Queen's UNIVERSITY

DEPARTMENT OF ANESTHESIOLOGY

JOURNAL CLUB

Wednesday November 18, 2015
1800 HOURS

LOCATION:
Curry Original
253A Ontario Street

PRESENTING ARTICLES:
Dr. Joel Parlow & Dr. Yuri Koumpan

SUGGESTED GUIDELINES FOR CRITICAL APPRAISAL OF PAPERS
ANESTHESIOLOGY JOURNAL CLUB
QUEEN'S UNIVERSITY

Two presenters will be assigned to choose and present summaries of their papers. Ideally the two papers will represent similar topics but contrasting research methodologies. The focus remains on critical appraisal of the research and manuscript, more than on the actual contents of the article. Each presenter will then lead an open discussion about the article, based around the guidelines below. The object is to open up the appraisal to wide discussion involving all participants, who will be expected to contribute pending suspension of bar privileges.

GENERAL

1. Title of paper: Does it seem like an important problem? Does it reflect the purpose/results?
2. Authors, institution and country of origin

INTRODUCTION

1. What is the problem being addressed?
2. What is the current state of knowledge of the problem studied?
3. What is the hypothesis being tested?
4. How does testing the hypothesis help solve the stated problem?

METHODOLOGY

1. Study design:
    a) Clinical trial vs. systematic review/meta-analysis
    b) Prospective vs. retrospective
    c) Observational vs. Experimental
    d) Randomized or not
    e) Blinded or not

2. Population studied:
    a) Human, animal, other
    b) Justification
    c) Control groups: experimental vs. historical
    d) Is the sample size/power calculated, and how?
    e) Is the population similar to your own practice?
    f) Single vs. multi-centre

3. Is the study ethically sound?
    a) Clinical equipoise
    b) Does treatment meet standard of care (esp controls)?
    c) Appropriate consent and institutional ethics approval

4. Exclusions: what groups are excluded and why?

5. Experimental protocol
    a) Is it designed to test the hypothesis?

b) Is it detailed enough to be reproducible?
c) Is the methodology validated?
d) Are the drugs/equipment used detailed?
e) How does the randomization take place?

6. What are the primary endpoints?
7. Is power sufficient to justify secondary endpoints?
8. Is the protocol clinically relevant?
9. Data collection and analysis
10. Statistical analysis: Is it appropriate? Are results

RESULTS

1. Are the groups comparable?
2. Were any subjects/data eliminated?
3. Analyzed by intent to treat?
4. Are adequate details of results provided? - data, graphs, tables

DISCUSSION

1. What is the main conclusion of the study?
2. Do the results support this conclusion?
3. Do the results address the stated purpose/hypothesis of the study?
4. How do the authors explain the results obtained?
5. Are there any alternative interpretations to the data?
6. Are the results clinically as well statistically relevant?
7. How do the results compare with those of previous studies?
8. What do the results add to the existing literature?
9. What are the limitations of the methods or analysis used?
10. What are the unanswered questions for future work?

APPLICABILITY OF THE PAPER

1. Have you learned something important from reading this paper?
2. Will the results of this study alter your clinical practice?
3. Was the food and wine up to the high standards expected by self-respecting anesthesiologists?

Association Between Postoperative Troponin Levels and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery

The Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators

Context Of the 200 million adults worldwide who undergo noncardiac surgery each year, more than 1 million will die within 30 days.

Objective To determine the relationship between the peak fourth-generation troponin T (TnT) measurement in the first 3 days after noncardiac surgery and 30-day mortality.

Design, Setting, and Participants A prospective, international cohort study that enrolled patients from August 6, 2007, to January 11, 2011. Eligible patients were aged 45 years and older and required at least an overnight hospital admission after having noncardiac surgery.

Main Outcome Measures Patients' TnT levels were measured 6 to 12 hours after surgery and on days 1, 2, and 3 after surgery. We undertook Cox regression analysis in which the dependent variable was mortality until 30 days after surgery, and the independent variables included 24 preoperative variables. We repeated this analysis, adding the peak TnT measurement during the first 3 postoperative days as an independent variable and used a minimum *P* value approach to determine if there were TnT thresholds that independently altered patients' risk of death.

Results A total of 15 133 patients were included in this study. The 30-day mortality rate was 1.9% (95% CI, 1.7%-2.1%). Multivariable analysis demonstrated that peak TnT values of at least 0.02 ng/mL, occurring in 11.6% of patients, were associated with higher 30-day mortality compared with the reference group (peak TnT ≤ 0.01 ng/mL): peak TnT of 0.02 ng/mL (adjusted hazard ratio [aHR], 2.41; 95% CI, 1.33-3.77); 0.03 to 0.29 ng/mL (aHR, 5.00; 95% CI, 3.72-6.76); and 0.30 ng/mL or greater (aHR, 10.48; 95% CI, 6.25-16.62). Patients with a peak TnT value of 0.01 ng/mL or less, 0.02, 0.03-0.29, and 0.30 or greater had 30-day mortality rates of 1.0%, 4.0%, 9.3%, and 16.9%, respectively. Peak TnT measurement added incremental prognostic value to discriminate those likely to die within 30 days for the model with peak TnT measurement vs without (C index=0.85 vs 0.81; difference, 0.4; 95% CI, 0.2-0.5; $P<.001$ for difference between C index values). The net reclassification improvement with TnT was 25.0% ($P<.001$).

Conclusion Among patients undergoing noncardiac surgery, the peak postoperative TnT measurement during the first 3 days after surgery was significantly associated with 30-day mortality.

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Worldwide, more than 200 million adults have major noncardiac surgery annually.[1,2] Despite benefits associated with surgery, major perioperative complications, including death, occur.[3] More than 1 million adults worldwide will die within 30 days of noncardiac surgery each year.[1,2]

Perioperative risk estimation identifies patients who require more intensive monitoring and management in the postoperative period. Current preoperative risk prediction models for 30-day mortality have limitations.[4,5] Some clinicians advocate monitoring troponin measurements after vascular surgery,[6] and inconclusive evidence suggests that troponin measurements after abdominal aortic surgery may enhance prediction of short-term mortality.[7] Little is known about optimal troponin threshold(s) for predicting mortality after noncardiac surgery.

A large international study called the VISION Study (Vascular Events in Noncardiac Surgery Patients Cohort Evaluation; clinicaltrials.gov identifier, NCT00512109) is evaluating major complications after noncardiac surgery. Participating patients have troponin T (TnT) levels measured after noncardiac surgery. We assessed the relationship between the peak fourth-generation TnT measurement after noncardiac surgery and 30-day mortality.

METHODS

Study Design and Eligibility Criteria

The VISION Study is a prospective cohort study of a representative sample of patients undergoing noncardiac surgery. VISION was designed to recruit 40 000 patients in North and South America, Africa, Asia, Australia, and Europe to evaluate major complications after noncardiac surgery. At the beginning of this study, patients had fourth-generation TnT measurements after noncardiac surgery. The first 15 000 pa-

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tients experienced event rates at approximately 3 times what was expected. Recognizing that we had sufficient events to address our objectives related to the fourth-generation TnT measurements, the operations committee decided to henceforth monitor the fifth-generation high-sensitivity TnT assay. This publication is restricted to patients during the period of fourth-generation TnT use.

Eligible patients for the VISION Study had noncardiac surgery, were at least 45 years of age, received a general or regional anesthetic, and underwent elective, urgent, or emergency surgery during the day or at night on a weekday or weekend. Additional eligibility criteria restricting patients to those with data allowing prognostic evaluation of fourth-generation TnT included patients who had a fourth-generation TnT assay measurement and complete data for the 24 potential preoperative predictors of 30-day mortality that we evaluated. Patients were excluded if they did not require an overnight hospital admission after surgery, were previously enrolled in the VISION Study, or declined consent. The research ethics board at each site approved the protocol prior to patient recruitment.

Patient Recruitment

Patients gave consent prior to surgery or, for those from whom we could not obtain consent preoperatively (eg, emergency night surgical case), research personnel obtained consent within the first 24 hours after surgery. Eight centers used a deferred consent process for patients unable to provide consent (eg, patients sedated and mechanically ventilated) and for whom no next of kin was available. This allowed collection of TnT measurements while awaiting patient or next-of-kin consent.

Patients were identified by screening daily patient lists in preoperative assessment clinics, on surgical wards, and in intensive care units; daily and previous-day surgical lists; and patients in the preoperative holding area. In some centers, surgical volume exceeded the capacity of research staff to enroll all eligible patients on consecutive weeks. In these centers, the project office either created a recruitment schedule consisting of random weeks of nonrecruitment or randomly selected surgical services. At the end of each week, research personnel reviewed the surgical logbook and reported the number of patients eligible but not enrolled.

Procedures

Research personnel interviewed and examined patients and reviewed medical records to obtain information on potential predictors of major perioperative complications. At each site, an investigator reviewed and approved all data. Patients had blood collected to measure a Roche 4th-generation Elecsys TnT assay 6 to 12 hours postoperatively and on the first, second, and third days after surgery. Patients enrolled between 12 and 24 hours after surgery had a TnT drawn immediately, and testing continued as previously reported. All TnT measurements were analyzed at the participating hospitals. TnT results were reported to the attending physicians.

Throughout each patient's hospital stay, research personnel performed clinical evaluations, reviewed medical records, ensured patients had TnT measurements drawn, and noted outcome events. The primary outcome was mortality at 30 days after surgery. Centers also reported the cause of death (vascular or nonvascular, definitions in eAppendix 2 available at http://www.jama.com). Patients were phoned at 30 days after surgery. If patients (or next of kin) indicated the occurrence of an outcome, their physicians were contacted to obtain documentation. Research personnel at participating centers submitted the case report forms and supporting documentation directly to the data management system (iDataFax, coordinating center, McMaster University, Hamilton, Ontario, Canada).

Data monitoring in VISION consisted of central data consistency checks, statistical monitoring, and on-site monitoring for all centers. For the on-site monitoring, the central coordinator randomly selected participants with and without a perioperative complication, and independent monitors audited their medical records and all other supporting documents. No center stood out regarding results from central data consistency checks or statistical monitoring. On-site monitoring demonstrated no major discrepancies between the submitted data and the monitoring findings, except for a systematic error in recording the duration of perioperative hemodynamic compromise at 2 centers. This was corrected and subsequent on-site monitoring at these 2 centers demonstrated no substantial errors.

Statistical Analyses

The analyses related to the association between TnT and 30-day mortality were planned prior to evaluating any of the data. Patients who did not complete the 30-day follow-up were censored on the last day their vital status was known. We determined the percentage of patients who died within 30 days after surgery and the associated 95% CI. We undertook a Cox proportional hazards model in which the dependent variable was mortality until 30 days after surgery, and the independent variables included 24 preoperative variables (eAppendix 3). The model was repeated adding the peak fourth-generation TnT measurement during the first 3 days after surgery as an independent variable and a minimum *P* value approach was used to determine if there were TnT threshold values that independently altered the patients' risk of mortality.[8] This approach evaluated every possible threshold of TnT (eg, $\leq$0.01 vs $>$0.01; $\leq$0.02 vs $>$0.02) in the multivariable model with the 24 preoperative variables. This analysis showed the TnT value that demonstrated the smallest statistically significant *P* value was a TnT threshold that independently predicted 30-day mortality. Subsequently, this threshold was fixed and the multivariable analysis was repeated to determine if there was another statistically significant threshold

in addition to the first threshold. The multivariable analysis was repeated until we were no longer able to identify another statistically significant TnT threshold. The Kruskal-Wallis test was used to identify any statistically significant differences in the median time from the peak TnT value to death across the TnT thresholds that independently predicted mortality.

