sensitivity analysis (Supplemental Digital Content, http://links.lww.com/AA/B414). Although a few interactions were statistically significant for individual troponin/time categories, none was consistent across either troponin concentration or time. In addition, likelihood ratio tests between the models including and not including the interactions were not significant. Therefore, the final model did not include these interaction terms.

DISCUSSION

Although cTn elevation is most frequently thought of as a biomarker of ACS, studies have demonstrated its importance outside of this setting. Terms, such as myocardial injury, troponin leak, and secondary unstable angina, are all used to describe the situation in which these biomarkers are released from the heart in the absence of coronary artery blockage.[10] This situation has been documented in multiple settings (Table 3), such as sepsis,[11] pulmonary embolism,[12] renal failure,[13] and stroke,[14] and these non-ACS cTn elevations are associated with increased risk for mortality even in the general population.[6,7]

Although some of our patients may have had classical myocardial infarction, more than one-third (the entire low tercile and some of the medium tercile of troponin values) were classified as having normal troponin values by our laboratory, yet they were at increased risk of 30-day mortality. This suggests that our laboratory criteria for normal troponin values in this population need to be revised. Study is also needed to determine whether troponin values below our limit of detection are associated with increased risk.

This study expands our knowledge of the impact of cTn levels on surgical risk for those undergoing noncardiac

Table 2. Multivariable Regression

	OR	95% CI	P
Troponin/time categories			
Low/short	2.78	1.38–5.61	0.0044
Low/medium	1.13	0.60–2.13	0.7143
Low/long	0.58	0.25–1.31	0.1897
Medium/short	1.06	0.37–3.05	0.9153
Medium/medium	1.75	0.95–3.22	0.0707
Medium/long	2.05	1.19–3.54	0.0099
High/short	3.16	1.36–7.33	0.0075
High/medium	1.40	0.80–2.45	0.2437
High/long	1.24	0.68–2.25	0.4806
Age	1.03	1.02–1.04	<0.0001
Case duration	1.00	1.00–1.00	0.0703
Serum bicarbonate	0.97	0.94–1.00	0.0370
Creatinine	1.26	1.03–1.53	0.0221
Total bilirubin	1.19	1.09–1.30	0.0001
Serum bicarbonate squared	1.00	1.00–1.00	0.0347
Creatinine squared	0.97	0.93–1.01	0.1215
Total bilirubin squared	1.00	0.99–1.00	0.0095
Gender	1.15	0.88–1.51	0.2983
ASA physical status			
III	3.83	1.66–8.82	0.0016
IV	9.43	4.06–21.90	<0.0001
V	19.02	4.47–80.80	0.0001
Procedure type			
General (reference)			
Neurosurgery	1.41	0.83–2.39	0.2015
OB/Gyn	1.00	0.00, ∞	0.9700
Oral/maxillofacial	3.51	2.17–5.69	<0.0001
Orthopedics	0.89	0.55–1.44	0.6350
Otolaryngology	1.82	1.12–2.96	0.0150
Plastics	0.62	0.24–1.62	0.3308
Thoracic	2.82	1.76–4.54	<0.0001
Transplant	0.46	0.22–0.97	0.0402
Urology	0.74	0.38–1.43	0.3735
Vascular	0.83	0.49–1.41	0.4908

Troponin categories: low = 0.10–0.23 ng/dL, medium = 0.23–0.84 ng/dL, high = 0.34–494.2 ng/dL; time categories: short = 0–2.1 days, medium = 2.1–8.86 days, long = 8.86–30 days. The relationship between the continuous variables and outcome was assessed for linearity by including polynomial terms in the regression. Quadratic terms were included for serum bicarbonate, creatinine, and total bilirubin. There was no evidence for higher-order polynomials.

CI = confidence interval; OB/Gyn = obstetrics and gynecology; OR = odds ratio.

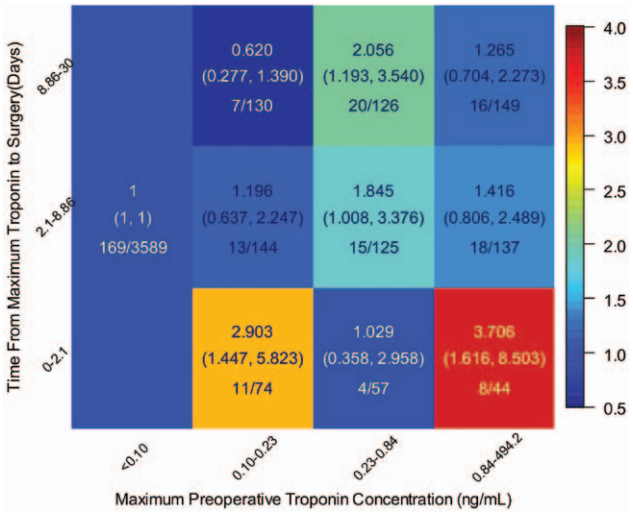

Figure 4. Adjusted heatmap based on multivariable logistic regression that includes preoperative patient characteristics. Text in each box provides the odds ratio, 95% confidence interval, and the proportion of individuals experiencing 30-day mortality. Even small levels of troponin remain associated with increased mortality when the time to surgery is <2.1 days.

