

Impact of Periprocedural Myocardial Biomarker Elevation on Mortality Following Elective Percutaneous Coronary Intervention



Hector M. Garcia-Garcia, MD, PhD,^{a,b} Eugène P. McFadden, MD, PhD,^c Clemens von Birgelen, MD, PhD,^d Tessa Rademaker-Havinga, BSc, MSc,^a Ernest Spitzer, MD,^{a,e} Neal S. Kleiman, MD,^f David J. Cohen, MD,^g Kevin F. Kennedy, MS,^g Edoardo Camenzind, MD,^h Laura Mauri, MD,ⁱ Philippe Gabriel Steg, MD,^{j,k} William Wijns, MD,^l Sigmund Silber, MD,^m Gerrit-Anne van Es, PhD,^a Patrick W. Serruys, MD, PhD,ⁿ Stephan Windecker, MD,^o Donald Cutlip, MD,^{p,q} Pascal Vranckx, MD, PhD^r

ABSTRACT

OBJECTIVES This study sought to explore the association between biomarker elevation, with creatine kinase-myocardial band (CK-MB) or cardiac troponin (cTn), following percutaneous coronary intervention (PCI) and mortality in patients undergoing PCI for stable angina with normal baseline values.

BACKGROUND Several studies have shown a strong association between post-PCI CK-MB elevation and subsequent mortality. However, the prognostic significance of troponin elevation following coronary intervention is still debated.

METHODS Patient-level data from 5 contemporary coronary stent trials and 1 large registry were pooled. Mortality of patients with stable angina, with normal baseline biomarkers, was compared between patients with and those without different cutoff values of cTn and CK-MB.

RESULTS A total of 13,452 patients were included in this pooled analysis. The overall percentage of patients with elevated biomarkers following PCI was 23.9% for CK-MB and 68.4% for cTn. In the patient cohort for whom both assays were available ($n = 8,859$), 2.4% had both CK-MB $\geq 5 \times$ the upper limit of normal (ULN) and cTn $\geq 35 \times$ ULN, while 92% had both CK-MB $< 5 \times$ ULN and cTn $< 35 \times$ ULN. Among patients with CK-MB $\geq 5 \times$ ULN ($n = 315$), 212 (67.3%) also had cTn $\geq 35 \times$ ULN. Conversely, 390 of patients (64.8%) who had cTn $\geq 35 \times$ ULN did not have CK-MB $\geq 5 \times$ ULN. A total of 259 patients (1.9%) died at 1 year; 20 (7.7%) had CK-MB $\geq 5 \times$ ULN, and 23 (8.8%) had cTn $\geq 35 \times$ ULN. In the Cox multivariate analysis, in which the CK-MB and cTn ratios post-procedure were forced into the model, age, prior myocardial infarction, lesion complexity, hyperlipidemia, and CK-MB ratio (≥ 10) post-procedure were associated with increased 1-year mortality.

CONCLUSIONS Following elective PCI in patients in stable condition treated with second-generation drug-eluting stent, CK-MB and cTn elevations remain common. After multivariate adjustment, there was an increased mortality rate with elevation of CK-MB after PCI, whereas cTn elevation was not independently associated with mortality at 1 year. (J Am Coll Cardiol Intv 2019;12:1954-62) © 2019 by the American College of Cardiology Foundation.

From ^aCardialysis, Rotterdam, the Netherlands; ^bInterventional Cardiology, MedStar Washington Hospital Center, Washington, District of Columbia; ^cInterventional Cardiology, Cork University Hospital, Cork, Ireland; ^dDepartment of Cardiology, Medisch Spectrum Twente, Thoraxcentrum Twente, Enschede, the Netherlands; ^eDepartment of Cardiology, Thoraxcenter, Erasmus University Medical Center, Rotterdam, the Netherlands; ^fInterventional Cardiology, Houston Methodist DeBakey, Houston, Texas; ^gMid America Heart Institute, University of Missouri, Kansas City, Missouri; ^hUniversity of Geneva, Geneva, Switzerland; ⁱDivision of Cardiovascular Medicine, Baim Institute for Clinical Research, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; ^jFACT, DHU FIRE, Département de Cardiologie, INSERM U-1148, Université Paris Diderot, Paris, France; ^kNational Heart and Lung Institute, Imperial College, Royal Brompton Hospital, London, United Kingdom; ^lCardiology Department, Cardiovascular Research Center Aalst, OLV Hospital, Aalst, Belgium; ^mDepartment of Cardiology, Heart Centre at the Isar, Munich, Germany; ⁿCentre for International Cardiovascular Health, Imperial College London, London,

