ORIGINAL ARTICLE

High-Sensitivity Troponin I after Cardiac Surgery and 30-Day Mortality

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ABSTRACT

BACKGROUND

Consensus recommendations regarding the threshold levels of cardiac troponin elevations for the definition of perioperative myocardial infarction and clinically important periprocedural myocardial injury in patients undergoing cardiac surgery range widely (from >10 times to ≥70 times the upper reference limit for the assay). Limited evidence is available to support these recommendations.

METHODS

We undertook an international prospective cohort study involving patients 18 years of age or older who underwent cardiac surgery. High-sensitivity cardiac troponin I measurements (upper reference limit, 26 ng per liter) were obtained 3 to 12 hours after surgery and on days 1, 2, and 3 after surgery. We performed Cox analyses using a regression spline that explored the relationship between peak troponin measurements and 30-day mortality, adjusting for scores on the European System for Cardiac Operative Risk Evaluation II (which estimates the risk of death after cardiac surgery on the basis of 18 variables, including age and sex).

RESULTS

Of 13,862 patients included in the study, 296 (2.1%) died within 30 days after surgery. Among patients who underwent isolated coronary-artery bypass grafting or aortic-valve replacement or repair, the threshold troponin level, measured within 1 day after surgery, that was associated with an adjusted hazard ratio of more than 1.00 for death within 30 days was 5670 ng per liter (95% confidence interval [CI], 1045 to 8260), a level 218 times the upper reference limit. Among patients who underwent other cardiac surgery, the corresponding threshold troponin level was 12,981 ng per liter (95% CI, 2673 to 16,591), a level 499 times the upper reference limit.

CONCLUSIONS

The levels of high-sensitivity troponin I after cardiac surgery that were associated with an increased risk of death within 30 days were substantially higher than levels currently recommended to define clinically important periprocedural myocardial injury. (Funded by the Canadian Institutes of Health Research and others; VISION Cardiac Surgery ClinicalTrials.gov number, NCT01842568.)

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More than 1 million patients undergo cardiac surgery in the United States and Europe annually.[1,2] Although cardiac surgery has the potential to improve the quality and prolong the duration of a patient's life,[3] it is associated with complications. Prognostically important myocardial injury — detected by an elevated concentration of either cardiac troponin or creatine kinase MB[4] — is one of the most common complications after cardiac surgery and is associated with increased mortality.[5-7]

Although an elevated level of creatine kinase MB was historically used to define myocardial injury after cardiac surgery,[5] the assay to measure it is no longer available in many hospitals worldwide,[8] and consensus statements have recommended high-sensitivity cardiac troponin as the preferred biomarker.[4] On the basis of expert opinion, the Fourth Universal Definition of Myocardial Infarction suggested that in patients who have normal concentrations of cardiac troponin at baseline, a concentration more than 10 times the upper reference limit should be the threshold used in the diagnosis of myocardial infarction (together with evidence of new myocardial ischemia) in the first 48 hours after coronary-artery bypass grafting (CABG).[4] Although the Academic Research Consortium-2 consensus document stated that there was no evidence-based threshold for cardiac troponin levels after CABG, it endorsed a threshold for the diagnosis of myocardial infarction of 35 times the upper reference limit together with new evidence of ischemia (as determined on the basis of expert opinion).[9] The Academic Research Consortium-2 also defined a threshold of 70 times the upper reference limit as a stand-alone criterion for clinically important periprocedural myocardial injury.

Globally, many hospitals now use high-sensitivity cardiac troponin assays[10]; however, limited data are available to define a prognostically important degree of myocardial injury after cardiac surgery on the basis of those assays. We undertook the Vascular Events in Surgery Patients Cohort Evaluation (VISION) Cardiac Surgery study to examine clinical outcomes after cardiac surgery. A primary objective was to determine the relationship between postoperative high-sensitivity cardiac troponin I levels and the risk of death within 30 days after cardiac surgery.