Table 3. Noncoronary Causes of Troponin Elevation[2,4,11–14]

Sepsis
Pulmonary embolism
Renal failure
Stroke
Perimyocarditis
Endocarditis
Takotsubo cardiomyopathy
Radiofrequency catheter ablation
Cardiac contusion
Strenuous exercise
Sympathomimetic drugs

surgery. Weber et al.[9] previously demonstrated that, in a high-risk population undergoing noncardiac surgery, high-sensitivity cTnT values provide additional prognostic information to the revised cardiac risk index. Although they examined cTnT rather than cTnI, their study found an association between small changes in cTnT concentrations and mortality, with levels >14 ng/L associated with a 160% (27%–431%) increase in the death hazard. Our study extends their results by demonstrating a dose-response relationship between the amount of time that elapses between a small peak troponin value and survival, especially in those with lower troponin levels. In other words, the increased risk of death is partially ameliorated by a longer wait from peak cTnI to surgery for those with small increases in preoperative troponin levels. Until now, the effect of time between peak cTnI levels and surgery was unstudied. Although our retrospective study cannot establish a causal relationship, it suggests that waiting a longer time after cTn elevation before surgery might reduce 30-day mortality in certain patients. We have no explanation why the patients with an intermediate cTnI elevation demonstrated a time-to-surgery trend in the opposite direction from the small and large cTnI elevation groups. This study raises the question of why a similar trend was not seen in all of the troponin concentration groups. Possible explanations include that these represent a different disease process with different characteristics, that longer periods of time are necessary for larger troponin elevations, or that these patients are being managed differently.

Until now, the effect of time between peak cTnI levels and surgery was unstudied. Although our retrospective study cannot establish a causal relationship, it suggests that waiting a longer time after cTn elevation before surgery might reduce 30-day mortality. Unfortunately, our study does not provide any insight on preoperative management, such as β-blockers and antiplatelet agents, or intraoperative management, such as different arterial blood pressure and heart rate goals that might modify outcome in these patients. Obtaining a better understanding of the pathophysiology of cTn release and how it relates to myocardial injury and death will lead to strategies to reduce its occurrence and association with mortality in the surgery population.[15]

Although we found that longer time between cTn elevation and surgery was associated with lower risk of death before adjusting for other patient characteristics, additional studies are needed to determine whether surgery should be delayed for individuals with a recent troponin elevation and, if so, to what level troponin values should be decreased. Our results suggest this may be longer than a month given that some individuals remained at increased risk in our multivariable model (details pertaining to this model are provided as Supplemental Digital Content, http://links.lww.com/AA/B414). Some guidance may be inferred from studies of myocardial injury after radiofrequency ablation. In this setting, higher levels of cTn were associated with greater inflammation that persisted long after resolution of cTn levels, which was associated with greater risk of recurrence.[16] Given that patients remain at elevated risk for 3 months after an ablation procedure,[16–18] perhaps this would be a reasonable time to wait after myocardial injury before proceeding with a surgical procedure until future studies bring more clarity to this situation.

Our findings should be interpreted in light of several limitations. First, this study was retrospective, and, therefore, factors not measured may confound the results. For example, given the high mortality rate of those both with and without detectable troponin levels, our study population is clearly skewed toward those with a high baseline risk of mortality. Based on this, these findings may not apply to individuals who clinicians do not feel are at risk of myocardial ischemia. However, since serum troponins are not typically used as a screening test before noncardiac surgery, this selection bias does not negate the findings of this study. Second, differences in clinical practice among institutions may limit the ability to generalize our findings to locations that are more or less likely to measure cTn. Third, our laboratory only reports concentrations >0.10 ng/mL; therefore, these results do not provide information about values lower than this level. We also do not know the reasons for the surgery and for the timing of the surgery. Although we adjusted for surgical specialty, we do not know the specific surgeries, and it is possible that patients with greater elevations of troponin underwent more complicated operations within each specialty. Emergency surgery may not be able to be delayed and the patients and physicians most consider the elevated risks associated with having an elevated cTn. Finally, because we do not know the either the cause of the cTn elevation or the cause of mortality, we do not know whether the myocardial injury as shown by the elevated cTnI contributed to death or the underlying pathology that led to the myocardial injury, and cTnI elevation was the contributing factor. Further study is needed to clarify this.

The main strength of our study is that, by using an electronic medical record, we were able to analyze a large group of patients, thus giving us sufficient statistical power to determine the relationship of cTnI level and time to surgery on mortality. By excluding subjects who underwent preoperative percutaneous coronary intervention, our findings are most applicable to patients with disease entities involving presumed coronary blood flow-demand imbalance rather than type 1 myocardial infarction.[2]

In conclusion, we found that the mortality risk is both magnitude and time related. Higher levels of preoperative cTnI were associated with higher postoperative mortality, and longer time to surgery appeared to reduce this risk for individuals with mild preoperative troponin elevations. Prospective studies are needed to determine whether delaying surgery in patients with elevated preoperative troponin levels improves postoperative outcomes.

DISCLOSURES

Name: Michael D. Maile, MD, MS.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Michael D. Maile has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
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Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Elizabeth S. Jewell has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Name: Milo C. Engoren, MD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Milo C. Engoren has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
This manuscript was handled by: Sorin J. Brull, MD.

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CME

One-Year Mortality, Causes of Death, and Cardiac Interventions in Patients with Postoperative Myocardial Injury

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BACKGROUND: To evaluate the role of routine troponin surveillance in patients undergoing major noncardiac surgery, unblinded screening with cardiac consultation per protocol was implemented at a tertiary care center. In this study, we evaluated 1-year mortality, causes of death, and consequences of cardiac consultation of this protocol.

METHODS: This observational cohort included 3224 patients ≥60 years old undergoing major noncardiac surgery. Troponin I was measured routinely on the first 3 postoperative days. Myocardial injury was defined as troponin I >0.06 μg/L. Regression analysis was used to determine the association between myocardial injury and 1-year mortality. The causes of death, the diagnoses of the cardiologists, and interventions were determined for different levels of troponin elevation.

RESULTS: Postoperative myocardial injury was detected in 715 patients (22%) and was associated with 1-year all-cause mortality (relative risk [RR] 1.4, $P = 0.004$; RR 1.6, $P < 0.001$; and RR 2.2, $P < 0.001$ for minor, moderate, and major troponin elevation, respectively). Cardiac death within 1 year occurred in 3%, 5%, and 11% of patients, respectively, in comparison with 3% of the patients without myocardial injury ($P = 0.059$). A cardiac consultation was obtained in 290 of the 715 patients (41%). In 119 (41%) of these patients, the myocardial injury was considered to be attributable to a predisposing cardiac condition, and in 111 patients (38%), an intervention was initiated.