The treatment of coronary stenoses with the use of second-generation drug-eluting stents (DES) has been associated with a decrease in the rate of major adverse coronary events (1). Despite this overall trend toward a lower event rate in current practice, the clinical and prognostic significance of periprocedural biomarker elevation after percutaneous coronary intervention (PCI) has generated widespread debate (2,3). The classification of threshold biomarker elevations with or without ancillary criteria as significant myocardial injury or myocardial infarction (MI) has potential consequences for patients, for physicians when used as a metric for quality of care, and for the development and appropriate assessment of new therapies in clinical trials. Periprocedural events may have a significant association with hard clinical outcomes when they reflect substantial loss of myocardium. Several studies have shown a strong association of post-PCI creatine kinase-myocardial band (CK-MB) elevation with subsequent cardiovascular events (4); unfortunately, CK-MB is no longer an assay in routine use at most institutions. The universal definition of myocardial infarction task force (5) embraced cardiac troponin (cTn) as the biomarker of choice because is a more sensitive and specific biomarker for the early detection of myocardial necrosis and thus facilitates early diagnosis and triage in patients presenting acutely with chest pain. By default, it has thus become the only biomarker generally available in the periprocedural setting. This increased sensitivity may permit the detection of subtle differences, among devices, in clinical trials. However, attempts to unravel the prognostic significance of troponin elevation related to coronary intervention, alone or in association with other criteria such as proposed by the universal definition of myocardial infarction task force, have produced conflicting results.

SEE PAGE 1963

The objective of this study was to explore the association between biomarker elevation with CK-MB or cTn following PCI and mortality in patients undergoing elective PCI for stable angina with normal baseline values.

METHODS

Patient-level data from 5 contemporary coronary stent trials and 1 large registry (LEADERS [Limus Eluted From a Durable Versus Erodable Stent Coating] [6], TWENTE [The Real-World Endeavor Resolute Versus XIENCE V Drug-Eluting Stent Study in Twente] [7], DUTCH PEERS [Durable Polymer-Based Stent Challenge of Promus Element Versus Resolute Integrity in an All Comers Population] [8], RESOLUTE AC [Randomized, Two-Arm, Non-Inferiority Study Comparing Endeavor-Resolute Stent With Abbot XIENCE-V Stent] [9], PROTECT [Randomized Study Comparing Endeavor With Cypher Stents] [10], and EVENT [Evaluation of Drug Eluting Stents and Ischemic Events] [11]) were pooled (Table 1). All-cause mortality of patients with stable angina and with normal baseline biomarkers was compared between patients with and those without different cutoff values of cTn and CK-MB.

All studies were conducted following the Guidelines of Good Clinical Research Practice and were approved by the various institutional review committees, and subjects gave informed consent to participate in each individual study.

Because there are multiple sponsors and investigators involved in this research and because specific approval was required from some Institutional Review Boards for this analysis, the data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

STATISTICAL ANALYSIS. The individual patient-based data were collected from the aforementioned clinical studies. The pooling of the different datasets was performed by Cardialysis (Rotterdam, the Netherlands), an independent academic research organization. Continuous variables are presented as mean \pm SD, and categorical variables are summarized as frequencies. All-cause mortality of stable angina patients, with normal baseline biomarkers, was compared between patients with and those without

ABBREVIATIONS AND ACRONYMS

CK-MB = creatine kinase-myocardial band

cTn = cardiac troponin

DES = drug-eluting stent(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

SCAI = Society for Cardiovascular Angiography and Interventions

ULN = upper limit of normal

United Kingdom; ^oBern University Hospital, Bern, Switzerland; ^pBaim Institute for Clinical Research, Boston, Massachusetts; ^qBeth Israel Deaconess Medical Center, Boston, Massachusetts; and the ^rDepartment of Cardiology and Critical Care Medicine, Hartcentrum Hasselt, Jessa Ziekenhuis & Faculty of Medicine and Life Sciences Hasselt University, Hasselt, Belgium. This work was supported by Cardialysis. Dr. von Birgelen has received institutional research grants from Biotronik, Boston Scientific, and Medtronic. Dr. Steg has received research grants from Bayer, Merck, Sanofi, and Servier; and has received speaking or consulting fees from Amarin, Amgen, AstraZeneca, Bayer/Janssen, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck Novartis, Pfizer, Regeneron, Sanofi, and Servier. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

TABLE 1 Major Characteristics of the Included Studies

Study	Stent Type	n	Age (yrs)	Female (%)	DM (%)	Non-ACS (n)
LEADERS	BES and SES	1,707	64.5	24.7	24.3	639
TWENTE	EES and ZES	1,391	64.2	27.5	21.6	670
DUTCH PEERS	EES and ZES	1,811	64.5	27.0	17.5	747
RESOLUTE AC	EES and ZES	2,292	64.3	23.1	23.4	1,130
PROTECT	ZES and SES	8,709	62.2	23.5	27.5	3,998
EVENT	BMS and DES	6,347	64.7	32.5	35.4	6,268

Including silent ischemia.