Methods

Study Organization and Funding

The VISION Cardiac Surgery study was a prospective cohort study involving patients who underwent cardiac surgery. The study protocol is available with the full text of this article at NEJM.org. The members of the project office operations committee (all of whom are authors; see the Supplementary Appendix, available at NEJM.org) designed the study. The Population Health Research Institute was the coordinating center and was responsible for the database, data validation, analyses, and study coordination. All centers obtained ethics approval from their respective ethics committees or institutional review boards before recruitment began.

The study had 23 funding sources, most of which were peer-reviewed grants. No study funder had a role in the study design, conduct, data collection, or analyses. Abbott Laboratories provided grant support and the high-sensitivity cardiac troponin I assays used in the study. The members of the project office operations committee vouch for the completeness and accuracy of the data and for the fidelity of the study to the protocol.

Patients

We recruited patients from a convenience sample of 24 hospitals in 12 countries from May 2013 through April 2019. Further details on screening of patients, procedures intended to ensure a representative sample of eligible patients from participating centers, and criteria for inclusion and exclusion are provided in Sections S1 and S2 in the Supplementary Appendix. Patients were eligible if they were at least 18 years of age and underwent any cardiac surgical procedure, excluding an isolated pericardial window, pericardiectomy, or implantation of a pacemaker or defibrillator. Patients were excluded if they had a preoperative myocardial infarction on the same day or the day before their cardiac surgery or if they had a preoperative high-sensitivity cardiac troponin I level of 300 ng per liter or more within 12 hours before surgery.

Most patients gave written informed consent before surgery. For those who did not (e.g., patients who underwent emergency surgery at night), research personnel obtained consent with-

in 24 hours after surgery. Details regarding deferred consent and waived need for consent are provided in Section S3.

PROCEDURES

Research personnel interviewed patients and reviewed their charts to obtain data on potential predictors of perioperative complications, including the components of the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II).[11] The EuroSCORE II consists of 18 variables (including age, sex, and other factors, such as renal impairment), each assigned a weight, which are used to estimate a patient's risk of death after cardiac surgery (Table S1). Blood samples were obtained for measurement of cardiac troponin I levels with the ARCHITECT STAT (Abbott Laboratories) assay (upper reference limit, 26 ng per liter; limit of detection, 1 to 2 ng per liter) before surgery, 3 to 12 hours after surgery, and on days 1, 2, and 3 after surgery (Section S4). In the case of patients who were identified and enrolled between 12 and 24 hours after undergoing surgery, blood samples were obtained immediately, and testing continued as described. Patients, health care providers, and data collectors were unaware of the results of troponin tests.

The primary outcome was death within 30 days after surgery. The secondary outcome, a major vascular complication, was a composite of death from a vascular complication during the first 30 days after surgery, a myocardial infarction occurring between day 4 and day 30 after surgery, and insertion of a mechanical assist device during the patient's initial stay in an intensive care unit after surgery. Further details on patient follow-up and data management processes and on the secondary outcome are provided in Sections S5 and S6.

STATISTICAL ANALYSIS

The sample size was determined on the basis of the original study plan, which called for the inclusion of 21 prediction variables in a Cox proportional-hazards regression model for death at 30 days. To minimize the risk of overfitting, we planned to include at least 10 events for each independent variable, or a total of 210 deaths.[12,13] This plan resulted in a target sample size of 15,000 patients (9750 undergoing CABG and 5250 undergoing other surgeries) (Section S7). We subsequently revised the statistical analysis plan to include only the EuroSCORE II (based on 18 variables) in the regression models. Missing components for the calculation of scores on the EuroSCORE II were imputed with the use of multiple imputation.[14] Data from patients lost to follow-up were censored at the last day that the vital status of the patient was known.