CONCLUSIONS: Postoperative myocardial injury was associated with an increased risk of 1-year all-cause but not cardiac mortality. A cardiac consultation with intervention was performed in less than half of these patients. The small number of interventions may be explained by a low suspicion of a cardiac etiology in most patients and lack of consensus for standardized treatment in these patients. (Anesth Analg 2016;123:29–37)

Postoperative adverse cardiovascular events are a leading cause of morbidity and mortality after noncardiac surgery.[1] The reported incidence of postoperative myocardial infarction (POMI) among patients undergoing noncardiac surgery is between 3% and 6%.[2–4] Prevention of POMI by perioperative suppression of the compensatory sympathetic effects of surgery or by the inhibition of platelet function has showed no beneficial effect in several major clinical trials.[2,3,5] Failure of such preventive strategies has led to strategies aimed at early recognition and subsequent treatment of POMI after surgery.[1,6,7] Therefore, routine monitoring of cardiac biomarkers has been advocated to identify patients at risk of postoperative cardiovascular events early after surgery.[8]

Routine troponin I (TnI) measurements on the first 3 days after surgery followed by a cardiac consultation in patients with troponin elevation were implemented in our hospital. This clinical protocol was part of our standard postoperative care in patients aged 60 years or older undergoing all types of intermediate- to high-risk noncardiac surgery. In a previous study, we showed that postoperative myocardial injury as measured by troponin elevation above the clinical cutoff level of 0.06 μg/L with or without clinical symptoms occurred in 19% of these patients. Myocardial injury was strongly associated with short-term mortality, and troponin elevation improved risk stratification of patients at risk for death.[7] Consequently, we hypothesized that this clinical protocol would facilitate cardiovascular optimization to prevent further myocardial injury, POMI, and long-term cardiovascular mortality.

The primary aim of this study was therefore to determine the association between myocardial injury and long-term death and to assess the causes of death in patients with myocardial injury. Furthermore, we aimed to evaluate the effects of implementing routine postoperative troponin measurements by studying their impact on cardiologists' consultation recommendations and whether specific interventions were implemented in such patients.

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METHODS

Patients

This observational cohort study included consecutive patients undergoing noncardiac surgery between January 1, 2011, and December 31, 2012, at the University Medical Center, Utrecht, The Netherlands, a 1000-bed tertiary referral hospital. Some of this cohort was used in a previous study.[7] Patients were eligible if they were aged 60 years or older, were undergoing intermediate- to high-risk noncardiac surgery under general or spinal anesthesia, and had an expected postoperative length of hospital stay of at least 24 hours. For patients who underwent surgery more than once, the first surgery was included in the analyses. A reoperation was included as a novel case if this surgery took place at least 1 year after the first surgery. Patients were excluded if they were lost to follow-up within 1 year after surgery.

The local medical ethics committee approved the study protocol. The need for informed consent was waived because only routinely collected patient data were used, and data were anonymized before analysis (University Medical Center Utrecht Medical Research Ethics Committee 11–120/C).

Routine Postoperative Troponin Measurements

Routine troponin measurements were implemented as part of the standard postoperative care protocol on January 1, 2011. According to this protocol, troponin was measured daily on the first 3 days after surgery. In the first phase of the protocol implementation, troponin measurements were ordered by the attending anesthesiologist. In case of a troponin elevation above the clinical cutoff level of 0.06 μg/L, the ward physician was notified. Because the optimal treatment of patients with postoperative troponin elevation was not protocolized, it was left to the discretion of the treating physician (surgical specialist) whether further diagnostic procedures including an electrocardiogram (ECG) or cardiology consult were indicated. Thus, troponin elevation was simply considered a marker for myocardial injury, warranting additional attention.

The logistics of the protocol were changed in May 2012 because troponin was not consistently measured in all eligible patients previously, and cardiology consultations were not performed in all patients with troponin elevation. Thus, troponin measurements were subsequently ordered by dedicated anesthesiology nurses, who also requested a postoperative ECG and a cardiology consultation in positive patients. Further diagnostic procedures, such as cardiac or pulmonary computed tomography angiography, and coronary angiography (CAG), were only performed if indicated according to the consultant cardiologist. Cardiac interventions including prescription of medication were performed in concurrence with the treating physician.

Myocardial Injury

Troponin was analyzed using the third-generation enhanced AccuTnI assay (Beckman Coulter, Brea, CA). Myocardial injury was defined as a TnI above the clinical cutoff level of 0.06 μg/L, which was the lowest value measurable with a 10% coefficient of variation above the 99th percentile of 0.04 μg/L.[7] For each patient, the highest value of all routine troponin measurements was used in the analysis.

Data Collection

All preoperative and postoperative data were obtained from electronic medical and administrative records. Data collected in all patients included patient characteristics, preoperative physical status, comorbidities including factors from the Revised Cardiac Risk Index,[9] postoperative troponin measurements, and death within 1 year. In addition, data on postoperative symptoms, ECG changes, the occurrence of in-hospital POMI and other diagnoses, and the treatment initiated by the consultant cardiologist were collected in those patients who had a postoperative cardiac consultation. The unique hospital patient identifier was used to merge databases. The municipal personal record database was consulted for 1-year mortality data. Causes of death were obtained from general practitioners.

Outcomes

The primary outcome was defined as all-cause mortality within 1 year after surgery. Secondary outcomes included cardiac death within 1 year and the incidence of in-hospital POMI. Cardiac death was defined as death resulting from a cardiac arrest or heart failure. Myocardial infarction was defined according to the third universal definition of myocardial infarction.[8]

Cardiac Consultations

In patients with a cardiology consultation, we determined the suspected etiology of the troponin elevation as proposed by the consultant cardiologist. These were divided into predisposing cardiac conditions and perioperative triggers.[1,10] Predisposing cardiac conditions included tachyarrhythmias (supraventricular or ventricular tachycardia), preexistent coronary artery disease, cardiomyopathy, left ventricular hypertrophy, and cardiac contusion. Perioperative triggers included tachycardia, anemia, hypertension, sympathetic storm in the presence of intracranial pathology, hypotension, inflammation and sepsis, pulmonary embolism, renal failure, fluid overload, and hypoxia. Furthermore, we recorded the interventions recommended by the cardiologist.