For all independent predictors of 30-day mortality, we report the adjusted hazard ratio (aHR), 95% CI, and associated *P* value (a priori 2-sided $\alpha = .05$ was designated as statistically significant). For the TnT thresholds that independently predicted 30-day mortality, we determined the aHRs and their 95% CIs through bootstrapping 1000 samples. We undertook a random-effects (frailty) Cox model to adjust for any potential site-clustering effect.[9] We calculated the population attributable risk for the independent predictors of 30-day mortality.[10,11] The population attributable risk represents the proportion of all deaths potentially attributable to the relevant risk factor (eg, an elevated TnT measurement) if causality were proven. For the TnT thresholds that independently predicted 30-day mortality, we determined the likelihood ratios. For the model that included the peak TnT measurement, discrimination was assessed through evaluation of the C index and calibration with a goodness-of-fit test.[12-14] The difference in the C index between the model that included the peak TnT measurement and the model that only included preoperative variables was examined using 1000 bootstrap samples. Assessment of improved risk classification, as demonstrated in the model that included the peak TnT measurement vs the model that only included preoperative variables, was made by calculating the net reclassification improvement.[15] For this analysis we classified 30-day mortality as low risk (<1%), intermediate risk (1%-5%), high risk (>5%-10%), and very high risk (>10%).

In patients for whom preoperative creatinine was measured, we analyzed whether there was an interaction between patients' preoperative estimated glomerular filtration rate (eGFR) (<30 mL/min per 1.73 m^2 or receiving dialysis, 30 to 44 mL/min per 1.73 m^2, 45 to 59 mL/min per 1.73 m^2, and ≥60 mL/min per 1.73 m^2)[16,17] and the TnT thresholds that independently predicted 30-day mortality. For these analyses, we used a Cox proportional hazard model that incorporated a test for interaction and a priori $\alpha = .01$ was designated as statistically significant.

We undertook sensitivity analyses that excluded patients with a preoperative history of coronary artery disease, recent high-risk coronary artery disease, or congestive heart failure and a separate analysis excluding patients who died within 36 hours after surgery. In the sensitivity analyses that included the other preoperative variables, we determined if the TnT thresholds established in our model that included the peak TnT measurement continued to predict 30-day mortality. Additional sensitivity analyses were used to determine if the TnT thresholds that independently predict overall 30-day mortality predicted both vascular mortality and nonvascular mortality, based on the center's determination of the cause of death.

For all models, forced simultaneous entry (all candidate variables remained in the models) was used rather than automated stepwise selection because simulations demonstrate a higher risk of overfitting with the latter approach.[18,19] We assessed colinearity using the variance inflation factor that measures the extent to which the variance of the model coefficients are inflated (because of the correlation of a variable with other predictor variables) if that variable is included in the model. We considered variables with a variance inflation factor of greater than 10 to be colinear.[20] All analyses were performed using SAS version 9.2, except for the random-effect (frailty) Cox model that was performed using R, version 2.14.1.

RESULTS

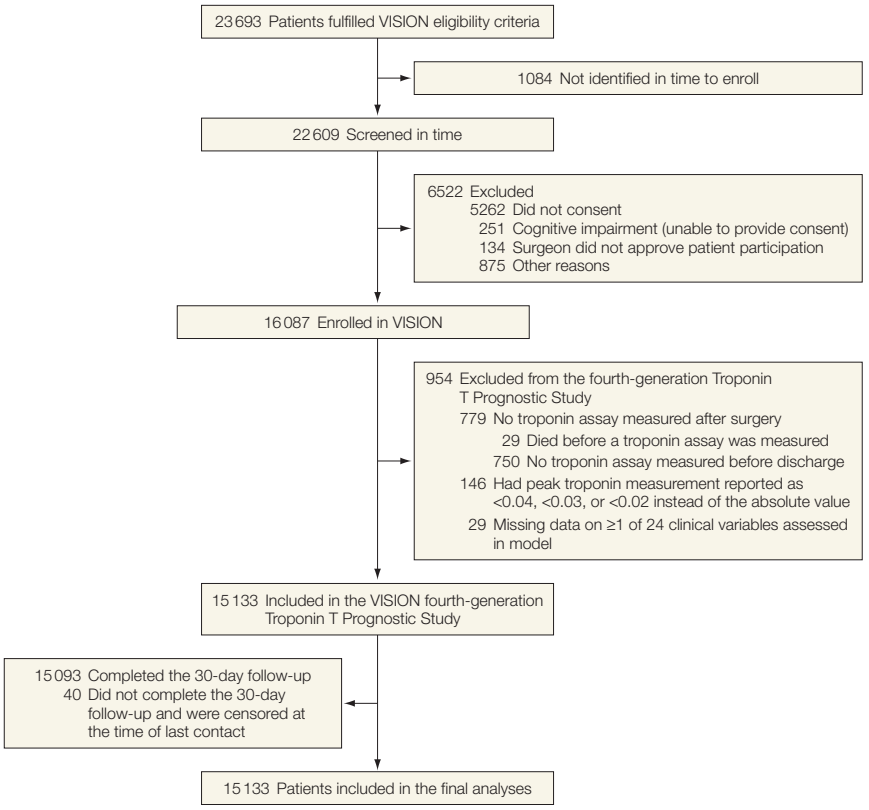
FIGURE 1 reports the patient flow. Of the 15 133 patients included in the VISION fourth-generation TnT prognostic study, 99.7% of the patients completed the 30-day follow-up. Centers that recruited patients from August 6, 2007 to January 11, 2011, are listed by location and number of patients in eTable 1.

eTable 2 reports the preoperative patient characteristics and the type of surgery. Approximately 1 in 4 patients (24.2%) were at least 75 years of age and 51.5% were women. The most common vascular risk factors were hypertension (50.9%) and diabetes (19.5%), and 26.5% of the patients had active cancer. The most common surgeries were major orthopedic surgery (20.4%), major general surgery (20.3%), and low-risk surgeries (39.4%). The median number of fourth-generation TnT measurements in the first 3 days after surgery was 3 (interquartile range [IQR] 2-4).

The 30-day mortality rate was 1.9% (282 deaths; 95% CI, 1.7%-2.1%), with 26.6% dying after hospital discharge (median time from discharge to death was 11.0 days; IQR, 4.0-15.0 days). **TABLE 1** presents the results of the preoperative Cox proportional hazards model. Eleven of the 24 variables assessed were independent predictors of 30-day mortality. Urgent/emergency surgery was the strongest preoperative predictor of 30-day mortality (aHR, 4.62; 95% CI, 3.57-5.98).

Using a minimum *P* value approach, multivariable analysis demonstrated that peak TnT threshold values of 0.02 ng/mL, 0.03 ng/mL, and 0.30 ng/mL were independently associated with 30-day mortality (Table 1). The random-effects (frailty) Cox model that adjusted for any potential site clustering effect produced similar results. A history of congestive heart failure and major vascular surgery independently predicted mortality in the preoperative model, but not in the model in-

Figure 1. Patient Flow Chart



cluding the peak TnT measurement. The strongest independent predictors of 30-day mortality were a peak TnT value of 0.03 to 0.29 ng/mL (aHR, 5.00; 95% CI, 3.72-6.76) and 0.30 ng/mL or greater (aHR, 10.48; 95% CI, 6.25-16.62). The independent prognostic factors identified in this model potentially explain the majority of the deaths that occurred (ie, the total population attributable risk was 89.0%; 95% CI, 85.3-92.4); the prognostically relevant peak TnT values had the largest population attributable risk (41.8%).

Peak TnT values of 0.01 ng/mL or less, 0.02 ng/mL, 0.03 to 0.29 ng/mL, and 0.30 ng/mL or greater occurred in 88.4%, 3.3%, 7.4%, and 0.9% of the patients, respectively. The incidence of 30-day mortality was 1.0%, 4.0%, 9.3%, and 16.9% in patients with a peak TnT values of 0.01 or less, 0.02, 0.03 to 0.29, and 0.30 ng/mL or greater, respectively. eTable 3 reports the likelihood ratios for these TnT thresholds. Patients with TnT values that were independently associated with mortality demonstrated the following median times from the peak TnT measurement to death: 0.02 ng/mL (13.5 days; IQR, 8.5-20 days); 0.03 to 0.29 ng/mL (9.0 days; IQR, 3.5-16 days); and 0.30 ng/mL or greater (6.5 days; IQR, 1.5-15 days), $P=.01$ for differences among time to death. FIGURE 2 reports Kaplan-Meier estimates for death based on the peak TnT values. eTable 4 reports the results of our sensitivity analysis that excluded patients who had a preoperative history of coronary artery disease, recent high-risk coronary artery disease, or congestive heart failure, and eTable 5 reports the results of our sensitivity analysis that excluded patients who died within the first 36 hours after surgery. Both sensitivity analyses demonstrated that results for the TnT thresholds did not appreciably differ from the model that included all 15 133 patients.

Each variable included in the models demonstrated a variance inflation factor of less than 10, suggesting no colinearity. The model that included the peak TnT measurement demonstrated good calibration (goodness-of-fit test $P=.43$). The model that included the peak TnT measurement demonstrated good discrimination, as did the preoperative model without TnT measurement (C index=0.85 vs 0.81; [difference, 0.4; 95% CI, 0.2-0.5] $P<.001$ for difference between C index values). Among the patients who died, the percentage correctly reclassified to a higher risk category with the model that included the peak TnT measurement compared with the model that only included preoperative risk factors was 18.8% (TABLE 2). Among the patients who survived, the percentage correctly reclassified to a lower risk category with the model that included the peak TnT measurement compared with the model that only included preoperative risk factors was 6.2%. The net reclassification improvement associated with TnT measurement was 25.0% (95% CI, 17.2%-32.8%; $P<.001$).

Of the 14 008 (92.6%) patients in whom preoperative creatinine levels were measured, 520 patients (3.7%) had an eGFR of less than 30 mL/min per 1.73 m^2 or were receiving dialysis; 760 patients (5.4%) had an eGFR of 30 to 44 mL/min per 1.73 m^2; 1496 patients (10.7%) had an eGFR of 45 to 59 mL/min per 1.73 m^2; and 11 232 patients (80.2%) had an eGFR of at least 60 mL/min per 1.73 m^2. There was no interaction between preoperative eGFR and the TnT thresholds ($P=.05$).

Among the 282 patients who died within 30 days of surgery, centers reported a vascular cause of death in 127 patients (45.0%) and a nonvascular cause in 155 patients (55.0%). TABLE 3 reports the independent predictors of 30-day vascular mortality and nonvascular mortality separately. The results for the TnT thresholds that independently predicted 30-day mortality were not appreciably different for vascular and nonvascular mortality. Among patients who experienced a TnT elevation 0.02 ng/mL or greater, this occurred at 6 to 12 hours after surgery, post-

operative day 1, postoperative day 2, and postoperative day 3 in 45.9%, 28.3%, 17.7%, and 8.2% of these patients, respectively. Considering the most serious nonvascular complications, the median time to a diagnosis of pneumonia was 6.0 days (IQR, 3.0-12.0 days), and the median time to a diagnosis of sepsis was 7.0 days (IQR, 4.0-12.0 days).