ACS = acute coronary syndrome; BES = biolimus-eluting stent; BMS = bare-metal stent; DES = drug-eluting stent; DM = diabetes mellitus; DUTCH PEERS = Durable Polymer-Based Stent Challenge of Promus Element Versus Resolute Integrity in an All Comers Population; EES = everolimus-eluting stent; EVENT = Evaluation of Drug Eluting Stents and Ischemic Events; LEADERS = Limus Eluted From a Durable Versus Erodeable Stent Coating; PROTECT = Randomized Study Comparing Endeavor With Cypher Stents; RESOLUTE AC = Randomized, Two-Arm, Non-Inferiority Study Comparing Endeavor-Resolute Stent With Abbot XIENCE-V Stent; SES = sirolimus-eluting stent; TWENTE = The Real-World Endeavor Resolute Versus XIENCE V Drug-Eluting Stent Study in Twente; ZES = zotarolimus-eluting stent.

different cutoff values of cTn and CK-MB (≥ 1 to <3 , ≥ 3 to <5 , ≥ 5 to <10 , ≥ 10 to <20 , ≥ 20 to <35 , ≥ 35 to <70 , and ≥ 70 times the upper limit of normal [ULN]). Kaplan-Meier curves were created to compare groups as follows: CK-MB <5 versus $\geq 5 \times$ ULN and cTn <35 versus $\geq 35 \times$ ULN. Following univariate analysis for the selection of significant variables, a multivariate analysis using Cox regression was performed to investigate the independent predictors of death.

Biomarkers were forced into the model as categorical covariates (model A: CK-MB $\geq 10 \times$ ULN; model B: cTn $\geq 70 \times$ ULN). The analysis was performed using SAS version 9.3 (SAS Institute, Cary, North Carolina); p values < 0.05 were considered to indicate statistical significance.

RESULTS

A total of 13,452 patients were included in this pooled analysis. Most (72.7%) were men, and the mean age was 64.2 years; 31.3% of patients had diabetes. The left anterior descending coronary artery was the most frequent (48.5%) target vessel, and the majority of lesions were of moderate or severe complexity (type B1, 30.0%; type B2, 30.6%; type C, 28.7%). Most patients had 1-vessel disease (78%). Nearly all patients (96.5%) were treated with DES. A mean of 1.7 stents per patient were implanted, with a mean stented length of 31.3 mm (Table 2).

BIOMARKER RESULTS. In total, 11,613 and 10,639 patients, respectively, had CK-MB and cTn measurements. Both biomarkers were measured in 8,859 patients. The frequencies of biomarker elevations by

different ratios are presented in Table 3. The overall percentage of patients with elevated biomarkers following PCI was 23.9% for CK-MB and 68.4% for cTn. Thresholds that have been proposed, on the basis of the Society for Cardiovascular Angiography and Interventions (SCAI) or universal definition of MI definition with or without additional criteria, are CK-MB or cTn $\geq 5 \times$ ULN or $\geq 10 \times$ ULN or cTn $\geq 5 \times$ ULN, $\geq 35 \times$ ULN, and $\geq 70 \times$ ULN. The frequencies of those elevations vary considerably, as shown in Table 3. The mortality rates by these different thresholds are presented in Figure 1. In the patient cohort for whom both assays were available (n = 8,859), 2.4% had both CK-MB $\geq 5 \times$ ULN and cTn $\geq 35 \times$ ULN, while 92% had both CK-MB $<5 \times$ ULN and cTn $<35 \times$ ULN. In patients with CK-MB $\geq 5 \times$ ULN (n = 315), 212 (67.3%) also had cTn $\geq 35 \times$ ULN. Conversely, the remaining 103 patients (32.7%) with CK-MB $\geq 5 \times$ ULN did not have cTn $\geq 35 \times$ ULN, and 390 patients (64.8%) who had cTn $\geq 35 \times$ ULN did not have CK-MB $\geq 5 \times$ ULN.