Statistical Analysis

Baseline characteristics were compared between patients with and without postoperative myocardial injury by using the χ^2 test or 2-sample t test, as appropriate. The incidence of 1-year mortality was compared using the χ^2 test and a relative risk with 95% confidence interval (CI) was calculated. The median time to death was compared by using the Mann-Whitney U test.

Multivariable log-binomial regression analysis was used to adjust the association between myocardial injury and 1-year mortality for patient and surgery characteristics and comorbidities. For this purpose, univariable regression analysis was used to identify the variables that were associated with 1-year mortality. Variables with a P value of ≤0.10 were included in the multivariable model. In this model, patients were classified according to their highest postoperative troponin value. Therefore, we defined more or less equally sized groups for the patients with troponin elevation, based on 1, 2, and 10 times the TnI cutoff level: TnI ≤0.06 μg/L, TnI 0.07–0.12 μg/L

(minor elevation), TnI 0.13–0.60 μg/L (moderate elevation), and TnI >0.60 μg/L (major elevation). High-risk surgery was defined as intraabdominal, intrathoracic, or suprainguinal vascular surgery,[9] and emergency surgery was defined as surgery required within 72 hours after the indication for surgery was set. Ischemic heart disease was defined as previous myocardial infarction and/or coronary revascularization, heart failure was defined as a left ventricular ejection fraction <40%, and preoperative renal failure was defined as a glomerular filtration rate <45 mL/min/1.73 m^2. Next, we checked for interaction of troponin with any of the significant variables in the multivariable model by including interaction terms. We used log-binomial regression analysis to facilitate presenting effect measures as risk ratios.[11]

A Kaplan-Meier survival analysis was used to determine the survival of patients in each category of troponin elevation. Survival was compared by using the log rank test. Furthermore, causes of death were compared between these groups. Finally, we recorded the number of cardiology consultations and the diagnoses and interventions by the cardiologist.

All hypothesis testing was conducted 2 sided, and throughout the analyses, we used a level of significance of 0.05. The analysis was performed using SPSS (release 21.0.0 for Windows IBM SPSS Statistics for Windows, Version 21.0, IBM Corp., Armonk, NY).

RESULTS

During the study period, 4099 patients were eligible for inclusion, of which 49 patients (1%) were excluded from the analyses (Fig. 1). Of the remaining 4050 patients, 826 patients (20%) were excluded because troponin was not measured during the first 3 postoperative days. Thus, 3224 patients were included in this study (Table 1). Myocardial injury occurred in 715 patients (22%): 344 (11%) had minor troponin elevations (TnI 0.07–0.12 μg/L), 255 (8%) had moderate troponin elevations (TnI 0.13–0.60 μg/L), and 116 (4%) had major troponin elevations (TnI >0.60 μg/L).

One-Year All-Cause Mortality

Of the 715 patients with myocardial injury, 182 patients (26%) died within 1 year after surgery compared with 318 (13%) of the 2509 patients without myocardial injury (RR 2.0; 95% CI, 1.7–2.4; $P < 0.001$). The median time to death was 55 days (interquartile range [IQR], 11–173) in patients with myocardial injury when compared with 135 days (IQR, 47–236) in patients without myocardial injury ($P < 0.001$). The 1-year mortality rates in patients with minor, moderate, and major troponin elevations were 21%, 25%, and 40%, respectively ($P < 0.001$) (Fig. 2). After adjustment for variables that are known to predict death, the RR of 1-year mortality was 1.4 (95% CI, 1.1–1.8; $P = 0.004$) in patients with minor troponin elevations, 1.6 (95% CI, 1.3–2.1; $P < 0.001$) in patients with moderate troponin elevations, and 2.2 (95% CI, 1.7–2.8; $P < 0.001$) in patients with major troponin elevations when compared with patients without myocardial injury (Table 2). Other independent predictors of death were age, preoperative renal failure, preoperative insulin use, and emergency surgery. Interaction terms for each of these predictors with troponin in the multivariable model were not statistically significant.

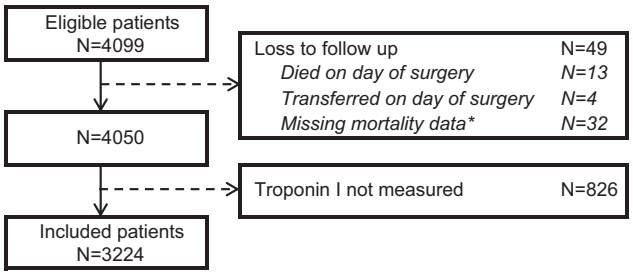

Figure 1. Flow chart of patient inclusion. *These patients were not known by the municipal personal records database.

Table 1. Baseline Characteristics in Patients With and Without Postoperative Myocardial Injury