We conducted separate analyses of data from patients who underwent isolated CABG or aortic-valve replacement or repair (AVR) and patients who underwent other cardiac surgery (i.e., any other cardiac surgery, including CABG or AVR in combination with another procedure). We performed Cox analyses using a regression spline that explored the relationship between log-transformed peak high-sensitivity cardiac troponin I measurements within 1 day after surgery and 30-day mortality, adjusting for scores on the EuroSCORE II. From the fitted model, we identified the lowest high-sensitivity cardiac troponin I measurement that corresponded to an adjusted hazard ratio estimate of more than 1.00. After excluding patients who had a peak troponin measurement within 1 day after surgery that exceeded the lowest measurement associated with an adjusted hazard ratio of more than 1.00, we repeated the Cox analysis using the peak high-sensitivity cardiac troponin I measurement on day 2 or 3 after surgery. We plotted the adjusted hazard ratios for death within 30 days as a smooth function of peak troponin values using a regression spline and plotted receiver operating characteristic curves with 95% confidence bands we derived using fivefold cross-validation.

For the lowest high-sensitivity cardiac troponin I measurement associated with an adjusted hazard ratio of more than 1.00 and an adjusted hazard ratio of 2.00 or more, we determined the 95% confidence interval from 1000 bootstrapped samples. We repeated these calculations for troponin measurements on day 2 or 3 after surgery only for an adjusted hazard ratio of more than 1.00, because there were fewer patients included in the day 2 or 3 analyses owing to the exclusion of patients who had a hazard ratio of more than 1.00 on day 1 after surgery. Similar methods were used to analyze the relationship between high-sensitivity cardiac troponin I measurements and the secondary outcome of major vascular

Table 1. Characteristics of the Patients at Baseline.

Variable	Total (N=13,862)
Mean age (±SD) — yr*	63.3±12.3
Male sex — no. (%)*	9822 (70.9)
Clinical history	
Myocardial infarction — no. (%)	4066 (29.3)
Myocardial infarction within 90 days before surgery — no./total no. (%)*	2099/13,721 (15.3)
Canadian Cardiovascular Society class 4 angina — no./total no. (%)*	1095/13,855 (7.9)
Stroke — no. (%)	711 (5.1)
Peripheral arterial disease — no. (%)*	924 (6.7)
Hypertension — no. (%)	9146 (66.0)
Heart failure — no. (%)	2259 (16.3)
New York Heart Association class — no. (%)*	
II	919 (6.6)
III	849 (6.1)
IV	326 (2.4)
Previous cardiac surgery — no./total no. (%)*	501/13,846 (3.6)
Chronic obstructive pulmonary disease — no. (%)*	1129 (8.1)
Tobacco use — no./total no. (%)	7138/13,849 (51.5)
Diabetes — no. (%)	4015 (29.0)
Diabetes, receiving insulin — no./total no. (%)*	1713/13,856 (12.4)
Poor mobility — no./total no. (%)*	548/13,861 (4.0)

* This variable is a component of the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II), which estimates the risk of death after cardiac surgery on the basis of 18 variables (Table S1 in the Supplementary Appendix).

complications. Section S8 includes further details of the statistical analyses, including the approach used for additional sensitivity analyses. Statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute), and R software, version 3.6.3 (R Foundation for Statistical Computing).

RESULTS

STUDY POPULATION

Among the 15,984 patients enrolled in the VISION Cardiac Surgery study, data for 13,862 were included for analysis (Fig. S1). Patients were enrolled from North America (35.9%), Asia (28.3%), Europe (26.2%), South America (6.3%), and Australia (3.3%) (Table S2). We obtained 30-day mortality data on 13,480 patients (97.2%); data on the remaining 382 patients were censored at the time of hospital discharge.

The mean age of the study cohort was 63.3 years, 70.9% of the patients were men, 29.3% had a history of myocardial infarction (Table 1), and 70.2% were White (Table S3). The sample was representative of patients undergoing cardiac surgery (Table S4). The median preoperative high-sensitivity cardiac troponin I value was 9 ng per liter (interquartile range, 4 to 20). Patients underwent isolated CABG (46.9%), isolated AVR (12.5%), or other cardiac surgery (40.6%). The mean score on the EuroSCORE II was 2.4% (Table S5).