BIOMARKER ELEVATION AND MORTALITY. A total of 259 patients (1.9%) died within the first year following index PCI; in Table 4, rates of death are presented for each of the following categories: CK-MB $\geq 5 \times$ ULN or $\geq 10 \times$ ULN and cTn $\geq 35 \times$ ULN or $\geq 70 \times$ ULN and combinations thereof. Kaplan-Meier curves were created to compare groups as follows: CK-MB $<5 \times$ ULN versus $\geq 5 \times$ ULN and cTn $<35 \times$ ULN versus $\geq 35 \times$ ULN (Figure 2, Central Illustration). For the lower biomarker thresholds, patients who had both CK-MB $\geq 5 \times$ ULN and cTn $\geq 35 \times$ ULN had significantly increased mortality compared with their counterparts (Figure 2A). For the higher biomarker thresholds, patients with CK-MB $\geq 10 \times$ ULN (irrespective of cTn ratio) had significantly increased mortality compared with those with CK-MB $<10 \times$ ULN (Figure 2B).

Several clinical variables were tested for their univariate associations with mortality (Table 5). The following had significant associations: age, prior MI, lesion complexity (when multiple lesions were treated, the worst lesion category was taken), prior coronary artery bypass grafting, diabetes mellitus, hyperlipidemia, number of stents implanted, and sex. In the Cox multivariate analysis of model A, in which CK-MB ≥ 10 ratio post-procedure was forced into the model, age, prior MI, lesion complexity, hyperlipidemia, diabetes mellitus, and CK-MB ratio post-procedure were associated with increased 1-year mortality. Furthermore, in the Cox multivariate analysis of model B, in which cTn ≥ 70 ratio

TABLE 2 Baseline Demographics and Clinical Characteristics (n = 13,452)

Age, yrs	
Mean ± SD	64.2 ± 10.6
Range	24-95
Median (IQR)	65.0 (57-72)
Male, %	72.7
BMI, kg/m ²	
Mean ± SD	28.7 ± 4.8
Range	12.7-45.0
Median (IQR)	28.08 (25.4-31.5)
Diabetes mellitus, %	31.3
Hypertension, %	73.6
Hypercholesterolemia, %	72.6
Current smoker, %	20.9
Congestive heart failure, %	6.5
Peripheral arterial disease, %	6.0
Previous MI, %	29.3
Previous PCI, %	30.7
Previous stroke, %	6.5
Previous CABG, %	15.6
GFR, ml/min/1.73 m ²	
Mean ± SD	79.3 ± 21.5
Median (IQR)	79.59 (64.5-95.6)
Chronic renal failure, %	3.9
Renal dialysis, %	1.3
LM, %	2.0
LAD, %	48.5
LCx, %	28.5
RCA, %	35.5
SVG, %	4.6
Lesion complexity (worst)	
A, %	10.6
B1, %	30.0
B2, %	30.6
C, %	28.7
Maximum stenosis pre-procedure	
Mean ± SD	81.3 ± 14.5
Range	3-100
Median (IQR)	82.0 (70-91)
Diseased vessels (>50% DS)	
Mean ± SD	1.1 ± 0.4
Range	1-4
Median (IQR)	1.0 (1-1)
1-vessel disease, %	78.0
2-vessel disease, %	17.8
3-vessel disease, %	4.0
4-vessel disease, %	0.2
Multivessel PCI, %	19.0
Bifurcation lesion, %	16.9

Continued in the next column

TABLE 2 Continued

Number of stents	
Mean ± SD	1.7 ± 1.0
Range	1-8
Median (IQR)	1.0 (1-2)
Total stent length, mm	
Mean ± SD	31.3 ± 21.6
Median (IQR)	24.0 (16-40)
Average stent diameter, mm	
Mean ± SD	2.97 ± 0.39
Median (IQR)	3.0 (2.75-3.25)
Rotational atherectomy, %	2.5
Cutting balloon, %	5.1
Direct stenting, %	33.3
Pre-dilation, %	72.3
Drug-eluting stent, %	96.5
Bare-metal stent, %	10.7
LV ejection fraction, %	
Mean ± SD	60.4 ± 12.6
Median (IQR)	60.0 (55-69)

Values are mean ± SD, %, median (interquartile range), unless otherwise stated.
 BMI = body mass index; CABG = coronary artery bypass graft; DS = diameter stenosis; GFR = glomerular filtration rate; IQR = interquartile range; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LM = left main coronary artery; LV = left ventricular; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery; SVG = saphenous vein graft.