	No myocardial injury, *N* = 2509	Myocardial injury, *N* = 715	*P*
Male	1282 (51)	424 (59)	<0.001
Mean age (SD)	70 (7)	73 (8)	<0.001
Smoking[a]	446 (19)	122 (20)	0.452
Hypertension	1243 (50)	434 (61)	<0.001
Diabetes mellitus	404 (16)	150 (21)	0.002
COPD	233 (9)	76 (11)	0.282
History of myocardial infarction	193 (8)	106 (15)	<0.001
History of coronary revascularization	251 (10)	130 (18)	<0.001
History of heart failure	56 (2)	38 (5)	<0.001
(Paroxysmal) atrial fibrillation	262 (10)	107 (15)	0.001
Pacemaker/implantable cardioverter Defibrillator	50 (20)	36 (5)	<0.001
History of cerebrovascular disease	361 (14)	135 (19)	0.003
Renal failure	223 (9)	151 (21)	<0.001
Peripheral vascular disease	245 (10)	111 (16)	<0.001
Medication use			
β-Blockers	722 (29)	268 (38)	<0.001
Calcium antagonists	414 (17)	134 (19)	0.159
RAS inhibitors	845 (34)	294 (41)	<0.001
Diuretics	630 (25)	219 (31)	0.003
Aspirin	688 (27)	264 (37)	<0.001
Warfarin	264 (11)	100 (14)	0.010
Statins	863 (34)	300 (42)	<0.001
Insulin	130 (5)	55 (8)	0.011
Oral antidiabetics	309 (12)	99 (14)	0.278
ASA physical status			<0.001
I	355 (14)	58 (8)	
II	1641 (65)	401 (56)	
III	497 (20)	237 (33)	
IV	16 (1)	19 (3)	
General anesthesia	2333 (93)	693 (97)	<0.001
High-risk surgery	725 (29)	311 (44)	<0.001
Emergency surgery	437 (17)	256 (36)	<0.001
Reoperation within 1 y	408 (16)	172 (24)	<0.001
Surgical specialty			<0.001
General surgery	517 (21)	240 (34)	
Neurosurgery	630 (25)	147 (21)	
Vascular surgery	365 (15)	145 (20)	
ENT and dental surgery	339 (14)	65 (9)	
Orthopedic surgery	267 (11)	78 (11)	
Gynecology/urology	391 (16)	40 (6)	

Figures are numbers of patients (%), unless indicated otherwise.
COPD = chronic obstructive pulmonary disease; ENT = ear, nose, and throat; RAS = renin-angiotensin system.
[a]N = 2354 and N = 601, respectively, due to missing data on smoking.

Causes of Death

Data on the cause of death were available for 358 of the 500 patients (72%) who died within 1 year (Table 3). Cardiac death occurred in 2 (3%), 3 (5%), and 5 patients (11%) with minor, moderate, and major troponin elevations, respectively, when compared with 9 patients (3%) without myocardial injury (P = 0.059). Predominant causes of death in patients with major troponin elevations were sepsis (20%), cerebrovascular disease (15%), and cardiac disease (11%), whereas most of the patients without myocardial injury died of cancer (43%).

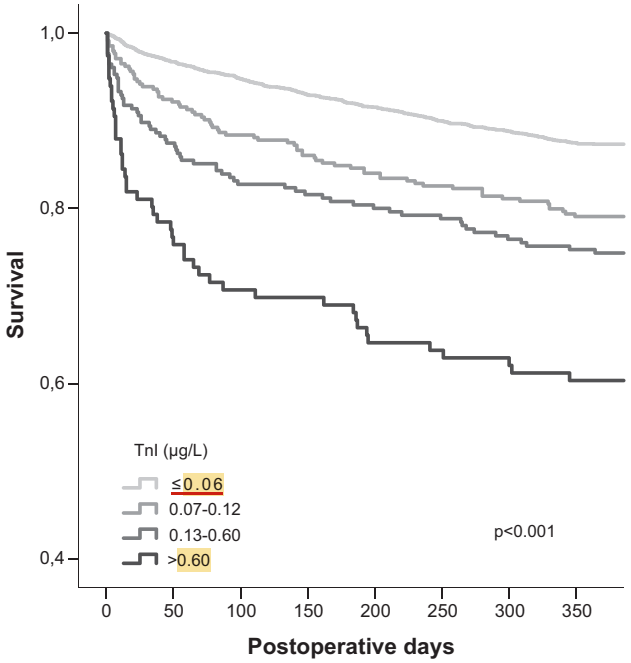

Figure 2. Kaplan-Meier plot of patients with different levels of troponin elevation. TnI = troponin I.

ECG Results

A postoperative ECG was performed in 424 of the 715 patients (59%) with myocardial injury. ECG changes suggestive of new ischemia were found in 96 of the 424 patients (23%) and were more frequent in patients with major troponin elevations (43 of 112 patients, 38%) when compared with patients with moderate troponin elevations (32 of 187 patients, 17%) or minor troponin elevations (21 of 135 patients, 16%). Three (0.7%) of these ECGs showed ST elevation ≥1 mm, 52 (12%) ECGs showed ST depression ≥1 mm, and 41 (10%) ECGs showed ST depression <1 mm or T-wave inversion, respectively. Twenty-five of the 715 patients (3%) with myocardial injury had typical chest pain.

Cardiology Consultations

A cardiology consultation followed in 290 of the 715 patients (41%) with myocardial injury (i.e., 9% of the total study population). The proportion of patients with a cardiac consultation was 18%, 54%, and 79% in patients with a minor, moderate, and major troponin elevation, respectively.

For the 290 patients who had cardiology consultation, the suspected etiologies of myocardial injury as determined by the consultant cardiologist are given in Figure 3. In 119 of the 290 patients (41%) with a cardiac consultation, the myocardial injury was considered to be attributable to predisposing cardiac conditions, including tachyarrhythmia and preexistent coronary artery disease, and in 81 patients (28%), the myocardial injury was considered to be attributable to perioperative triggers. In 126 patients (43%), the etiology of myocardial injury was not specified. Of note, the number of patients within the different groups of suspected etiologies exceeds the total number of patients because 36 patients (12%) were assigned to >1 group (e.g., a patient with myocardial injury because of anemia in the presence of left ventricular hypertrophy).