Table 1. Models to Predict 30-Day Mortality

			Model				
	Death Within 30 Days Postsurgery		Preoperative Variables Only		Preoperative Variables and Peak TnT		
Potential Risk Factor	No. Died/Total No.	% (95% CI)	aHR (95% CI)	*P* Value	aHR (95% CI)	*P* Value	Population AR (95% CI)
Age, y							
45-64	68/7697	0.9 (0.7-1.1)	1 [Reference]		1 [Reference]		39.7 (26.2-52.8)
65-74	68/3779	1.8 (1.4-2.3)	1.67 (1.18-2.36)	.004	1.57 (1.11-2.23)	.01	
≥75	146/3657	4.0 (3.4-4.7)	3.03 (2.20-4.18)	<.001	2.37 (1.71-3.28)	<.001	
Recent high-risk CAD	15/173	8.7 (5.3-13.8)	3.12 (1.71-5.68)	<.001	2.13 (1.17-3.88)	.01	2.4 (0.0-5.4)
No recent high-risk CAD	267/14 960	1.8 (1.6-2.0)	1 [Reference]		1 [Reference]		
PVD history	45/809	5.6 (4.2-7.4)	2.13 (1.47-3.10)	<.001	1.83 (1.27-2.66)	.001	7.9 (2.8-13.0)
No PVD history	237/14 324	1.7 (1.5-1.9)	1 [Reference]		1 [Reference]		
Stroke history	42/696	6.0 (4.5-8.1)	2.01 (1.42-2.84)	<.001	1.82 (1.29-2.57)	<.001	7.2 (2.5-12.1)
No stroke history	240/14 437	1.7 (1.5-1.9)	1 [Reference]		1 [Reference]		
COPD	65/1282	5.1 (4.0-6.4)	2.15 (1.61-2.89)	<.001	2.07 (1.54-2.78)	<.001	12.6 (6.7-18.5)
No COPD	217/13 851	1.6 (1.4-1.8)	1 [Reference]		1 [Reference]		
Active cancer	106/4015	2.6 (2.2-3.2)	2.38 (1.79-3.18)	<.001	2.32 (1.74-3.10)	<.001	20.6 (12.6-28.6)
No active cancer	176/11 118	1.6 (1.4-1.8)	1 [Reference]		1 [Reference]		
Urgent/emergency surgery[a]	123/2142	5.7 (4.8-6.8)	4.62 (3.57-5.98)	<.001	3.55 (2.73-4.60)	<.001	32.9 (25.8-40.1)
No urgent/emergency surgery	159/12 991	1.2 (1.0-1.4)	1 [Reference]		1 [Reference]		
Major general surgery	113/3076	3.7 (3.1-4.4)	3.25 (1.64-6.45)	<.001	3.16 (1.59-6.29)	.001	23.6 (15.9-31.3)
No major general surgery	169/12 057	1.4 (1.2-1.6)	1 [Reference]		1 [Reference]		
Major neurosurgery	25/888	2.8 (1.9-4.1)	3.72 (1.68-8.20)	.001	3.44 (1.55-7.62)	.002	5.6 (2.3-9.2)
No major neurosurgery	257/14 245	1.8 (1.6-2.0)	1 [Reference]		1 [Reference]		
Peak TnT measurement							
≤0.01 ng/mL	134/13 376	1.0 (0.8-1.2)	1 [Reference]		1 [Reference]		41.8 (34.5-49.0)
0.02 ng/mL	20/494	4.0 (2.6-6.2)			2.41 (1.33-3.77)	<.001	
0.03-0.29 ng/mL	104/1121	9.3 (7.7-11.1)			5.00 (3.72-6.76)	<.001	
≥0.30 ng/mL	24/142	16.9 (11.6-23.9)			10.48 (6.25-16.62)	<.001	
Predictive in the Preoperative Model but Not Predictive in the Model That Included TnT Measurements							
CHF history	37/703	5.3 (3.8-7.2)	1.60 (1.09-2.36)	.02	1.20 (0.82-1.77)	.35	NA
No CHF history	245/14 430	1.7 (1.5-1.9)	1 [Reference]		1 [Reference]		
Major vascular surgery	19/504	3.8 (2.4-5.8)	2.38 (1.04-5.47)	.04	2.10 (0.92-4.79)	.08	NA
No major vascular surgery	263/14 629	1.8 (1.6-2.0)	1 [Reference]		1 [Reference]		
Not Predictive in the Preoperative Model or the Model That Included TnT Measurements							
Men	151/7339	2.1 (1.8-2.4)	1 [Reference]	.55	1 [Reference]	.96	NA
Women	131/7794	1.7 (1.4-2.0)	0.93 (0.72-1.19)		1.01 (0.79-1.29)		
CAD history	56/1832	3.1 (2.4-3.9)	0.85 (0.60-1.21)	.37	0.73 (0.51-1.05)	.09	NA
No CAD history	226/13 301	1.7 (1.5-1.9)	1 [Reference]		1 [Reference]		
Cardiac arrest history	1/68	1.5 (0.3-7.9)	0.63 (0.09-4.62)	.65	0.70 (0.10-5.05)	.72	NA
No cardiac arrest history	281/15 065	1.9 (1.7-2.1)	1 [Reference]		1 [Reference]		
TIA history	7/376	1.9 (0.9-3.8)	0.54 (0.25-1.15)	.11	0.48 (0.22-1.04)	.06	NA
No TIA history	275/14 757	1.9 (1.7-2.1)	1 [Reference]		1 [Reference]		
DVT or PE history	11/475	2.3 (1.3-4.1)	1.09 (0.59-2.01)	.78	1.03 (0.56-1.90)	.92	NA
No DVT or PE history	271/14 658	1.8 (1.6-2.1)	1 [Reference]		1 [Reference]		
Diabetes	74/2952	2.5 (2.0-3.1)	1.16 (0.88-1.54)	.29	1.08 (0.81-1.43)	.60	NA
No diabetes	208/12 181	1.7 (1.5-2.0)	1 [Reference]		1 [Reference]		
Hypertension	180/7709	2.3 (2.0-2.7)	1.05 (0.80-1.38)	.71	0.93 (0.71-1.22)	.61	NA
No hypertension	102/7424	1.4 (1.1-1.7)	1 [Reference]		1 [Reference]		
Current atrial fibrillation	20/504	4.0 (2.6-6.0)	0.98 (0.60-1.59)	.92	1.03 (0.63-1.66)	.91	NA
No current atrial fibrillation	262/14 629	1.8 (1.6-2.0)	1 [Reference]		1 [Reference]		
Obstructive sleep apnea	11/773	1.4 (0.8-2.5)	0.90 (0.49-1.65)	.73	0.94 (0.51-1.72)	.83	NA
No obstructive sleep apnea	271/14 360	1.9 (1.7-2.1)	1 [Reference]		1 [Reference]		
Major orthopedic surgery	63/3094	2.0 (1.6-2.6)	1.74 (0.84-3.63)	.12	1.64 (0.79-3.41)	.18	NA
No major orthopedic surgery	219/12 039	1.8 (1.6-2.1)	1 [Reference]		1 [Reference]		
Major URO/GYN surgery	10/1888	0.5 (0.3-1.0)	0.59 (0.27-1.27)	.18	0.55 (0.26-1.18)	.12	NA
No URO/GYN surgery	272/13 245	2.1 (1.8-2.3)	1 [Reference]		1 [Reference]		
Major thoracic surgery	7/376	1.9 (0.9-3.8)	1.70 (0.64-4.49)	.28	1.61 (0.60-4.33)	.34	NA
No major thoracic surgery	275/14 757	1.9 (1.7-2.1)	1 [Reference]		1 [Reference]		

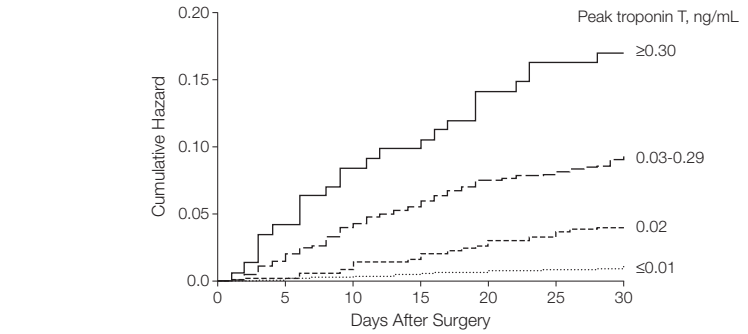
Abbreviations: aHR, adjusted hazard ratio; AR, attributable risk; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DVT, deep venous thrombosis; GYN, gynecological; NA, not applicable; PE, pulmonary embolus; PVD, peripheral vascular disease; TnT, troponin T; URO, urological.

[a] First, urgent and emergency surgery variables were evaluated separately, giving very similar hazard ratios. Next, these 2 surgical categories were combined.

COMMENT

In this international prospective cohort study of 15 133 patients who were at least 45 years of age and underwent noncardiac surgery that required hospital admission, multivariable analysis demonstrated that fourth-generation peak TnT thresholds of 0.02 ng/mL, 0.03 ng/mL, and 0.30 ng/mL independently predicted 30-day mortality. Peak TnT values after noncardiac surgery proved the strongest predictors of 30-day mortality, and the population attributable risk analysis suggested elevated TnT measurements after surgery may explain 41.8% of the deaths. Based on the identified peak TnT values, there were marked increases in the absolute risk of 30-day mortality (ie, 1.0% for a TnT value ≤0.01 ng/mL; 4.0% for a value of 0.02 ng/mL; 9.3% for a value of 0.03-0.29 ng/mL; and 16.9% for a value ≥0.30 ng/mL); 11.6% of patients had a prognostically relevant peak TnT value of at least 0.02 ng/mL. The higher the peak TnT value, the shorter the median time to death. Our net reclassification improvement analysis demonstrated that monitoring TnT values for the first 3 days after surgery substantially improved 30-day mortality risk stratification compared with assessment limited to preoperative risk factors.

Figure 2. Kaplan-Meier Estimates of 30-Day Mortality Based on Peak Troponin T Values



No. at risk

Peak troponin T, ng/mL							
≥0.30	142	136	129	127	121	118	117
0.03-0.29	1121	1103	1075	1058	1036	1030	1018
0.02	494	492	489	485	480	477	473
≤0.01	13376	13348	13300	13271	13250	13230	13209

Strengths and Limitations

Strengths of this study include the large sample of patients undergoing noncardiac surgery from 8 countries in 5 continents. Our results were consistent across sites for the TnT thresholds, suggesting they are relevant to contemporary surgery worldwide. All patients had the same fourth-generation TnT assay measured after surgery. A total of 99.7% of the patients completed the 30-day follow-up. We had complete data on the 24 preoperative variables that we evaluated. The model that included the peak TnT measurement demonstrated good discrimination and calibration.