DISCUSSION

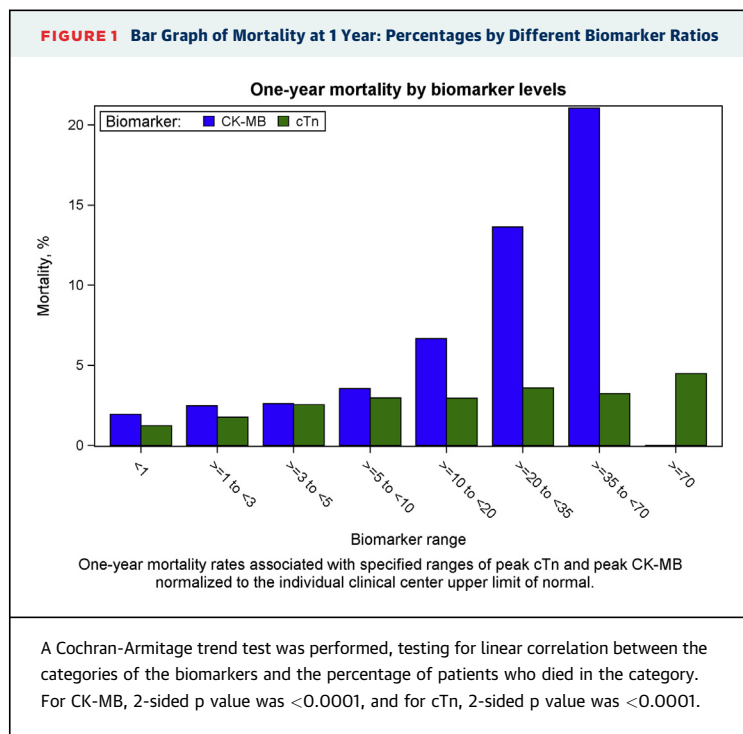
Our results show that, with second generation DES, CK-MB and/or cTn elevation frequently occurred after elective PCI in patients in stable condition; the overall percentage of patients with elevated biomarkers following PCI was 23.9% for CK-MB and 68.4% for cTn. A total of 259 patients (1.9%) died at 1 year; 20 (7.7%) had CK-MB ≥ 5 × ULN, and 23 (8.8%) had cTn ≥ 35 × ULN. In the Cox multivariate analysis, in which the cTn and CK-MB ratios post-procedure were forced into the model, age, prior

TABLE 3 Frequency of Creatine Kinase-Myocardial Band and Cardiac Troponin Elevations at Different Ratios

Threshold	Percentage of Patients With CK-MB Above Threshold	Percentage of Patients With cTn Above Threshold
≥ 1 × ULN	23.94	68.43
≥ 2 × ULN	10.76	38.87
≥ 3 × ULN	6.43	31.22
≥ 5 × ULN	3.16	23.67
≥ 10 × ULN	1.30	15.27
≥ 35 × ULN	0.24	6.10
≥ 70 × ULN	0.03	2.93

CK-MB = creatine kinase-myocardial band; cTn = cardiac troponin; ULN = upper limit of normal.

post-procedure was forced into the model, age, prior MI, lesion complexity, hyperlipidemia, and diabetes mellitus were associated with increased 1-year mortality. Of note, cTn ratio was not an independent predictor of mortality in this model (Table 6).



MI, lesion complexity, hyperlipidemia, and CK-MB ratio ($\geq 10 \times \text{ULN}$; model A) post-procedure were associated with increased 1-year mortality.

We found that elevations of CK-MB ($\geq 10 \times \text{ULN}$) were associated with increased 1-year mortality. However, cTn elevations were not associated with increased mortality. Although any single threshold value of CK-MB is an arbitrary choice that represents a trade-off between sensitivity and specificity in predicting subsequent mortality, such thresholds are nonetheless important because they are frequently used as endpoints for clinical trials of both

cardiovascular drugs and devices (12). However, cTn has become the cardiac biomarker of choice in the acute setting and has largely replaced CK-MB in all settings, such as periprocedural, in most clinical sites around the world. CK-MB is often no longer available as a routine clinical chemistry test at many institutions. As a result, cTn has or will become the default biomarker to assess periprocedural myocardial injury, except when core laboratory collection and testing of assays is implemented, a measure that is often costly and impractical. In the ABSORB II [A Clinical Evaluation to Compare the Safety, Efficacy, and Performance of Absorb Everolimus Eluting Bioresorbable Vascular Scaffold System Against XIENCE Everolimus Eluting Coronary Stent System in the Treatment of Subjects With Ischemic Heart Disease Caused by De Novo Native Coronary Artery Lesions] study (501 patients), 3 types of cardiac biomarkers (creatinine kinase, CK-MB, and cTn) were obtained and analyzed in central core laboratory (13). In the XIENCE arm, 4% of patients had CK-MB $>5 \times \text{ULN}$, and 1% had CK-MB $>10 \times \text{ULN}$; in this report, the corresponding percentages were 3.16% and 1.3%, respectively. Conversely, in the XIENCE arm, 6% of patients had cTn $>35 \times \text{ULN}$, and 2% had cTn $>70 \times \text{ULN}$; in this report, the corresponding percentages were 6.10% and 2.93% respectively. Overall, these values, derived from a central reference biomarker core laboratory or based on site-reported biomarker values, are remarkably consistent in the contemporary DES era.