TROPONIN LEVELS AND OUTCOME EVENTS

The median number of postoperative high-sensitivity cardiac troponin I measurements was 4 (interquartile range, 3 to 4) per patient. Figure S2 shows the median high-sensitivity cardiac troponin I measurements during the first 3 days after surgery. The median peak troponin mea-

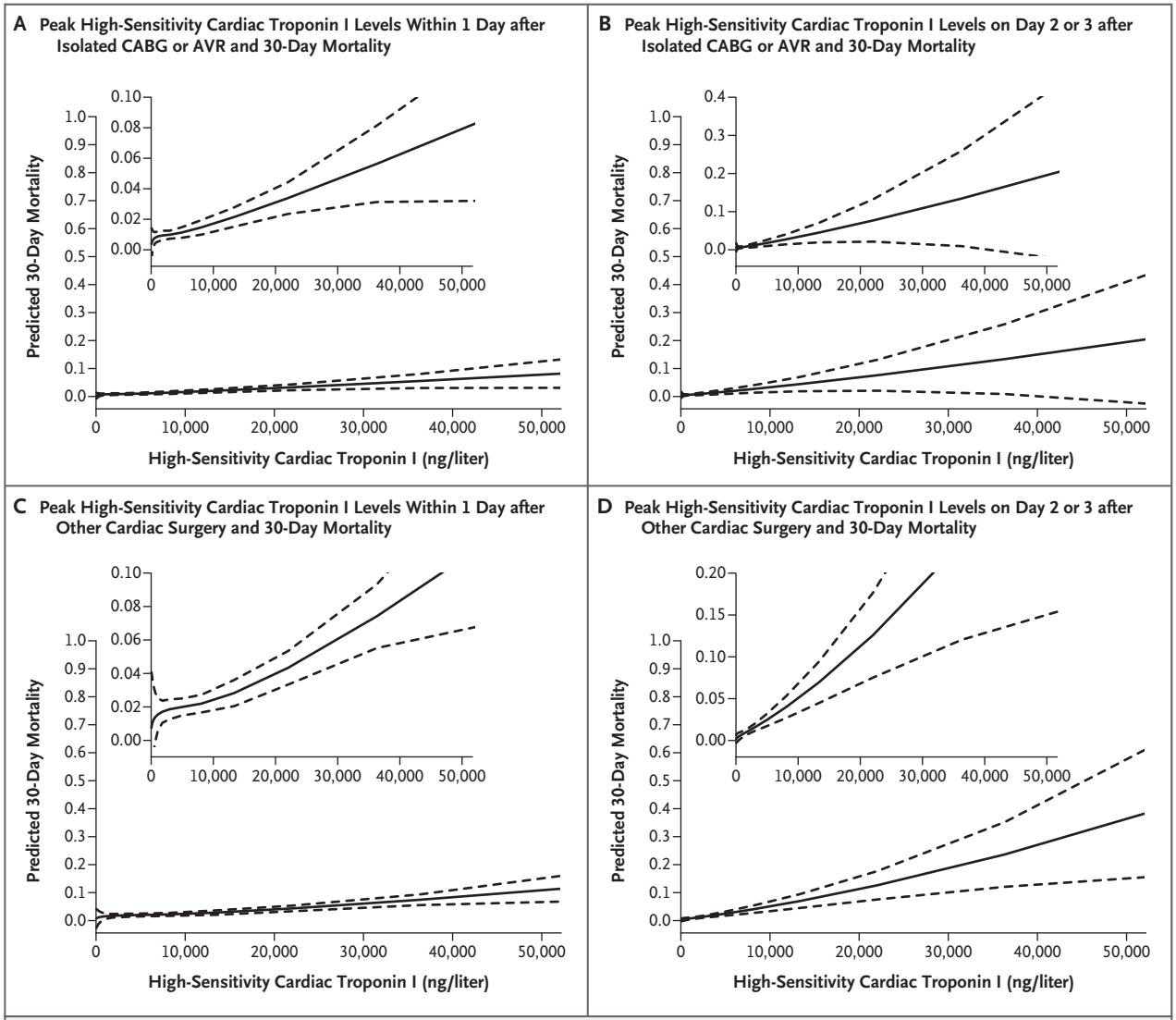

Figure 1. Unadjusted Relationships between Peak High-Sensitivity Cardiac Troponin I Measurements and 30-Day Mortality.