Rather than evaluating predetermined values, we statistically identified prognostically relevant TnT thresholds. Thresholds based on 99th percentiles or coefficients of variation of less than 10%, although commonly used, are arbitrary. Studies that demonstrate worse prognosis above these thresholds do not confirm these thresholds are where risk is actually changing. Such results may be driven by the poor outcomes of patients with TnT measurements substantially above these thresholds. Further, some patients with troponin values immediately below these thresholds may have poor outcomes, but their signal may get washed out by the larger patient population with even lower troponin values who have few or no events. It is for this reason that we believe statistically

Table 2. Net Reclassification Improvement of Predicted Probability of 30-Day Mortality With the Model That Included the Peak TnT Measurement Compared With the Model Based Only on the Preoperative Risk Factors[a]

	Models for 30-Day Probability of Death							
	Includes Peak TnT Measurement							
	Died, No.				Survived, No.			
Preoperative Risk Factors Only	<1%	1%-5%	>5%-10%	>10%	<1%	1%-5%	>5%-10%	>10%
<1%	25	16	0	0	8014	496	15	0
1%-5%	10	68	21	22	1488	3398	290	183
>5%-10%	0	20	13	30	0	419	148	133
>10%	0	1	5	51	0	35	92	140

Abbreviation: TnT, troponin T.

[a] The number of patients who were reclassified to a higher risk category based on the model that included the peak TnT measurement compared with the model that only included preoperative risk factors was 89 among the patients who died and 1117 among those who survived. The number of patients who were reclassified to a lower risk category based on the model that included the peak TnT measurement compared with the model that only included preoperative risk factors was 36 among the patients who died and 2034 among those who survived. Among the patients who died, the percentage correctly reclassified to a higher risk category when both models were compared was 89 minus 36, divided by the total number of patients who died (282), which equals 18.8%. Among the patients who survived, the percentage correctly reclassified to a lower risk category when both models were compared was 2034 minus 1117, divided by the total number of patients who survived (14 851), which equals 6.2%. The net reclassification improvement is the sum of the percentages of correctly reclassified individuals who did and did not survive (ie, 18.8% + 6.2% = 25.0% [95% CI, 17.2%-32.8%] $P<.001$).

identifying prognostically relevant TnT thresholds based on the actual data are a more appropriate method.

This study also has limitations. We did not measure a TnT value prior to surgery and cannot comment on how a preoperative value would impact risk prediction. We only measured the fourth-generation TnT assay, and therefore cannot comment on the prognostic relevance of other troponin assays. Despite our large sample size, only 1263 patients had a peak troponin threshold of 0.03 ng/mL or greater. Therefore, it is possible with an even larger cohort that we may have identified another statistically significant and prognostically relevant TnT threshold between 0.03-0.29 ng/mL and at greater than 0.30 ng/mL. Although we did not demonstrate an interaction between preoperative eGFR and the TnT thresholds, we cannot exclude an interaction, especially at lower levels of renal function. Our results are, however, consistent with a prior large (N=7033) acute coronary syndrome study that demonstrated TnT levels predicted 30-day mortality regardless of patients' baseline eGFR.[21] We did not capture whether patients were recruited prior to or after surgery, and therefore we cannot evaluate these subgroups of patients separately. We did not record whether any actions were taken based on the TnT values reported to physicians, and therefore we cannot comment on the potential impact of any such interventions. If physicians implemented therapies based upon these TnT measurements and these interventions impacted 30-day mortality, then our 30-day mortality rates associated with elevated TnT measurements likely represent the mortality rates future unblinded physicians can expect in their clinical practice.

Comparison to Other Studies

Levy et al[22] undertook a meta-analysis of 10 studies (N=1728 patients) that assessed the independent prognostic capabilities of an elevated troponin measurement after noncardiac surgery to predict intermediate-term (<12 months) mortality and demonstrated an odds ratio of 6.7 (95% CI, 4.1-10.9; I^2=0%).[22] The studies in this meta-analysis used several different troponin assays, numerous different troponin thresholds, and did not evaluate the impact on short-term mortality (<30 days). Le Manach et al[7] demonstrated in a study of 1136 abdominal aortic surgical cases that a Dade-Behring Troponin I measurement of greater than 1.5 ng/mL was an independent predictor of in-hospital mortality. Our study included a much broader spectrum of noncardiac surgeries and a much larger sample size.

Interpretation

We have demonstrated that the peak fourth-generation TnT measurement in the first 3 days after surgery strongly

Table 3. Perioperative Independent Predictors of 30-Day Causes of Death (Vascular and Nonvascular) as Reported by Centers

	Vascular Mortality (n = 127)			Nonvascular Mortality (n = 155)		
Potential Independent Predictors	No./No.[a]	% (95% CI)	Adjusted HR (95% CI)	No./No.[a]	% (95% CI)	aHR (95% CI)
Age, y						
45-64	24/7697	0.3 (0.2-0.5)	1 [Reference]	44/7697	0.6 (0.4-0.8)	1 [Reference]
65-75	25/3779	0.7 (0.4-1.0)	1.59 (0.90-2.81)	43/3779	1.1 (0.8-1.5)	1.56 (1.02-2.38)
≥75	78/3657	2.1 (1.7-2.7)	3.29 (2.03-5.35)	68/3657	1.9 (1.5-2.4)	1.83 (1.22-2.74)
Recent high-risk CAD	11/173	6.4 (3.6-11.0)	2.48 (1.30-4.73)	4/173	2.3 (0.9-5.8)	0.95 (0.34-2.60)
No recent high-risk CAD	116/14 960	0.8 (0.6-0.9)	1 [Reference]	151/14960	1.0 (0.9-1.2)	1 [Reference]
History of PVD	23/809	2.8 (1.9-4.2)	1.66 (1.03-2.67)	22/809	2.7 (1.8-4.1)	2.07 (1.29-3.32)
No history of PVD	104/14 324	0.7 (0.6-0.9)	1 [Reference]	133/14324	0.9 (0.8-1.1)	1 [Reference]
History of stroke	28/696	4.0 (2.8-5.8)	2.66 (1.72-4.10)	14/696	2.0 (1.2-3.3)	1.15 (0.66-2.03)
No history of stroke	99/14 437	0.7 (0.6-0.8)	1 [Reference]	141/14437	1.0 (0.8-1.2)	1 [Reference]
COPD	36/1282	2.8 (2.0-3.9)	2.65 (1.78-3.95)	29/1282	2.3 (1.6-3.2)	1.63 (1.07-2.47)
No COPD	91/13 851	0.7 (0.5-0.8)	1 [Reference]	126/13851	0.9 (0.8-1.1)	1 [Reference]
Active cancer	29/4015	0.7 (0.5-1.0)	1.14 (0.72-1.79)	77/4015	1.9 (1.5-2.4)	3.17 (2.22-4.53)
No active cancer	98/11 118	0.9 (0.7-1.1)	1 [Reference]	78/11118	0.7 (0.6-0.9)	1 [Reference]
Urgent/emergency surgery	58/2142	2.7 (2.1-3.5)	3.26 (2.24-4.75)	65/2142	3.0 (2.4-3.8)	4.26 (3.00-6.04)
No urgent/emergency surgery	69/12 991	0.5 (0.4-0.7)	1 [Reference]	90/12991	0.7 (0.6-0.9)	1 [Reference]
Major general surgery	36/3076	1.2 (0.8-1.6)	1.57 (1.04-2.38)	77/3076	2.5 (2.0-3.1)	3.04 (2.15-4.31)
No major general surgery	91/12 057	0.8 (0.6-0.9)	1 [Reference]	78/12057	0.6 (0.5-0.8)	1 [Reference]
Major neurosurgery	12/888	1.4 (0.8-2.3)	2.46 (1.32-4.58)	13/888	1.5 (0.9-2.5)	2.74 (1.49-5.03)
No major neurosurgery	115/14 245	0.8 (0.7-1.0)	1 [Reference]	142/14245	1.0 (0.8-1.2)	1 [Reference]
Peak TnT measurement						
≤0.01 ng/mL	56/13 376	0.4 (0.3-0.5)	1 [Reference]	78/13376	0.6 (0.5-0.7)	1 [Reference]
0.02 ng/mL	7/494	1.4 (0.7-2.9)	1.65 (0.74-3.67)	13/494	2.6 (1.5-4.4)	3.25 (1.78-5.94)
0.03-0.29 ng/mL	51/1121	4.5 (3.5-5.9)	4.81 (3.18-7.25)	53/1121	4.7 (3.6-6.1)	5.06 (3.47-7.38)
≥0.30 ng/mL	13/142	9.2 (5.4-15.0)	10.01 (5.30-18.90)	11/142	7.7 (4.4-13.3)	9.20 (4.79-17.65)

Abbreviations: aHR, adjusted hazard ratio; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; TnT, troponin T.
[a]No./No., number of patients who died in subgroup /total number of patients in subgroup.

predicts 30-day mortality and may explain a substantial proportion of the deaths (41.8%). Compared with our preoperative model, the model that included the peak TnT measurement demonstrated an absolute increase in the C index value of 0.04. We also classified 30-day mortality as low risk (<1%), intermediate risk (1%-5%), high risk (>5%-10%), and very high risk (>10%) and with our model that included the peak TnT measurement, we demonstrated among patients who died and also among those who survived an improvement in reclassification of 18.8% and 6.2%, respectively. Although these data suggest improvement in risk classification with postoperative troponin measurements, what is now required is to undertake clinical trials to determine if this risk is modifiable.

Based on the guideline recommendation that abnormal troponin values should have a coefficient of variation less than 10%, many laboratories consider a fourth-generation TnT measurement of at least 0.04 ng/mL abnormal.[23,24] Our study suggests that TnT values of less than the commonly used threshold of 0.04 ng/mL (ie, 0.02 ng/mL and 0.03 ng/mL) are, in the context of noncardiac surgery, strongly associated with 30-day mortality. Given that troponin biomarkers have nearly absolute myocardial tissue specificity and the median time to death from a peak TnT value of 0.02 ng/mL (ie, 13.5 days) and 0.03 ng/mL (9.0 days), these lower TnT values may represent a warning myocardial insult.[25]

Consideration that more than 200 million adults undergo major noncardiac surgery annually,[1] potentially half of these patients are at least 45 years of age,[2] and 11.6% of the patients in our study had a peak TnT value of at least 0.02 ng/mL, suggests that worldwide more than 10 million adults may have prognostically relevant troponin values after noncardiac surgery each year. Although no randomized controlled trial has established an effective treatment for patients with an elevated troponin measurement after noncardiac surgery, the prognosis of these patients may be modifiable. First, the high-quality evidence for acetylsalicylic acid (ASA) and statin therapy in the nonoperative setting,[26,27] and encouraging observational data from a large international perioperative trial showing an association with use of these drugs and decreased 30-day mortality in patients who have experienced a perioperative myocardial injury,[28] suggests that ASA and statin therapy may benefit patients with an elevated perioperative troponin measurement. We have previously demonstrated that a substantial proportion of patients experiencing a myocardial injury after noncardiac surgery do not receive these drugs.[28] Second, the timeline from the peak TnT value until death demonstrates that there is time to intervene.

Third, although study centers deemed approximately half the deaths as having nonvascular causes, it is possible that these events may also be modifiable through enhanced cardiovascular management. Because the majority of patients who experience a perioperative myocardial infarction after noncardiac surgery do not experience ischemic symptoms,[28] physicians may have missed diagnosing some of the patients with a prognostically relevant TnT value after surgery as having a cardiac event.