When biomarker ratios are categorized into different classes, as shown in Figure 1, it is apparent that the association of CK-MB and mortality increases considerably when the ratio is ≥ 5 to $10 \times \text{ULN}$ and above this level. Conversely, a similar gradient of risk does not appear to exist for cTn, as the mortality rate does not increase irrespective of the degree of cTn elevation. More important, CK-MB elevation, but not cTn, was an independent predictor of mortality when adjusted for other confounding factors.

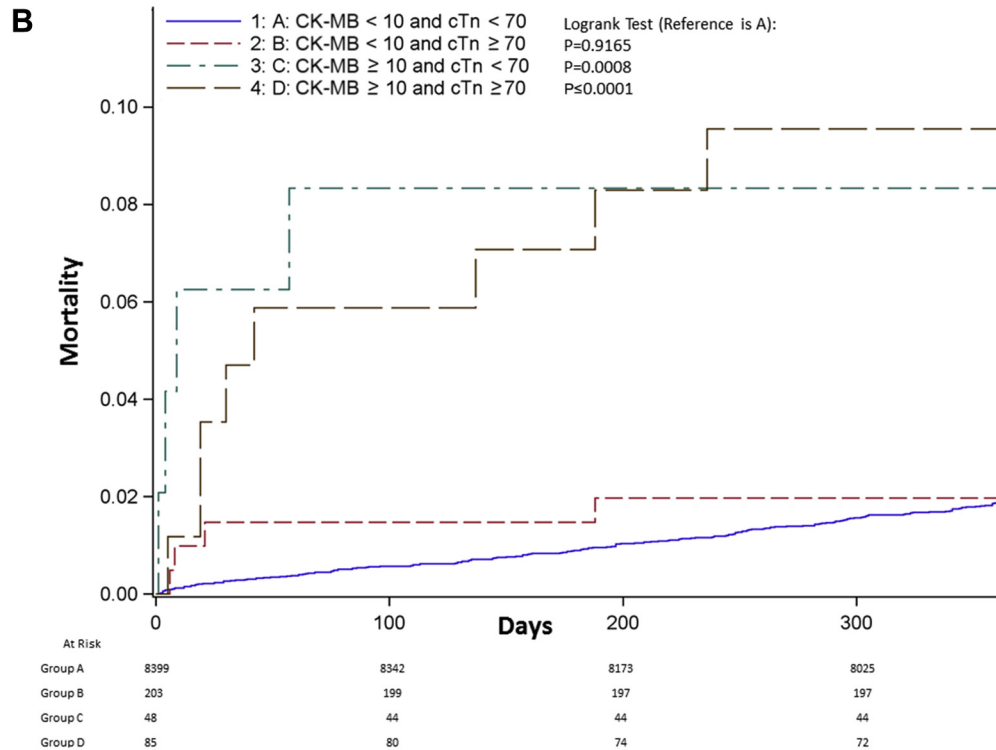
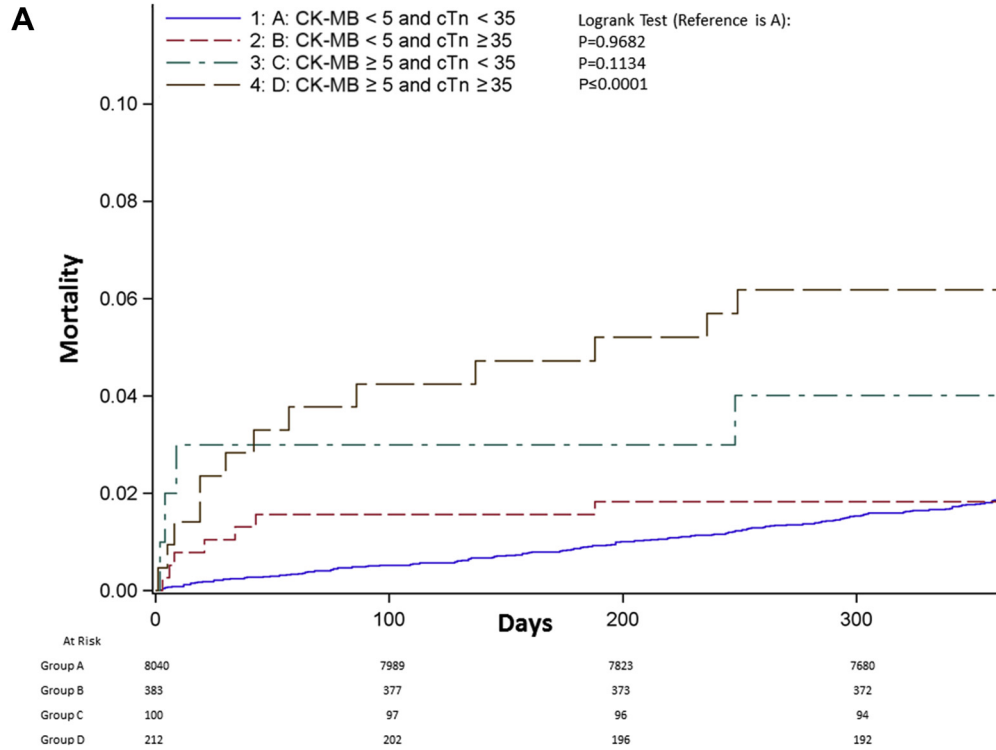
COMPARISON WITH PREVIOUS STUDIES. Although numerous previous studies have reported an association between elevated levels of CK-MB after PCI and long-term mortality, only a few have attempted to define a threshold for a clinically relevant periprocedural MI. In a meta-analysis of 7 studies evaluating the prognostic relevance of CK-MB elevation after PCI, Ioannidis et al. (14) found that there was a stepwise increase in the risk for death with increasing CK-MB levels, with the greatest risk for death among those with CK-MB $\geq 5 \times \text{ULN}$. These results are in line with our findings. In the Kaplan-Meier analysis showing the mortality rate in patients with CK-MB $\geq 5 \times \text{ULN}$ and their counterparts, there was a