Dashed lines represent 95% confidence intervals for the unadjusted relationship between peak high-sensitivity cardiac troponin I measurements and 30-day mortality among patients who underwent isolated coronary-artery bypass grafting (CABG) or aortic-valve replacement or repair (AVR) (Panels A and B) and among patients who underwent other cardiac surgery, including CABG or AVR in combination with another procedure (Panels C and D). The insets show the same data on an expanded y axis.

surement was 3920 ng per liter (interquartile range, 1799 to 8734). Within the first day after surgery, troponin was measured in 13,662 patients. Among these patients, 13,316 patients (97.5%) had a peak troponin measurement of more than 260 ng per liter (>10 times the upper reference limit), 12,217 patients (89.4%) had a peak troponin measurement of at least 910 ng per liter (≥35 times the upper reference limit), and 10,205 patients (74.7%) had a peak troponin measurement of at least 1820 ng per liter (≥70 times the upper reference limit). By 30 days after surgery, 296 patients (2.1%) had died and 399 patients (2.9%) had had a major vascular complication.

ASSOCIATIONS BETWEEN TROPONIN LEVELS AND OUTCOMES

Figure 1 shows the unadjusted relationship between high-sensitivity cardiac troponin I mea-

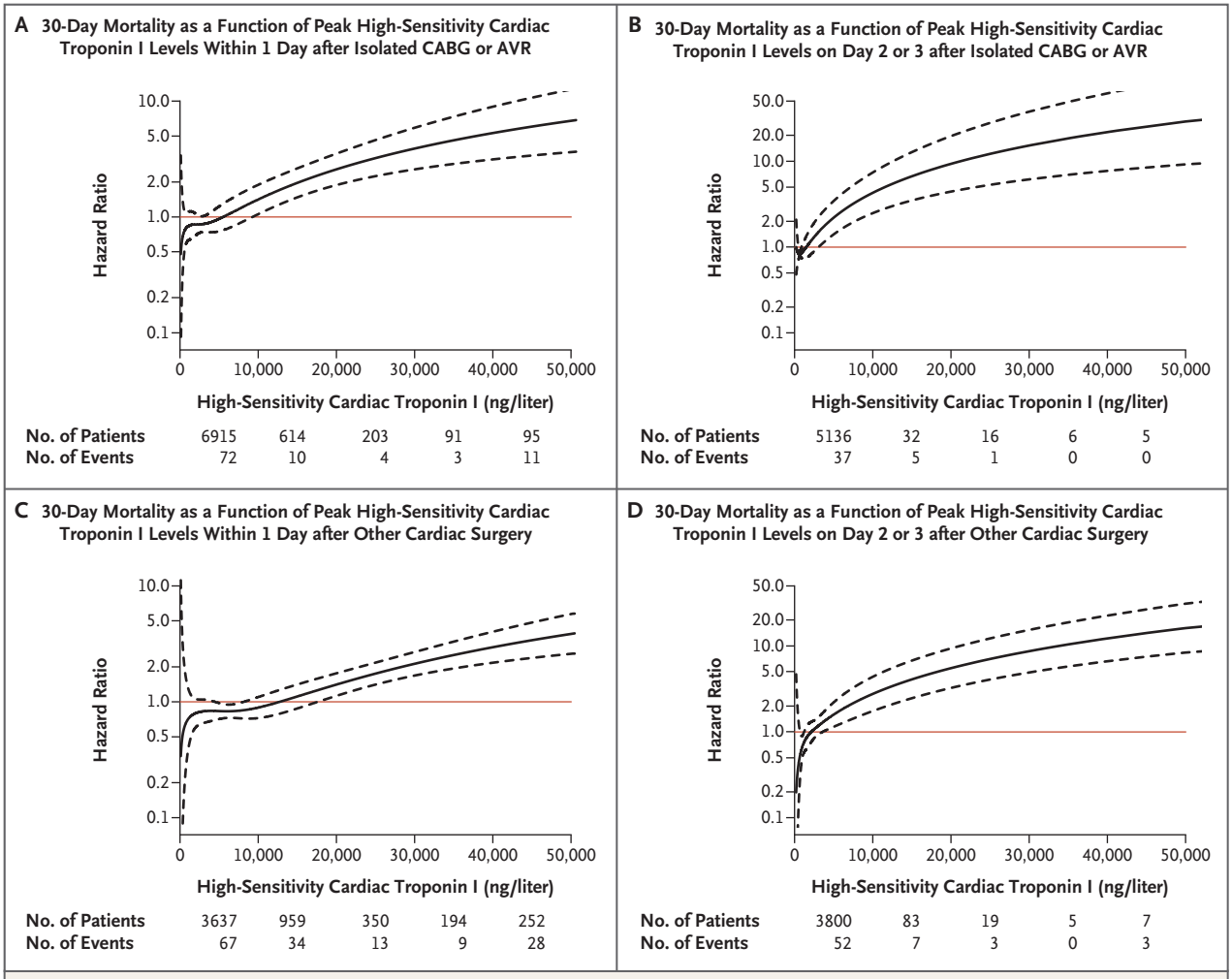

Figure 2. Adjusted Hazard Ratio Curves for 30-Day Mortality as a Function of Peak High-Sensitivity Cardiac Troponin I Measurements.

All hazard ratios are adjusted for the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II), which estimates the risk of death after cardiac surgery on the basis of 18 variables. The dashed lines represent 95% confidence intervals for the adjusted hazard ratio. Data shown in Panels B and D exclude all patients who had a peak postoperative high-sensitivity cardiac troponin I measurement within 1 day after surgery that exceeded the lowest measurement associated with an adjusted hazard ratio of more than 1.0 (indicated by the red horizontal line). Other cardiac surgery includes any other cardiac surgery, including CABG or AVR in combination with another procedure.