Further, undiagnosed and untreated myocardial injury may decrease the likelihood of surviving a nonvascular complication. For example, although pneumonia is a serious complication that can result in death after noncardiac surgery,[29] it is possible that patients who first experience a myocardial injury may have a higher likelihood of developing pneumonia, a greater risk of dying if they do develop pneumonia, or both. In this study, 74.2% of patients who would develop an elevated TnT measurement did so within the first 24 hours after surgery, whereas the median time to develop pneumonia was 6 days after surgery. These considerations may explain the association between the prognostically relevant TnT thresholds and nonvascular death in our sensitivity analysis, and suggest that intervention in those with elevated troponin could decrease deaths classified as nonvascular.

Although noncardiac surgery has enormous potential to help patients, many patients die within 30 days of surgery (1.9% in VISION). Our study demonstrates that prognostically relevant TnT measurements after surgery strongly predict who will die within 30 days of surgery. Although at present, troponin measurements are not commonly measured after noncardiac surgery, the simplicity of this test and its prognostic power suggest it may have substantial clinical utility. There is now a need for large randomized controlled trials to evaluate potential interventions to mitigate the high risk of death in patients who have an elevated troponin measurement after noncardiac surgery.

CONCLUSIONS

The peak fourth-generation TnT measurement in the first 3 days after noncardiac surgery is strongly associated with 30-day mortality. Our data suggest that 1 in 25 patients with a peak TnT measurement of 0.02 ng/mL, 1 in 11 patients with a peak TnT measurement of 0.03 to 0.29 ng/mL, and 1 in 6 patients with a peak TnT measurement of at least 0.30 ng/mL will die within 30 days of surgery. Monitoring postoperative TnT measurements can enhance risk stratification after noncardiac surgery. Although there are some encouraging observational data, clinical trials are needed to establish whether interventions can alter patients' risk of death based on an elevated troponin measurement after surgery.

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Online-Only Material: eAppendixes 1 through 3 and eTables 1 through 5 are available at http://www.jama.com.

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The Long-Term Impact of Early Cardiovascular Therapy Intensification for Postoperative Troponin Elevation After Major Vascular Surgery

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BACKGROUND: Acute cardiac events are a frequent cause of morbidity after vascular surgery. The impact of early evidence-based treatment for patients with an acute cardiac event after vascular surgery on long-term postoperative outcomes has not been extensively studied. We hypothesized that providing appropriate evidence-based treatment to patients with elevated postoperative cardiac troponin levels may limit long-term mortality.

METHODS: We conducted a study of 667 consecutive major vascular surgery patients with an elevated postoperative troponin I level. We then determined which of these patients received medical therapy as per the 2007 American College of Cardiology/American Heart Association recommendations for the medical management of patients with chronic stable angina. All patients with troponin elevation were then matched with 2 control patients without postoperative troponin elevation. Matching was done using logistic regression and nearest-neighbor matching methods. The primary study end point was 12 months survival without a major cardiac event (i.e., death, myocardial infarction, coronary revascularization, or pulmonary edema requiring hospitalization).

RESULTS: Therapy was intensified in 43 of 66 patients (65%) who suffered a troponin I elevation after surgery. Patients with a troponin I elevation not receiving intensified cardiovascular treatment had a hazard ratio (HR) of 1.77 (95% confidence interval (CI), 1.13–2.42; $P = 0.004$) for the primary study outcome as compared with the control group. In contrast, patients with a troponin I elevation who received intensified cardiovascular treatment had an HR of 0.63 (95% CI, 0.10–1.19; $P = 0.45$) for the primary outcome as compared with the control group. Patients with a troponin I elevation not receiving treatment intensification likely were at higher risk for a major cardiac event (HR, 2.80; 95% CI, 1.05–24.2; $P = 0.04$) compared with patients who did receive treatment intensification.

CONCLUSIONS: The main finding of this study was that in patients with elevated troponin I levels after noncardiac surgery, long-term adverse cardiac outcomes may likely be improved by following evidence-based recommendations for the medical management of acute coronary syndromes. (Anesth Analg 2014;119:1053–63)

Perioperative myocardial infarction (MI) after noncardiac surgery occurs commonly and as many as 1 in 10 of those who suffer a perioperative MI die within 30 days after surgery.[1] This increased mortality risk is also evident in patients with isolated postoperative troponin elevations (i.e., a postoperative troponin elevation without electrocardiogram (ECG) changes suggesting MI)[2–4] and is associated with a frequent incidence of short- and long-term adverse events, and prolonged hospitalization and increased costs.[5,6] The role of secondary prevention in patients suffering nonoperative MI has been well established, with guidelines advocating the aggressive use of medical therapy such as HMG-CoA reductase inhibitors (i.e., "statins"), antiplatelet drugs, β-adrenergic receptor blockers, and angiotensin-converting enzyme (ACE) inhibitors.[7,8] However, perioperative patient management has largely focused on MI prevention,[9–11] and few studies have attempted to determine the impact on patient outcome of using these secondary preventative therapies in patients with perioperative MI or isolated troponin elevation. A single retrospective study demonstrated that patients receiving combination therapy (i.e., ACE inhibitors, aspirin, β-blockers, statins) after vascular surgery had a lower 6-month mortality risk.[12] However, that study did not evaluate the impact on patients who suffered perioperative MI or isolated troponin elevation.

In this study of vascular surgery patients who suffered perioperative MI or isolated troponin elevation, we sought to determine the effect of early treatment with

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evidence-based medical therapy on short- and long-term major cardiac events. We hypothesized that providing appropriate secondary preventative treatment to patients with elevated postoperative cardiac troponin levels may limit long-term mortality.

METHODS

This observational study was performed in accordance with published guidelines for observational studies (Strengthening the Reporting of Observational Studies in Epidemiology [STROBE]),[13] with adaptations described below.

Study Design

We performed a retrospective, case-controlled study among all patients aged >18 years who underwent major vascular surgery between January 1, 2005, and July 15, 2008, in the Pitié-Salpêtrière Hospital, Paris, France, using the computerized Vascular Surgery Register. This system contains demographic and perioperative data for all patients admitted for vascular surgery since 1984.[5,14,15] The registry was established in 1984, and routine postoperative troponin surveillance was instituted in 1995. Our hospital switched from troponin I to high sensitivity troponin I in August 2008. As a result, we chose to conduct the current study by including patients undergoing surgery from January 1, 2005, to July 15, 2008.

Patients were considered eligible if they underwent elective infrarenal aortic reconstructive surgery (i.e., for aneurysm or occlusive disease of the aorta) during the study period. Patients undergoing emergency surgery or endoprosthetic procedures were not included. The study was approved by our institutional ethics committee (Comité de Protection des Personnes d'Ile-de-France VI, Groupe Hospitalier Pitié-Salpêtrière, Paris, France), and the requirement for written consent for this analysis was waived. To ensure full disclosure to our patients, we informed them that their data would be used for the purpose of this specific study and obtained their verbal consent before including them in the study.

Perioperative Management

All patients in this study underwent elective surgery and so were all investigated and managed according to standardized hospital protocols based on the recommendations of the American College of Cardiology/American Heart Association Task Force.[16,17] Surgery was performed under general anesthesia, with IV propofol, sufentanil, and atracurium. As previously described, patients presenting with postoperative hypertension >30% of baseline received nicardipine or clonidine, and those with tachycardia >80 bpm received an IV β blocker.[15] All patients received subcutaneous low molecular weight heparin until postoperative day 30. No uniform postoperative regimen for the treatment of perioperative MI or an isolated troponin elevation was prescribed, and the provision of all medications, including medical therapy of the treatment of coronary artery disease, was at the discretion of the attending physician.

Blood was obtained for measurement of cardiac troponin I (cTnI) in all patients on arrival at the postanesthetic care unit, on the first, second, and third postoperative days. This measurement was performed using an immunoenzymofluorometric assay on a Stratus autoanalyzer (Dade-Behring, Paris La Défense, France). An ECG was performed on arrival at the postanesthetic care unit, and on the first, second, and third postoperative days, and after the third day in the presence of clinical abnormalities and/or if the cTnI concentration was increased.

Definition of Variables and End Points

We defined an elevated troponin as an abnormal cTnI concentration at any time during the postoperative period.[18] The cutoff used defined normality was 0.15 ng/mL. This value corresponds to the 99th percentile for our laboratory during each study period.[19] The lower detection limit for cTnI assay was 0.03 ng/mL, and the interassay coefficient of variation was 8% at 1.5 ng/mL and 15% at 0.6 ng/mL.

Postoperative MI was defined as an elevated cTnI concentration associated with one of the following: symptoms of ischemia and/or ECG changes indicative of new ischemia (new ST–T changes or new left bundle branch block), development of pathological Q waves on the ECG, and/or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.[20]

The primary end point of the study was survival to 1 year after surgery, without experiencing a major cardiac event (i.e., MI, myocardial revascularization, or pulmonary edema requiring hospitalization).

Selection of Cases and Controls

Case subjects were patients with perioperative MI or an isolated troponin I elevation (hereafter referred to as a perioperative MI). From the remaining patients without perioperative MI, we selected 2 controls for each case. We used the following variables to match patients: the Revised Cardiac Risk Index,[21] age, sex, date, type of surgery (aneurysm or occlusive disease of the aorta), and presence of intraoperative complications. These variables were identified as independent predictors of adverse cardiac outcomes in a previous analysis of vascular patients from our hospital.[15]

Outcome and Postoperative Cardiovascular Treatment Analyses

Preoperative cardiovascular treatments and treatments at the time of hospital discharge were noted. Drug classes studied were antiplatelet drugs, statins, β-blockers, and ACE inhibitors. Each patient was subsequently interviewed by telephone at least 12 months after surgery to obtain information about the primary end point. The need for hospitalization for cardiac reasons after surgery was also determined. When patients indicated that an event had occurred, we contacted the patient's primary physician and obtained patient records to verify the diagnosis. When patients were hospitalized, medical records were checked to determine whether hospitalization was as a result of a cardiac complication.

Secondary Preventative Therapy Adjudication

Three cardiologists, each with a minimum of 10 years experience independently reviewed each patient's history to determine: (1) whether additional postoperative therapy

had been instituted as compared with the preoperative period; and (2) whether therapy at the end of the 1-year follow-up period was different from therapy at the time of hospital discharge.

Predefined rules were used to make this assessment. Additional cardiovascular therapy was defined as the new introduction of one of the 4 main cardiovascular drugs (antiplatelet, β-blockers, statins, or ACE inhibitors) during the postoperative period or a dose increase in those patients already taking such medication. Optimal cardiovascular treatment was defined as a patient receiving a drug from all 4 classes (i.e., antiplatelet, β-blocker, ACE inhibitor, and a statin) in compliance with the 2007 American College of Cardiology/American Heart Association recommendations for the medical management of patients with chronic stable angina.[22] The committee members reviewed the cases independently, were blinded for the outcome of the evaluated patients, and were not directly involved in any aspect of patient care.