TABLE 4 1-Year Mortality Rates by Different Combinations of Peak cTn and Peak CK-MB

Biomarker Group	No Death Within 1 Yr Post-Procedure
Panel A (Figure 2)	
CK-MB $<5 \times \text{ULN}$ and cTn $<35 \times \text{ULN}$	150/8,004 (1.9)
CK-MB $<5 \times \text{ULN}$ and cTn $\geq 35 \times \text{ULN}$	7/383 (1.8)
CK-MB $\geq 5 \times \text{ULN}$ and cTn $<35 \times \text{ULN}$	4/99 (4.0)
CK-MB $\geq 5 \times \text{ULN}$ and cTn $\geq 35 \times \text{ULN}$	13/199 (6.5)
Panel B (Figure 2)	
CK-MB $<10 \times \text{ULN}$ and cTn $<70 \times \text{ULN}$	158/8,362 (1.9)
CK-MB $<10 \times \text{ULN}$ and cTn $\geq 70 \times \text{ULN}$	4/202 (2.0)
CK-MB $\geq 10 \times \text{ULN}$ and cTn $<70 \times \text{ULN}$	4/44 (9.1)
CK-MB $\geq 10 \times \text{ULN}$ and cTn $\geq 70 \times \text{ULN}$	8/77 (10.4)

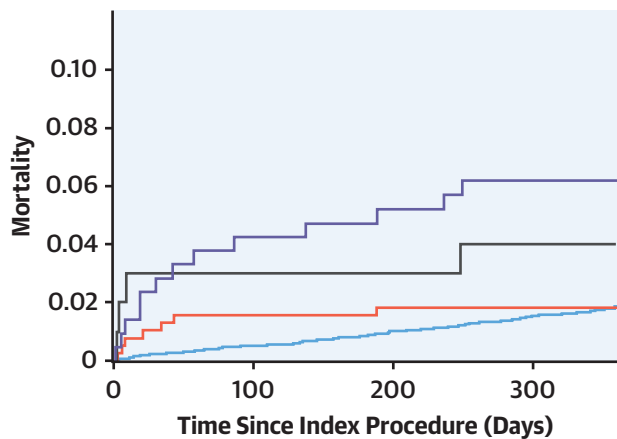
Values are n/N (%).
Abbreviations as in Table 3.