Table 2. The Association Between Postoperative Myocardial Injury for Different Categories of Troponin Elevation and 1-Year Mortality, Adjusted for Age, Comorbidities, and Surgery Characteristics

	Unadjusted analysis			Adjusted analysis		
	RR	95% CI	P	RR	95% CI	P
TnI (µg/L)						
≤0.06	Ref			Ref		
0.07–0.12	1.7	1.3–2.1	<0.001	1.4	1.1–1.8	0.004
0.13–0.60	2.0	1.6–2.5	<0.001	1.6	1.3–2.1	<0.001
>0.60	3.1	2.4–4.0	<0.001	2.2	1.7–2.8	<0.001
Age (per 10 y increase)	1.4	1.2–1.5	<0.001	1.2	1.1–1.3	<0.001
Female sex	0.9	0.8–1.1	0.920			
Ischemic heart disease	1.0	0.8–1.2	0.877			
Hypertension	0.9	0.8–1.1	0.203			
(Paroxysmal) atrial fibrillation	1.3	1.0–1.6	0.022	1.1	0.9–1.4	0.383
Heart failure	1.3	0.9–2.0	0.190			
Pacemaker and/or ICD	1.2	0.8–1.9	0.414			
Cerebrovascular disease	1.1	0.9–1.4	0.217			
Preoperative renal failure	1.8	1.5–2.2	<0.001	1.3	1.1–1.6	0.014
Preoperative insulin use	1.7	1.3–2.3	<0.001	1.4	1.1–1.7	0.012
COPD	1.0	0.8–1.4	0.730			
Peripheral vascular disease	1.0	0.8–1.3	0.851			
High-risk surgery	1.0	0.9–1.2	0.728			
Emergency surgery	1.9	1.6–2.2	<0.001	1.5	1.3–1.8	<0.001
Reoperation within 1 y	1.3	1.1–1.6	0.002	1.2	1.0–1.4	0.111

Figures are numbers (%) of patients.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; ICD = implantable cardioverter defibrillator; RR = relative risk; TnI = troponin I.

Table 3. Causes of Death Within 1 Year After Surgery for Each Category of Troponin Elevation (Total *N* = 500)

	TnI (μg/L)				
	<0.06, *N* = 318	0.07–0.12, *N* = 72	0.13–0.60, *N* = 64	>0.60, *N* = 46	*P*
Cardiac	9 (3)	2 (3)	3 (5)	5 (11)	0.059
Cardiac arrest	6 (2)	2 (3)	3 (5)	2 (4)	
Heart failure	3 (1)	0 (0)	0 (0)	3 (7)	
Pulmonary embolism	3 (1)	0 (0)	2 (3)	0 (0)	0.249
Other pulmonary	10 (3)	8 (11)	5 (8)	4 (9)	0.024
Cerebrovascular/brain injury	19 (6)	10 (14)	13 (20)	7 (15)	0.001
Malignancy	135 (43)	22 (31)	10 (16)	1 (2)	<0.001
Infection/sepsis	23 (7)	6 (8)	10 (16)	9 (20)	0.018
Other	18 (6)	5 (7)	8 (13)	11 (24)	<0.001
Unknown	101 (32)	19 (26)	13 (20)	9 (20)	0.125

Figures are numbers (%) of patients.
TnI = troponin I.

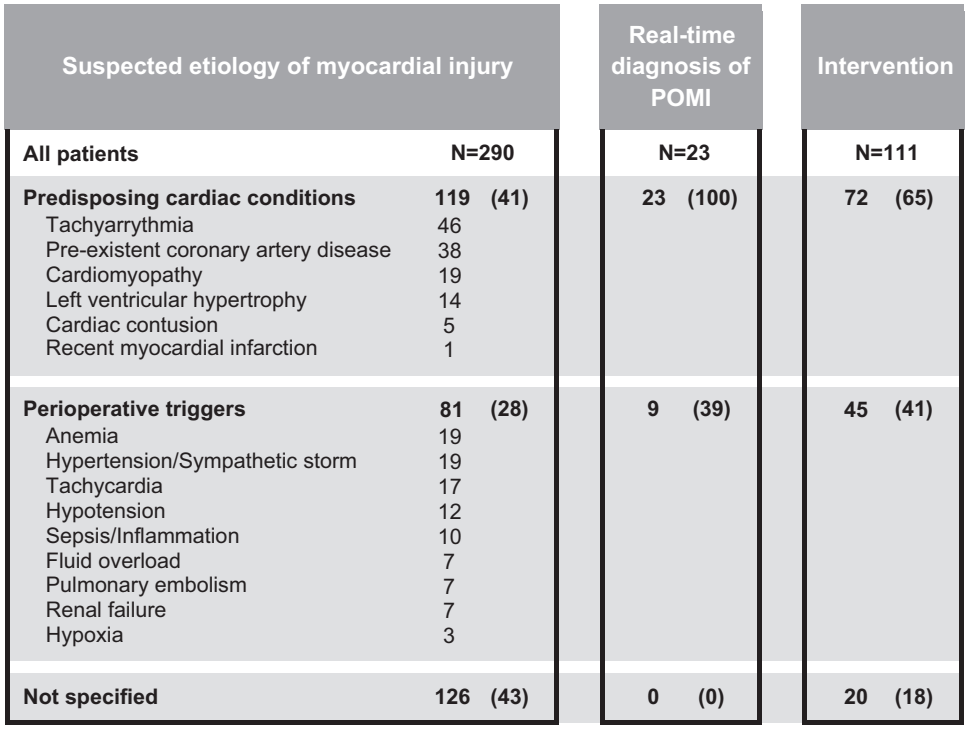

Figure 3. Suspected etiologies of myocardial injury, postoperative myocardial infarction (POMI), and interventions in the 290 patients with a cardiac consultation. The suspected etiologies as determined by the consultant cardiologist were classified as predisposing cardiac conditions and perioperative triggers. The number of patients with POMI and the number of patients with a cardiac intervention are given for each of these groups. Of note, the number of patients in each column exceeds the total number of patients because the myocardial injury was suspected to be due to both a predisposing cardiac condition and perioperative triggers in 36 patients. Figures are numbers (%) of patients.