Statistical Analysis

Summary statistics were constructed using frequencies and proportions for categorical data and means, medians, and interquartile ranges for continuous variables. We compared the baseline characteristics of patients with perioperative MI with those patients who did not suffer a perioperative MI. χ^2 and z tests were used to assess the relationship between a perioperative MI and any potential confounders.

The reliability of agreement among the 3 blinded experts was assessed using Fleiss κ test. The bootstrapped 95% confidence interval (CI) of the Fleiss κ was calculated, and the lower limit of the 95% CI is reported. It is assumed that a κ value between 0.61 and 0.80 denotes agreement, whereas a value higher than 0.81 relates to near substantial agreement. To evaluate the potential impact of allocation errors in this study, we reported any incomplete agreement among experts as allocation error, and we conducted simulations (Appendix) to evaluate their impact on the estimation of the treatment effect.

To select controls for patients with a perioperative MI, we first developed a propensity score to determine the estimated probability of suffering a perioperative MI based on preoperative and intraoperative predictors. We did this by creating a semiparsimonious logistic regression model to derive the probability of presenting with a perioperative MI. This model included 2 classes of predictors.[23] The first class of predictors reflects the preoperative state of each patient (history of coronary artery disease, preoperative renal failure, diabetes, etc.) and can be summarized by the Revised Cardiac Risk Index. For the second set of predictors, we used intraoperative variables that have been demonstrated to predict a perioperative MI, that is, the number of packed red blood cells transfused and the need for surgical reintervention, of any type, in the first 3 postoperative hours.[5,15] Model discrimination was assessed by calculating the area under the receiver operating characteristic curve (c-index), and its calibration was assessed using the Hosmer-Lemeshow statistic ($P > 0.05$ for no significant difference between the predictive model and the observed data). We performed cross validation, using a leave-one-out cross-validation method, to test the internal validity of the model and determined the prediction error of the model.

We then used a nearest neighbor matching technique to create case-control pairs. Nearest neighbor matching selects a patient with a perioperative MI (case) and then finds a patient among those without a perioperative MI (control) who has the closest propensity score to that of the case. For each case, we identified 2 controls. The goal of matching is to ensure that case and control groups resemble each other in everything but the presence of a perioperative MI. In well-matched groups, the distribution of the covariates of all variables will be similar, and such groups are referred to as "balanced." We evaluated the success of matching by comparing the standardized differences of all variables, including those not included in the matching procedure. The standardized difference is a percentage that is calculated by dividing the difference in the mean of a variable between the groups by the standard deviation (SD) of the variable. An absolute standardized difference above 10% to 15% is considered a meaningful imbalance.

The final step of the analysis was to estimate the effect additional cardiovascular treatment had on the study outcome. We created a survival curve (survivors without major cardiac events) for the 3 groups of patients (perioperative MI, perioperative MI with intensification, and control). To consider the matched nature of the population, we used a Cox proportional hazard model stratified on the matched pairs. Hazard ratios (HRs) were presented after bootstrap estimates. We have evaluated the robustness of our results with specific additional statistical analyses (Appendix). R 2.14 software (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analyses.[24]

RESULTS

Of the 667 patients screened, 20 (3%) were excluded due to missing data. Sixty-six (10%) of the 647 remaining patients suffered a perioperative MI. The study flowchart is shown in Figure 1, and the main clinical characteristics of the perioperative MI group are compared with the other patients in the study population in Table 1. Patients were followed for a mean of 14 months (range, 6–31 months). In the 66 patients who suffered a perioperative MI, 39 (59%) patients survived to follow-up without suffering a major adverse cardiac event.

The expert committee determined that 43 (65%) of the patients with a perioperative MI received additional cardiovascular medication during their hospitalization (κ = 0.90, lower 95% CI limit 0.79, incomplete agreement observed in 4 patients) and that of these 43 patients, 38 (88%) patients had received optimal cardiovascular treatment (i.e., a drug from all 4 classes) (κ = 0.81, lower 95% CI limit 0.46, incomplete agreement observed in 3 patients). Fifty-one (77%) patients with a perioperative MI had no modification to their cardiovascular treatment at the end of the follow-up (Fleiss κ = 0.90, lower 95% CI limit 0.74, incomplete agreement observed in 4 patients).

The logistic model used for matching cases with controls included age, sex, Revised Cardiac Risk Index, coronary artery disease, history of MI and/or heart failure, the type of aortic disease (aneurysm or occlusive disease of the

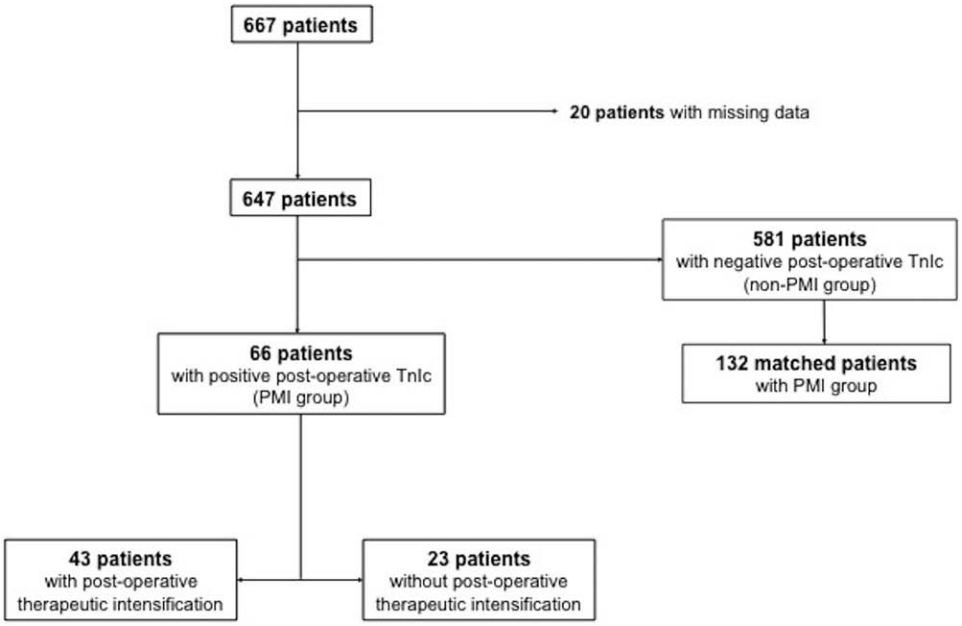


Figure 1. Flowchart of studied population.

Table 1. Preoperative and Surgical Characteristics of Entire Cohort

	No PMI group *n* = 581	PMI group *n* = 66	*P*
Demographic characteristics			
Age, y	67 ± 11	69 ± 10	0.2
Men	516 (88.8)	55 (83.3)	0.22
Medical history of			
Coronary artery disease	192 (33.0)	32 (48.5)	0.01
Previous myocardial infarction	111 (19.1)	16 (24.2)	0.33
Previous coronary revascularization	117 (20.1)	24 (36.4)	0.01
Previous CABG	48 (8.3)	6 (9.1)	0.82
Previous PCI	76 (13.1)	19 (28.8)	0.01
Heart failure	130 (22.4)	23 (34.8)	0.03
Hypertension	375 (64.5)	46 (69.7)	0.50
COPD	196 (33.7)	21 (31.8)	0.78
Chronic renal failure	71 (12.2)	14 (41.2)	0.05
Diabetes	89 (15.3)	11 (16.7)	0.72
Previous hemodialysis	6 (1.0)	2 (3.0)	0.19
RCRI stratification			
Mean Lee's Risk Index	1.83 ± 1.1	2.2 ± 1.1	0.01
1	311 (53.5)	25 (37.9)	0.03
2	113 (19.4)	13 (19.7)	
3	107 (18.4)	17 (25.8)	
≥4	50 (8.6)	11 (16.7)	
Surgical characteristics			
Abdominal aortic aneurysm	416 (71.6)	44 (66.7)	0.39
Combined surgery	184 (31.7)	26 (39.4)	0.2
Reoperation	46 (7.9)	19 (29.0)	<0.001
Perioperative transfusion >3 transfusion units	227 (39.1)	41 (62.1)	0.01

Values are mean ± SD or number (%).
CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; COPD = chronic obstructive pulmonary disease; PMI = perioperative myocardial infarction; RCRI = Revised Cardiac Risk Index.

aorta), the need for surgical reintervention, of any type, in the first 3 postoperative hours, and transfusion of >3 units of packed red blood cells. The c-index associated with this model was 0.73, and the Hosmer-Lemeshow test was $P = 0.80$ (4.62, degrees of freedom = 8). Furthermore, a cross-validation estimate of prediction error of 12.2% was retrieved after 10-fold cross validation (12.3% with the leave-one-out cross-validation method). This suggests that the model used to match the patients was robust, well-calibrated, and had a relatively good discriminative ability to predict a perioperative MI. After matching, the absolute standardized differences showed no severe imbalance between the characteristics of patients with a perioperative MI and those of the control group (Table 2).

Table 2. Characteristics of Matched Patients

	No PMI group *n* = 132	PMI group *n* = 66	Absolute standardized differences	
			Before matching	After matching
Demographic characteristics				
Age, y	70 ± 9	69 ± 11	23.5	4.2
Men	115 (87.1)	55 (83.3)	24.1	10.1
Medical history of				
Coronary artery disease	60 (45.5)	32 (48.5)	45.6	6.1
Previous myocardial infarction	31 (23.1)	16 (24.2)	18.3	1.8
Previous coronary revascularization	40 (30.1)	24 (36.4)	55.5	12.5
Heart failure	41 (31.1)	23 (34.8)	41.5	7.9
Hypertension	96 (72.7)	46 (69.7)	15.3	6.5
COPD	46 (34.8)	21 (31.8)	5.7	6.5
Chronic renal failure	27 (20.5)	14 (41.2)	37.6	1.8
Diabetes	25 (18.9)	11 (16.7)	5.3	6.1
Previous hemodialysis	0 (0)	2 (3.0)	25.6	17.6
RCRI stratification				
Mean Lee's Risk index	2.2 ± 1.2	2.2 ± 1.2	51.3	4.7
1	54 (41.9)	25 (37.9)	36.4	4.6
2	28 (21.2)	13 (19.7)		
3	27 (20.5)	17 (25.8)		
≥4	23 (17.4)	11 (16.7)		
Surgical characteristics				
Abdominal aortic aneurysm	98 (74.2)	44 (66.7)	15.4	15.9
Combined surgery	48 (36.4)	26 (39.4)	23.3	6.2
Reoperation	39 (29.5)	19 (29.0)	98.1	1.7
Perioperative transfusion > 3 transfusion units	87 (65.9)	41 (62.1)	66.3	7.7

Values are mean ± SD, number (%). Combined surgery: aortic surgery associated with another surgical vascular procedure (distal artery bypass, carotid endarterectomy).
COPD = chronic obstructive pulmonary disease; PMI = perioperative myocardial infarction; RCRI = Revised Cardiac Risk Index.