surements and 30-day mortality. The relationship was similar after adjustment for scores on the EuroSCORE II (Fig. S3). Multivariable analyses showed an increased risk of death within 30 days associated with each 1-unit increase in the natural log (i.e., equivalent to a 2.7-times increase) of the peak troponin measurement within 1 day after isolated CABG or AVR (adjusted hazard ratio, 1.62; 95% confidence interval [CI], 1.36 to 1.93) and after other cardiac surgery (adjusted hazard ratio, 1.75; 95% CI, 1.48 to 2.07) and with each 1-unit increase in the natural log of the peak troponin measurement on day 2 or 3 after isolated CABG or AVR (adjusted hazard ratio, 1.84; 95% CI, 1.41 to 2.40) and after other cardiac surgery (adjusted hazard ratio, 2.77; 95% CI, 2.19 to 3.51) (Figs. 2 and S4).

Among patients who underwent isolated CABG or AVR, the lowest high-sensitivity cardiac troponin I value, measured within 1 day after surgery, that was associated with an adjusted hazard ratio of more than 1.00 for death within

Table 2. Peak Postoperative High-Sensitivity Cardiac Troponin I Measurements within 1 Day after Cardiac Surgery.*

Surgical Procedure	Adjusted Hazard Ratio for 30-Day Mortality		
	1.00 (reference)	>1.00 to <2.00	≥2.00
Isolated CABG or AVR			
Patients who underwent the procedure — no./total no. (%)	5972/7918 (75.4)	1367/7918 (17.3)	579/7918 (7.3)
High-sensitivity cardiac troponin I level (95% CI) — ng/liter†	≤5669	5670–15,293 (1045–8260)	≥15,294 (10,717–22,495)
Death			
No. of patients/total no.	56/5972	24/1367	20/579
% (95% CI)	0.9 (0.7–1.1)	1.8 (1.1–2.5)	3.5 (2.0–5.0)
Other cardiac surgery‡			
Patients who underwent the procedure — no./total no. (%)	4058/5392 (75.3)	849/5392 (15.7)	485/5392 (9.0)
High-sensitivity cardiac troponin I level (95% CI) — ng/liter†	≤12,980	12,981–28,367 (2673–16,591)	≥28,368 (23,844–33,969)
Death			
No. of patients/total no.	83/4058	28/849	40/485
% (95% CI)	2.0 (1.6–2.4)	3.3 (2.1–4.5)	8.2 (5.8–10.6)