Postoperative Myocardial Infarction

POMI defined according to the third universal definition occurred in 97 of the 715 patients (14%) with myocardial injury: ST-segment elevation myocardial infarction (STEMI) in 3 patients and non-STEMI in 94 patients, that is, 3% of the total study population. However, only 18 of them who were in the group that received a cardiologist consultation were diagnosed by the cardiologist in real time as having POMI, including the 3 patients with STEMI. In addition, 5 patients who in retrospect did not fulfill the criteria of the third universal definition of myocardial infarction were diagnosed in real time as having POMI because of high TnI values with a rise-and-fall pattern in 4 patients and high TnI values with ventricular tachycardia in 1 patient. In total, 23 patients were diagnosed with POMI by the cardiologist. In all of these 23 patients, POMI was considered to be attributable to a predisposing cardiac condition, and in 9 of these 23 patients, a perioperative trigger was suspected as well.

Interventions

A cardiac intervention was initiated in 111 of the 290 patients (38%) with a cardiology consultation. In the remaining 179 patients (62%), only follow-up of troponin was performed, and the clinical course was further awaited without any intervention. Interventions were more often done in patients with a major troponin elevation (48 of 92 patients, 52%) when compared with patients with a moderate troponin elevation (45 of 138 patients, 33%) or a minor troponin elevation (18 of 60 patients, 30%). In patients in whom the myocardial injury was considered to be attributable to predisposing cardiac conditions or perioperative triggers, a cardiac intervention was initiated in 72 of 119 patients (61%) and 45 of 81 patients (56%), respectively, whereas when the etiology of myocardial injury was not specified, a cardiac intervention was done in 20 of 126 patients (16%) (Fig. 3).

The cardiac interventions consisted of the following: in 104 of the 290 patients (36%), new medication or a dose increase was prescribed. This included β-blockers in

52 patients (18%); other antihypertensive agents, including renin-angiotensin inhibitors, diuretics, and calcium channel blockers in 21 patients (7%); aspirin in 34 patients (12%); other antiplatelet agents in 15 patients (5%); heparin (low molecular weight) in 28 patients (10%); statins in 22 patients (8%); and other medication in 25 patients (9%). In 14 patients (5%), red blood cell transfusion was advised by the cardiologist. Seventeen patients (6%) were transferred to the coronary care unit or medium care for cardiac monitoring. CAG was performed in 15 patients (5%). The median time to CAG was 10 days (IQR, 4–62). Significant coronary artery stenoses were found in 12 patients (4%). Nine patients (3%) underwent percutaneous coronary intervention (PCI), and 1 patient (0.3%) underwent coronary artery bypass graft surgery. Finally, in 2 patients (0.7%), coronary revascularization was not performed because the risk of intervention was considered too high or because it was considered not to be beneficial because of the patients' poor condition.

Of the 3 patients with STEMI, only 1 underwent CAG and PCI. In this patient, CAG and PCI were not performed in the acute phase because of an initial diagnostic delay (>6 hours) but 14 and 33 days after STEMI was diagnosed, respectively. This patient survived the follow-up time of 1 year. In 1 STEMI patient who underwent neurosurgery, CAG (and PCI) was not performed because the risk of intracranial bleeding with antiplatelet and anticoagulant therapy was considered too high. This patient died 15 days later of cerebral empyema. In another STEMI patient, a diagnostic delay occurred because of difficulties in interpreting the ECG (preexistent ST elevation in the anterior leads because of a prior anterior wall myocardial infarction). By the time STEMI was diagnosed, the ECG was normalized and CAG was no longer considered beneficial. The patient was admitted to the medium care unit for cardiac monitoring, treated with antiplatelet therapy, and survived the follow-up time of 1 year.

DISCUSSION

This study determined the association between postoperative myocardial injury and 1-year mortality in a large cohort of patients and assessed causes of death in patients with myocardial injury. In addition, we studied the diagnoses and cardiac interventions in these patients. Postoperative myocardial injury, as detected by troponin elevation, was found in 22% of the patients and was associated with a 1.5- to 3-fold increased risk of 1-year mortality. The protocol led to a cardiac intervention in only 111 (16%) of the 715 patients with myocardial injury.

Our hospital is one of the first that implemented routine troponin measurements after noncardiac surgery to improve early identification of patients with myocardial injury who are at risk of (silent) POMI and death. Because data from clinical care obtained in the implementation period of a new protocol were used in this study, the results represent daily care, instead of a controlled research setting.

Limitations

Several limitations must be addressed. First, because troponin was only measured on the first 3 days after surgery, myocardial injury that may have occurred after the third postoperative day was missed. However, previous research has shown that myocardial injury occurs primarily within the first 3 postoperative days.[12–14] Second, because troponin was not measured in 20% of patients, selection bias may have been present. However, we showed in a previous report including a part of this cohort that there were no large differences between patients with and without troponin measurements and that imputation of the missing troponin values did not alter the association between myocardial injury and death.[7] Third, exclusion of patients who were lost to follow-up (1%) may have introduced potential bias. Fourth, troponin was not measured before surgery; hence, the results could not be adjusted for possible preexisting troponin elevations.[15–17] Fifth, in evaluating postoperative troponin measurements, the occurrence of complications of resulting interventions (e.g., bleeding caused by anticoagulants)[3,18,19] would have been valuable to report, but these data were not available for all patients. Finally, data on the cause of death were not available for all patients. Because the cause of death may have been reported as "unknown" in some patients with sudden death, the incidence of sudden cardiac death may be underestimated.

Literature

The association between postoperative myocardial injury and long-term mortality has been assessed in several smaller cohort studies that included patients undergoing major surgery. Myocardial injury as measured by troponin elevation was reported to be associated with a 2- to 41-fold increased risk of death within 1 year after surgery, which is consistent with the result of our study.[20–33] In the Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) trial, even troponin levels below the upper limit of normal were found to be related to mortality.[4] Cardiac death occurred in 19 of the 3224 patients (0.6%) in our study, which is in accordance with the incidence of cardiovascular death in the PeriOperative ISchemic Evaluation-2 (POISE-2) trial (0.7%).[3] Furthermore, Chong et al.[20] reported that cardiovascular death occurred more frequently in patients who suffered from postoperative myocardial injury after orthopedic surgery, as in our study.