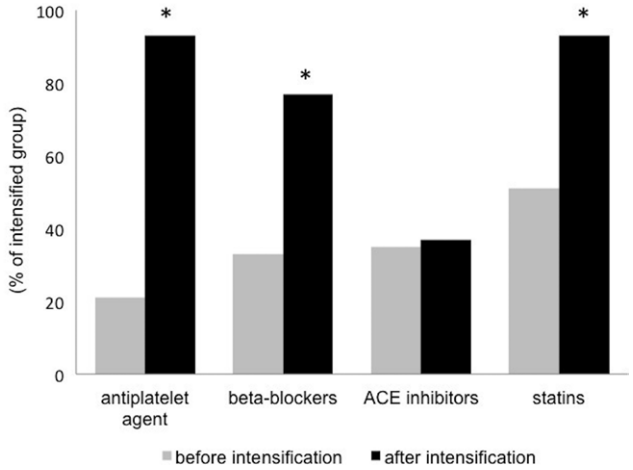


Figure 2. Evolution of cardiovascular treatments between the preoperative and postoperative periods in the treatment intensification group. Antiplatelet drugs, β-blockers, and statins were more frequently prescribed in the postoperative period than the preoperative period (93% vs 51%, 77% vs 33% and 93% vs 21%; respectively. *$P < 0.05$).

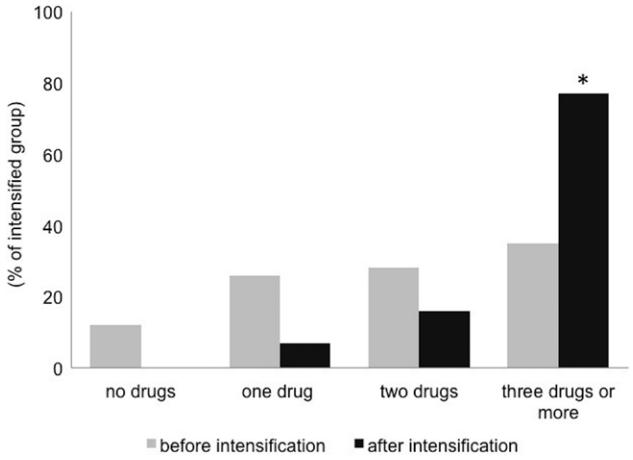


Figure 3. Use and combination of the 4 drug classes (antiplatelets, β-blockers, angiotensin-converting enzyme inhibitors, and statins) before and after intensification. Seventy percent of patients were treated with at least 3 drug classes during the postoperative period vs 35% during preoperative period (*$P < 0.05$).

Comparison Between Postoperative and Preoperative Periods

Figure 2 shows the type of medication that patients in the therapy intensification group were taking preoperatively and then at the time of hospital discharge. Statins, β-blockers, and antiplatelet drugs were prescribed significantly more frequently in the postoperative period than in the preoperative period (93% vs 51%; 77 vs 33%; and 93 vs 21%; $P < 0.001$, $P < 0.001$ and $P = 0.05$, respectively). Figure 3 shows the use of the 4 drug classes before surgery and after intensification of therapy. At least 77% of patients were treated with at least 3 drug groups vs 35% during the preoperative period. Seventy percent of patients were treated by a combination of antiplatelets, β-blockers, ACE inhibitors, and statins.

Survival Analysis

The first analysis evaluated the survival difference among 3 groups: (1) patients without perioperative MI, (2) patients with perioperative MI without treatment intensification, and (3) patients with perioperative MI with treatment

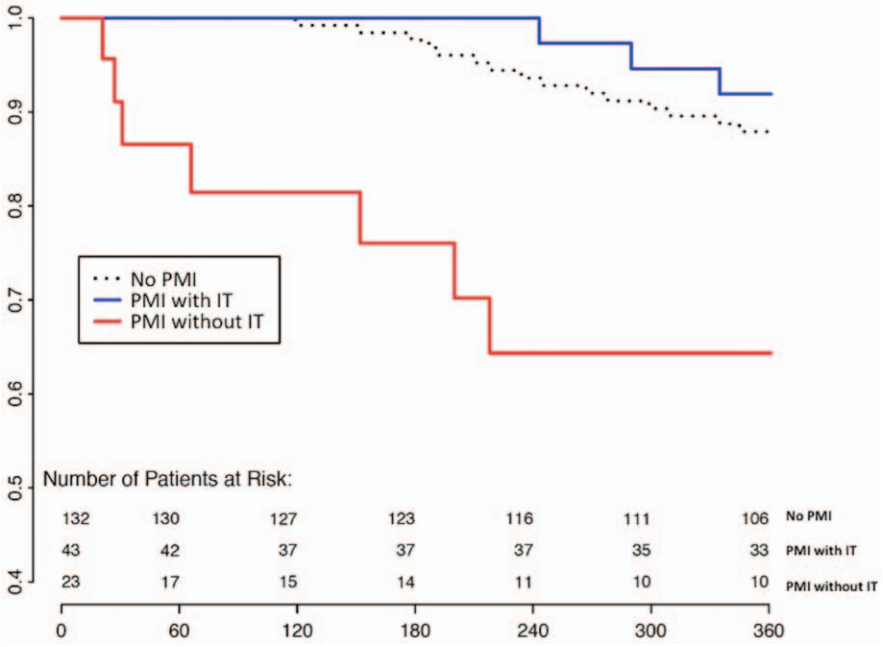


Figure 4. Major cardiac event-free survival of the 3 groups of patients: perioperative myocardial infarction with intensification (PMI with IT), perioperative MI without intensification (PMI without IT) and no perioperative MI). Patients not receiving treatment intensification were at higher risk for a major cardiac event (hazard ratio, 2.80; 95% confidence interval 1.05–24.2; $P = 0.04$) compared with patients who did receive treatment intensification. When patients with an elevated postoperative troponin received intensive postoperative therapy their life expectancy was similar to those who did not have a postoperative elevation ($P = 0.45$).

intensification. Patients with a perioperative MI and no modification of their cardiovascular treatment had a HR of 1.77 (95% CI, 1.13–2.42; $P = 0.004$) for the primary study outcome as compared with the control group. In contrast, patients with a perioperative MI who received intensified postoperative cardiovascular treatment had a HR of 0.63 (95% CI, 0.10–1.19; $P = 0.45$) for the primary outcome as compared with the control group (Fig. 4); When conducting the simulation analysis for this first survival analysis, we found that even when introducing 4 allocation errors, 95% of the simulated results still remained statistically significant (i.e., $P \leq 0.05$) (Appendix).

The second survival analysis compared 2 groups: (1) patients with perioperative MI receiving postoperative treatment intensification, and (2) patients with perioperative MI not receiving treatment intensification. Patients with a perioperative MI who did not receive treatment intensification had a HR of 2.80 (95% CI, 1.05–24.2; $P = 0.04$) compared with patients with a perioperative MI who did receive treatment intensification. The simulation analysis conducted in this smaller population found that the introduction of allocation errors had a greater impact on the robustness of our results (Appendix). The introduction of 3 allocation errors resulted in nonsignificant (i.e., $P > 0.05$) results in >35% of the cases.

DISCUSSION

The main finding of this study was that a long-term increase in adverse cardiovascular events (HR: 2.80; 95% CI, 1.05–24.2; $P = 0.04$) was observed in patients with perioperative cTnI elevation when they did not receive evidence-based medical therapy for the treatment of coronary artery disease. Furthermore, using Monte Carlo simulations, we demonstrated that this result was not dramatically affected by potential allocation errors related to the expert committee's disagreements (i.e., even when introducing 4 allocation errors, 54% of the simulated results still remained statistically significant). Our results further provide a rationale for a postoperative strategy of screening patients undergoing vascular surgery for elevations in cTnI after surgery and intensifying therapy using evidence-based medical treatments for coronary artery disease in patients demonstrating myocardial injury as a means for improving patient survival.

With the introduction of sensitive, cardiac-specific biomarkers such as cTnI, the ability to identify patients with perioperative MIs even in the absence of ECG changes or symptoms of myocardial ischemia has been greatly enhanced. Indeed, even small increases in perioperative cTnI concentrations have been found to be associated with poorer short-term[25] and long-term outcomes.[6] This correlation between perioperative cTnI concentration and the incidence of cardiac complications in the months after noncardiac surgery confirms the specificity of this biological marker as an indicator of myocardial injury. It is important to note that as was the case in this study, troponin elevations occur in most patients in the absence of anginal symptoms or ECG changes and, therefore, often go undetected by caregivers. Perioperative cTnI surveillance, thus, may not only enable early detection of patients at risk for short- and long-term morbidity and mortality, but they may also allow for the early initiation of appropriate therapeutic interventions.

Patients who suffer an acute coronary event are at very high risk of further coronary events. Although improvements in medical therapy over the past 2 decades have

reduced this risk significantly, it still remains high. In the medical setting, recent developments in secondary prevention have been suggested,[26] based on the findings of large, randomized trials. The routine use of 4 main prophylactic drug groups (antiplatelet drugs, β-blockers, ACE inhibitors, and statins) is now recommended by international guidelines for the secondary prevention of coronary artery disease.[27,28] Most postoperative patients suffer non-ST segment elevation MI[29], and it is likely that the use of these therapies in patients with isolated cTnI elevation[30] may improve patient outcomes.[31] It must, however, be appreciated that guidelines developed in nonoperative populations cannot necessarily be extrapolated to operative populations. The hemodynamic impact of instituting aggressive ACE or β-blocker therapy is unclear, and the bleeding risk associated with aggressive antiplatelet therapy remains to be investigated.

Our study has several limitations. First, this was a single-center, retrospective study, involving only 1 type of surgery (major vascular surgery), and therefore, we cannot generalize our results to all noncardiac surgeries. Second, elevation of cTnI plasma concentration was the single criterion for patient selection, and although troponin I offers high tissue specificity, it does not indicate the mechanism of myocardial injury.[32–34] We did not discern the etiology of the elevation of cTnI (coronary or otherwise) but treated it as a coronary injury using cardioprotective drugs. Third, there was a limited number of patients in this study that may further confound its interpretation for other groups of patients. As is the case in all survival analyses using a primary end point other than mortality, the possibility of competing risks cannot be excluded. Fourth, it is possible that, due to the small number of patients in the study, variation in how patients were allocated to treatment groups by the expert committee may impact the validity of the study finding. However, for both κ estimates, the lower bound of the 95% CI was well above 0.61, the threshold denoting substantial agreement. Finally, due to the small sample size, we were unable to obtain complete balance of the preoperative risk factors among the groups despite propensity matching.

CONCLUSIONS

The main finding of this study was that in patients with a perioperative MI, long-term outcomes may likely be improved by following evidence-based recommendations for the medical management of acute coronary syndromes.

APPENDIX

In our methodology, an expert committee evaluated whether, in their opinion, patients received postoperative intensification of cardiovascular treatment. Errors in the accuracy of this evaluation process would impact on the estimation of our treatment effect. We therefore conducted a simulation analysis to explore the impact of such errors on our results.

SIMULATION METHODS

We generated simulated populations using the original study population. Patients from the original population and their treatment allocations were changed to simulate allocation errors. When a randomly selected patient was "treated" in the original population, we considered him as "not treated" for the simulation. Conversely, when he was "not treated," we changed his allocation to "treated." We allowed the number of allocation errors (i.e., the number of patients who had their allocation changed) to vary from 1 to 4, and we conducted 10,000 replications for each scenario (i.e., 1 to 4 allocation changes). This procedure therefore generated 40,000 simulation populations.