* The Cox proportional-hazards models included scores on the EuroSCORE II as a covariate. AVR denotes aortic-valve replacement or repair, and CABG coronary-artery bypass grafting.
† The levels shown are the lowest high-sensitivity cardiac troponin I levels that correspond to the hazard ratios for mortality listed.
‡ Other cardiac surgery included any other cardiac surgery, including CABG or AVR in combination with another procedure.

Table 3. Peak Postoperative High-Sensitivity Cardiac Troponin I Measurements on Day 2 or 3 after Cardiac Surgery.*

Surgical Procedure	Adjusted Hazard Ratio for 30-Day Mortality	
	1.00 (reference)	>1.00
Isolated CABG or AVR		
Patients who underwent the procedure — no./total no. (%)	3997/5195 (76.9)	1198/5195 (23.1)
High-sensitivity cardiac troponin I level (95% CI) — ng/liter†	≤1521	≥1522 (1325–2433)
Death		
No. of patients/total no.	28/3997	15/1198
% (95% CI)	0.7 (0.4–1.0)	1.3 (0.7–1.9)
Other cardiac surgery‡		
Patients who underwent the procedure — no./total no. (%)	2295/3914 (58.6)	1619/3914 (41.4)
High-sensitivity cardiac troponin I level (95% CI) — ng/liter†	≤2502	≥2503 (1228–4033)
Death		
No. of patients/total no.	23/2295	42/1619
% (95% CI)	1.0 (0.6–1.4)	2.6 (1.8–3.4)

* The Cox proportional-hazards models included scores on the EuroSCORE II as a covariate.
† The levels shown are the lowest high-sensitivity cardiac troponin I levels that correspond to the hazard ratios for mortality listed.
‡ Other cardiac surgery included any other cardiac surgery, including CABG or AVR in combination with another procedure.

30 days was 5670 ng per liter (95% CI, 1045 to 8260), a level 218 times the upper reference limit. On day 2 or 3 after surgery, the threshold value was 1522 ng per liter (95% CI, 1325 to 2433), a level 59 times the upper reference limit (Tables 2 and 3). Among patients who underwent other cardiac surgery, the lowest high-sensitivity cardiac troponin I value, measured within 1 day after surgery, that was associated with an adjusted hazard ratio of more than 1.00 for death within 30 days was 12,981 ng per liter (95% CI, 2673 to 16,591), a level 499 times the upper reference limit. On day 2 or 3 after surgery, the threshold value was 2503 ng per liter (95% CI, 1228 to 4033), a level 96 times the upper reference limit. Sensitivity models that accounted for potential site-clustering effects and that were restricted to patients with complete EuroSCORE II data produced troponin thresholds associated with an adjusted hazard ratio of more than 1.00 that were similar to troponin thresholds identified with the use of the primary Cox model (Tables S6 through S9).

Among patients who underwent isolated CABG or AVR, the lowest high-sensitivity cardiac troponin I value, measured within 1 day after surgery, that was associated with an adjusted hazard ratio of more than 1.00 for a major vascular complication within 30 days after surgery was 4184 ng per liter (95% CI, 1488 to 7781), a level 161 times the upper reference limit. On day 2 or 3 after surgery, the threshold value was 1099 ng per liter (95% CI, 310 to 1972), a level 42 times the upper reference limit (Tables S10 and S11). Among patients who underwent other cardiac surgery, the lowest high-sensitivity cardiac troponin I value, measured within 1 day after surgery, that was associated with an adjusted hazard ratio of more than 1.00 for a major vascular complication within 30 days after surgery was 9654 ng per liter (95% CI, 5227 to 15,107), a level 371 times the upper reference limit. On day 2 or 3 after surgery, the threshold value was 1888 ng per liter (95% CI, 1495 to 2989), a level 73 times the upper reference limit.