The incidence of POMI according to the third universal definition of myocardial infarction (3%) is comparable to previous reports (3%–6%).[2–4] It should be noted that only 0.7% of patients were diagnosed with POMI in real time by the cardiologist. This implies that, in clinical practice, myocardial injury in the postoperative phase is evaluated differently than outside the perioperative setting, for example, in patients who are suspected of myocardial infarction in the emergency department. Also, POMI appears to be less often diagnosed in a daily clinical care setting than in a controlled research setting, even if routine postoperative monitoring of troponin is used.

Because many of the patients with postoperative myocardial injury do not fulfill the criteria of myocardial infarction, a new diagnosis of Myocardial Injury after Noncardiac Surgery, defined as prognostically relevant myocardial injury due to ischemia that occurs during or within 30 days after noncardiac surgery, was proposed to guide timely diagnosis and intervention.[34] Current guidelines concur that early postoperative troponin measurements could have therapeutic consequences and therefore that it may be

considered in high-risk patients,[35] but it is emphasized that its usefulness is uncertain in the absence of established risks and benefits of a defined management strategy,[36] which is confirmed by our study.

Although many causes of postoperative myocardial injury have been put forward, including noncardiac causes,[1,10] it is not known in how many patients and to what extent perioperative factors contribute to the development of myocardial injury. Furthermore, if POMI is diagnosed, there is uncertainty whether this is mainly caused by plaque rupture with thrombosis (type 1 myocardial infarction) or an imbalance between myocardial oxygen supply and demand (type 2 myocardial infarction),[37–40] which hampers the initiation of proper treatment options. Moreover, even in patients with type 2 myocardial infarction outside the perioperative setting, there are no established treatment guidelines.[41]

Few studies evaluated cardiac treatment initiated after surgery in patients with postoperative myocardial injury. Foucrier et al.[42] studied the effect of cardiovascular medical optimization in 667 patients undergoing elective major vascular surgery. They reported that patients with treatment optimization, consisting of prescription or a dose increase of antiplatelet drugs, β-blockers, angiotensin-converting enzyme inhibitors, and statins, had a lower risk of adverse cardiac events than patients without treatment optimization. Treatment interventions were much more frequent (65%) than in our study (16%), which may be explained by the type of patients included, that is, those at higher risk of cardiovascular complications who may have had more benefit from cardiovascular optimization. Chong et al.[43] randomly assigned 70 patients with troponin elevation after orthopedic surgery to cardiology care, consisting of assessment by a cardiologist and admission to a coronary care unit, versus standard treatment. Prescription of new medication, mainly β-blockers and aspirin, was more frequent (83% of the patients) compared with our study (36% of the patients with cardiology consultation). However, cardiology care had no effect on in-hospital cardiac complications and 1-year mortality.

Clinical Implications

Several strategies to prevent the occurrence of POMI, including suppression of the sympathetic nervous system and antiplatelet therapy, have failed to show an effect or the beneficial effect was outweighed by severe side effects.[3,5] As an alternative strategy, in those patients in whom postoperative myocardial injury has occurred, further myocardial injury and infarction may be prevented by adequate treatment early after surgery and, consequently, prognosis in terms of survival may be improved.[6,7] Indeed, we found that among patients with postoperative myocardial injury, the most common causes of death were cardiac disease, cerebrovascular disease, and sepsis (Table 3), whereas among the patients without myocardial injury, most patients died of cancer. Although we showed that it is feasible to identify these patients at risk early after surgery by routine troponin measurements, this resulted in treatment interventions in less than half (38%) of the patients who had a cardiac consultation. In patients in whom the myocardial injury was considered to be due to predisposing cardiac conditions, a cardiac intervention was performed in 60% of patients. However, in many patients (43%), the etiology of the myocardial injury was not clear; hence, it was likely not known what treatment should be initiated to prevent further injury and death. Furthermore, in about half of the patients with perioperative triggers for troponin elevation, no treatment was initiated. In a part of these patients who were at high risk of death, the myocardial injury may have been inherent to the underlying disease, for example, in patients with myocardial injury due to sympathetic storm in the presence of intracranial pathology or in patients with severe sepsis. Hence, it is conceivable that cardiac interventions were not performed in these patients because this may not have been beneficial.

The findings from the current study support that attempts to improve prognosis in patients with myocardial injury are limited by insufficient knowledge of the underlying pathophysiology, adequate treatment options in individual cases, and insufficient capability to select those patients in whom cardiac treatment may be beneficial. It is likely that 1 single intervention is not simply beneficial in all patients. Given the high mortality rate in patients who suffer from postoperative myocardial injury, future research efforts should first and foremost focus on unraveling the pathophysiology of postoperative myocardial injury to guide treatment options and on identifying the patients who may benefit from (different) treatments. As long as these questions are not answered, we would recommend carefully weighing the benefits and risks of measuring troponin routinely in all patients after noncardiac surgery.

CONCLUSIONS

Postoperative myocardial injury as detected by routine troponin measurements is associated with 1-year mortality. However, implementation of a clinical protocol including a cardiology consultation in patients with postoperative myocardial injury to improve the prognosis in these patients resulted in a cardiac consultation and intervention in less than half of the patients with myocardial injury. The low number of interventions may be explained by the suspicion of a cardiac condition in only a minority of the patients and the lack of a standardized treatment protocol in our study, which in turn is attributable to a lack of knowledge of the underlying pathophysiology and treatment options in patients with postoperative myocardial injury. ■

DISCLOSURES

Name: Judith A. R. van Waes, MD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Judith A. R. van Waes has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Name: Remco B. Grobben, MD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Remco B. Grobben approved the final manuscript.
Name: Hendrik M. Nathoe, MD, PhD.
Contribution: This author helped design the study, analyze the data, and write the manuscript.
Attestation: Hendrik M. Nathoe approved the final manuscript.

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Attestation: Linda M. Peelen approved the final manuscript.
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Attestation: Wilton A. van Klei has seen the original study data and approved the final manuscript.
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