Impact of Allocation Errors on the Survival Analyses

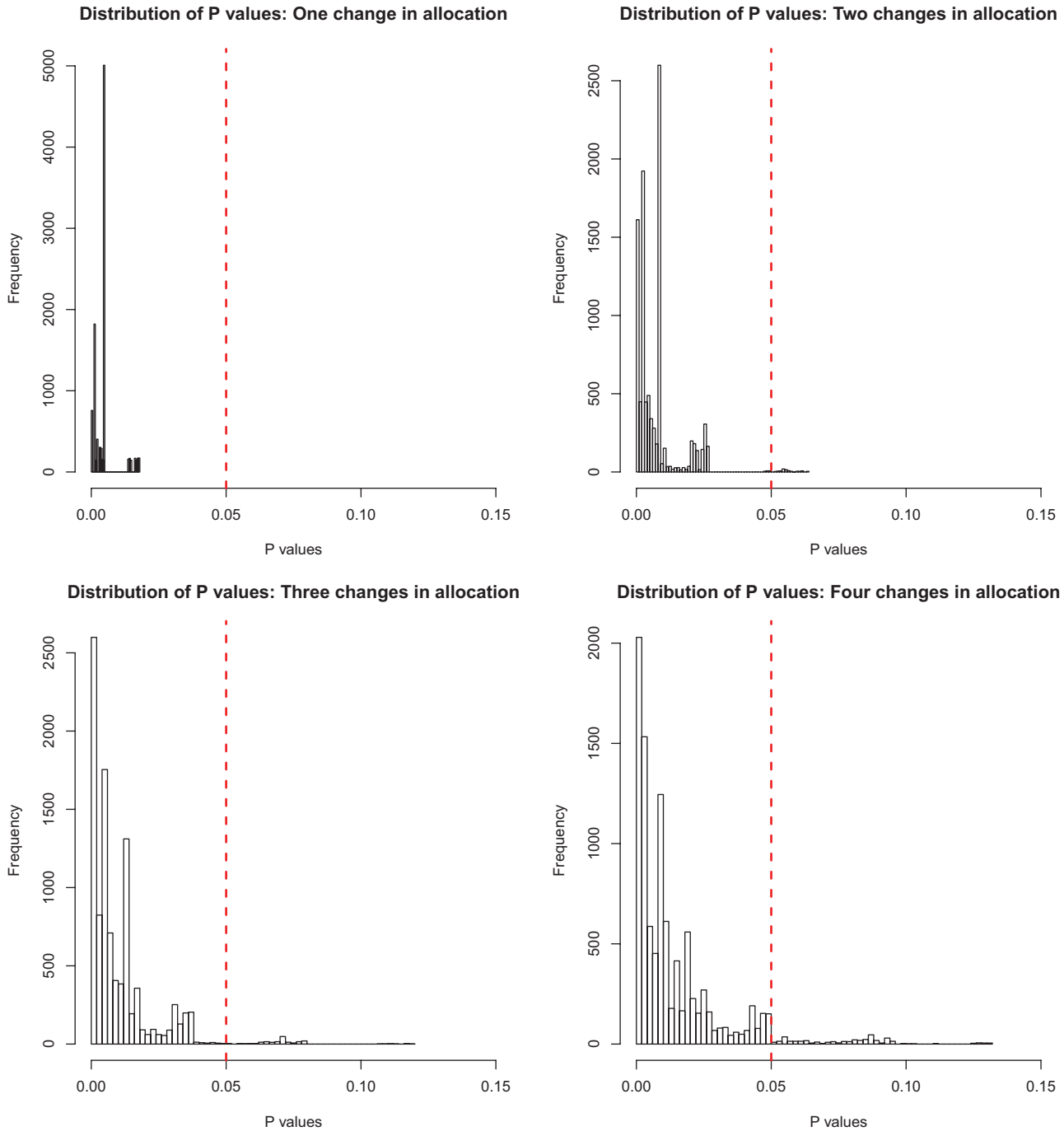
The first survival analysis included 198 patients and compared 3 groups: (1) patients without postoperative myocardial necrosis, (2) patients with postoperative myocardial necrosis without treatment intensification, and (3) patients with postoperative myocardial necrosis with treatment intensification. The results observed in the original population showed a HR of 1.77 (95% CI, 1.13–2.42; $P = 0.004$). When conducting the simulation analysis for this outcome (Appendix Figure 1), we found that even when introducing 4 allocation errors, 95% of the simulated results still remained statistically significant (i.e., $P \leq 0.05$). We therefore concluded that this analysis was unlikely to have been impacted by allocation errors made by the expert committee.

Although expert disagreements and allocation errors are not interchangeable, we considered that allocation errors are more likely to happen when incomplete agreement occurred. Pushing this argument to the extreme, we considered that any incomplete agreement (i.e., 1 expert disagreed with the 2 others regarding 1 patient's treatment) was an allocation error. As such, incomplete agreement was observed in 4 cases for this analysis; we concluded that these potential allocation errors had a limited impact on the estimation of the treatment effect in this analysis.

In a second simulation, we evaluate the survival analysis comparing patients with postoperative myocardial necrosis, with or without postoperative cardiovascular treatment intensification (2 groups, 66 patients). In the original population we found that long-term adverse cardiovascular events were more frequent (HR: 2.80; 95% CI, 1.05–24.2; $P = 0.04$) in patients without postoperative cardiovascular treatment intensification.

In this smaller population, the introduction of allocation errors had a greater impact on the robustness of our results (Appendix Figure 2). The introduction of 1 allocation error resulted in nonsignificant study results (i.e., $P > 0.05$) in 11.23% of cases, 3 allocation errors resulted in nonsignificant study results in 35% of cases, and 4 allocation errors resulted in nonsignificant study results in 45.41% of cases.

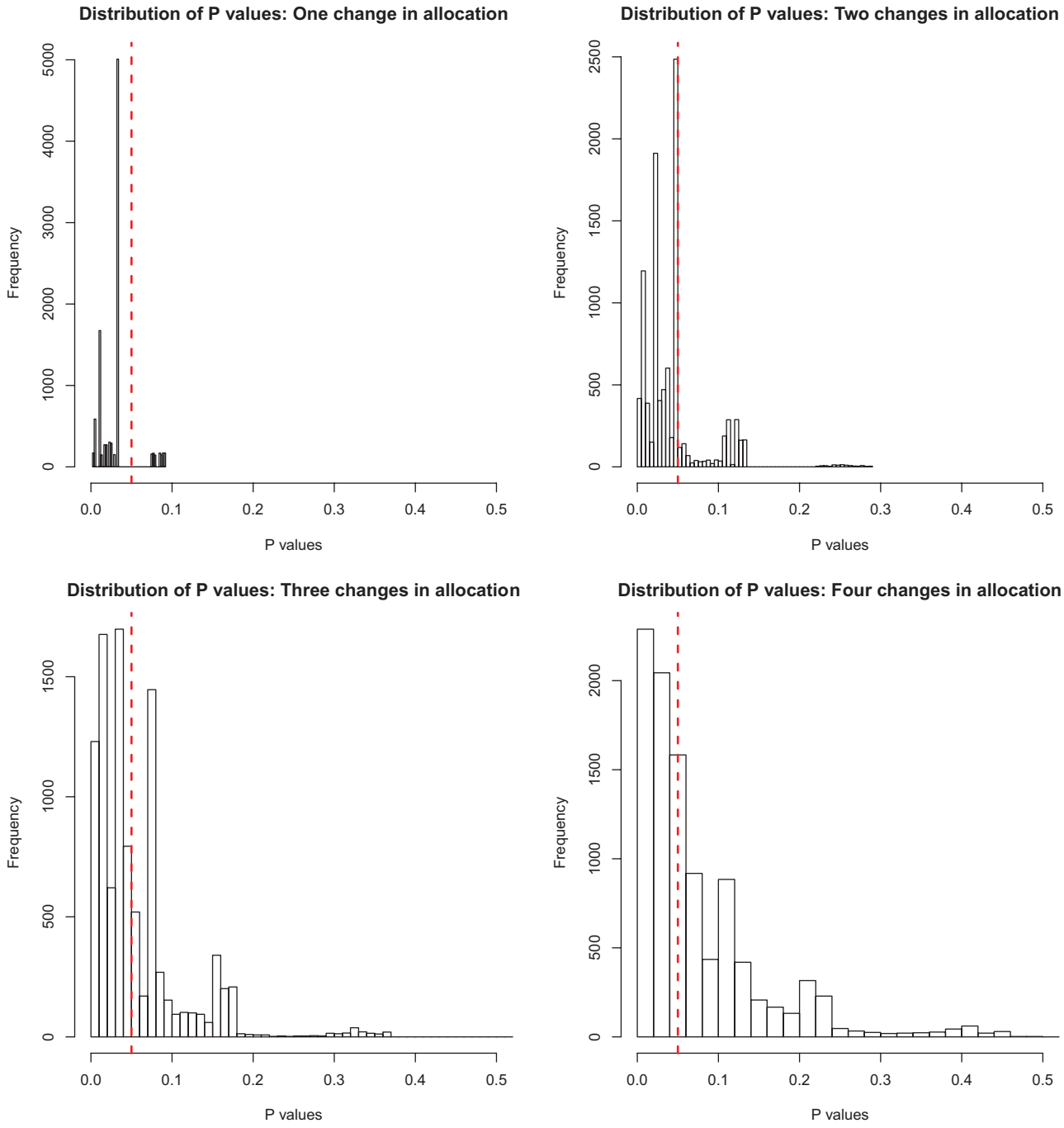
In this analysis, incomplete agreement was observed in 3 patients. Assuming that they all correspond to allocation errors, the observed treatment effect would remain significant in >65% of the cases (Appendix Figure 2). We therefore concluded that, while the results of this analysis were more sensitive to allocation errors, the robustness of the results warrant serious consideration.



Appendix Figure 1. Simulations conducted on the survival analysis including 198 patients (66 patients from perioperative myocardial infarction group and 132 matched patients) and comparing 3 groups: (1) patients without postoperative myocardial necrosis, (2) patients with postoperative myocardial necrosis without treatment intensification, and (3) patients with postoperative myocardial necrosis with treatment intensification.

DISCLOSURES

Name: Arnaud Foucrier, MD.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Arnaud Foucrier 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: Reitze Rodseth, MD.
Contribution: This author helped design the study, analyze the data, and write the manuscript.
Attestation: Reitze Rodesth has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Mohamed Aissaoui, MD.
Contribution: This author helped designand conduct the study and analyze the data.



Appendix Figure 2. Simulations performed on the survival analysis comparing patients with postoperative myocardial necrosis, with or without postoperative cardiovascular treatment intensification (2 groups, 66 patients).

Attestation: Mohamed Aissaoui has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Cristina Ibanes, MD.
Contribution: This author helped design and conduct the study and analyze the data.
Attestation: Cristina Ibanes has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Jean-Pierre Goarin, MD.
Contribution: This author helped write the manuscript.
Attestation: Jean-Pierre Goarin has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Paul Landais, MD, PhD.
Contribution: This author helped design the study and analyze the data.
Attestation: Paul Landais has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Pierre Coriat, MD.
Contribution: This author helped design the study and write the manuscript.

Attestation: Pierre Coriat has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Yannick Le Manach, MD, PhD.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Yannick Le Manach 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.
This manuscript was handled by: Charles W. Hogue, Jr, MD.

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