DISCUSSION

We examined the relationship between postoperative levels of high-sensitivity cardiac troponin I and clinical outcomes in a series of patients who underwent cardiac surgery. We estimated the threshold values of high-sensitivity cardiac troponin I that were associated with an increased risk of death within 30 days (adjusted hazard ratio, >1.00). Among patients who underwent isolated CABG or AVR, we estimated that the threshold troponin value was 5670 ng per liter (218 times the upper reference limit) within 1 day after surgery and 1522 ng per liter (59 times the upper reference limit) on day 2 or 3 after surgery. Among patients who underwent other cardiac surgery, we estimated that the threshold troponin value was 12,981 ng per liter (499 times the upper reference limit) within 1 day after surgery and 2503 ng per liter (96 times the upper reference limit) on day 2 or 3 after surgery.

We observed that the lowest troponin thresholds associated with an increased risk of death at 30 days after cardiac surgery were substantially higher than the levels that are currently recommended in consensus statements as the basis for diagnosis of perioperative myocardial infarction or clinically important perioperative myocardial injury. The recommended troponin thresholds in these consensus statements (>10, ≥35, and ≥70 times the upper reference limit)[4,9] were exceeded in 97.5%, 89.4%, and 74.7% of patients, respectively, within the first day after surgery.

Several previous studies have evaluated the relationship between biomarker elevations and death in patients undergoing cardiac surgery. A meta-analysis of individual patient data that included 7234 patients who underwent CABG showed that with a standard troponin I assay, the lowest threshold associated with an increased risk of death within 30 days was 40 to 100 times the upper reference limit (relative risk, 3.61; 95% CI, 1.08 to 12.04).[5] In a study involving 1122 patients who underwent cardiac surgery, 58 patients died within 30 days after surgery. Mortality began to increase with high-sensitivity cardiac troponin T elevations more than 40 times the upper reference limit.[15] The inconsistencies between these previous reports and our study are probably attributable, at least in part, to the different cardiac biomarker assays used. These inconsistencies suggest that thresholds for clinically important perioperative myocardial injury are probably specific to the cardiac biomarker evaluated.

Our study has several limitations. Our estimates of troponin thresholds are based on an increased risk of adverse clinical outcomes at 30 days; longer-term outcomes (such as the development of heart failure) may also be influenced by the extent of myocardial injury, and it is possible that the threshold of myocardial injury for such outcomes may be lower than those we have identified. Our analysis differs from the recommendations in consensus statements in that we did not take into account new evidence of ischemia (such as electrocardiographic, angiographic, or imaging data). Thus, our thresholds do not allow for direct comparison with the consensus definitions of periprocedural myocardial infarction. Our threshold estimates are subject to considerable uncertainty, as indicated by the wide 95% confidence intervals, and they do not distinguish between myocardial injury due to ischemia (e.g., acute coronary thrombosis) and myocardial injury from other causes (e.g., reperfusion injury or surgical trauma). Our results are specific to the high-sensitivity cardiac troponin I assay we evaluated and cannot be generalized to other cardiac troponin assays. Although we examined specific thresholds for isolated CABG or AVR as compared with other cardiac surgery, there are numerous other variables that we did not examine, such as on-pump as compared with off-pump surgery, the type of cardioplegia used, emergency surgery as compared with elective surgery, or patient characteristics such as age, sex, and preoperative cardiac function. Finally, validation of our findings in other cohorts of patients undergoing cardiac surgery would be desirable.

We examined the relationship between postoperative levels of high-sensitivity cardiac troponin I and clinical outcomes in a cohort of patients undergoing cardiac surgery. We found that the lowest threshold values of high-sensitivity cardiac troponin I associated with increased rates of death from any cause and major vascular complications at 30 days after surgery were markedly higher than the threshold values recommended in consensus statements for the detection of perioperative myocardial infarction and clinically important perioperative myocardial injury.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We dedicate this article to the memory of Dr. Yannick Le Manach, who was a valued colleague and VISION Cardiac Surgery investigator.

APPENDIX

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