FIGURE 2 1-Year Kaplan-Meier Curves: Mortality by Creatine Kinase-Myocardial Band and Cardiac Troponin Ratios

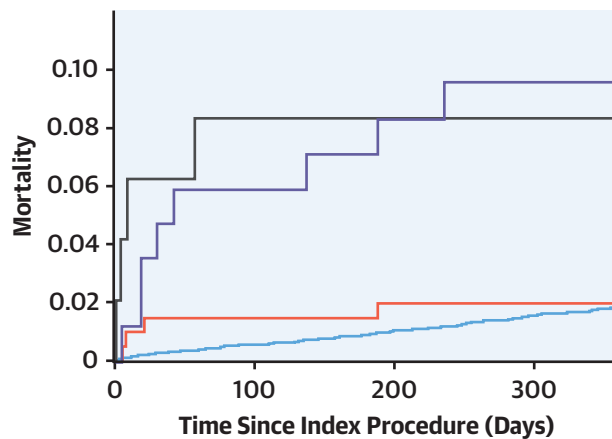


(A) Low thresholds. (B) High thresholds.

CENTRAL ILLUSTRATION Periprocedural PCI Biomarker Elevation Have a Significant Association With Hard Clinical Outcomes When They Reflect Substantial Loss of Myocardium



— A: CK-MB <5 and cTn <35 Log-rank Test (Reference is A):
 — B: CK-MB <5 and cTn ≥35 p = 0.9682
 — C: CK-MB ≥5 and cTn <35 p = 0.1134
 — D: CK-MB ≥5 and cTn ≥35 p ≤ 0.0001



— A: CK-MB <10 and cTn <70 Log-rank Test (Reference is A):
 — B: CK-MB <10 and cTn ≥70 p = 0.9165
 — C: CK-MB ≥10 and cTn <70 p = 0.0008
 — D: CK-MB ≥10 and cTn ≥70 p ≤ 0.0001

Garcia-Garcia, H.M. et al. J Am Coll Cardiol Interv. 2019;12(19):1954-62.

CK-MB = creatine kinase-myocardial band; cTn = cardiac troponin; PCI = percutaneous coronary intervention.

statistically significant difference between the 2 groups. Even in the bare-metal stent era, Stone et al. (15) found that only CK-MB elevations $\geq 5 \times$ ULN were independently associated with increased 2-year mortality.

A threshold post-PCI level of cTn above which long-term prognosis is affected has been suggested in prior studies (16). This threshold, however, was derived from a regression spline model in which the relationship between troponin and 1-year mortality was

TABLE 5 Univariable Predictors of 1-Year Mortality

	Parameter Estimate	p Value	Hazard Ratio	95% Lower Confidence Limit for Hazard Ratio	95% Upper Confidence Limit for Hazard Ratio
Age	0.06977	<0.0001	1.072	1.058	1.086
Prior MI	0.54003	<0.0001	1.716	1.337	2.202
Lesion complexity (worst)	0.24902	0.0003	1.283	1.122	1.467
Prior CABG	0.50646	0.0006	1.659	1.243	2.215
Diabetes mellitus	0.38720	0.0023	1.473	1.148	1.890
Male	-0.37568	0.0039	0.687	0.532	0.886
Total number of stents implanted per patient	0.11716	0.0326	1.124	1.010	1.252
Hyperlipidemia	-0.28090	0.0343	0.755	0.582	0.979
Hypertension	0.22658	0.1285	1.254	0.937	1.680
Prior percutaneous coronary revascularization	0.15735	0.2323	1.170	0.904	1.515
Total stent length per patient (mm)	0.00107	0.7121	1.001	0.995	1.007
Current smoker	0.04930	0.7457	1.051	0.780	1.415
Maximum stenosis (pre)	-0.00121	0.7850	0.999	0.990	1.007

Abbreviations as in Table 2.

TABLE 6 Multivariate Predictors of 1-Year Mortality

	Parameter Estimate	p Value	Hazard Ratio	95% Lower Confidence Limit for Hazard Ratio	95% Upper Confidence Limit for Hazard Ratio
Model A: CK-MB ratio $\geq 10 \times$ ULN					
Age	0.06813	<0.0001	1.071	1.055	1.086
Prior MI	0.58582	<0.0001	1.796	1.362	2.370
Lesion complexity, worst	0.24978	0.0029	1.292	1.092	1.530
CK-MB ratio $\geq 10 \times$ ULN	1.23250	0.0002	3.430	1.814	6.486
Hyperlipidemia	-0.33671	0.0237	0.714	0.533	0.956
Diabetes mellitus	0.29252	0.0410	1.340	1.012	1.774
Model B: cTn ratio $\geq 70 \times$ ULN					
Age	0.06333	<0.0001	1.06	1.05	1.08
Prior MI	0.66596	<0.0001	1.95	1.44	2.63
Lesion complexity, worst	0.24363	0.0024	1.28	1.09	1.49
Hyperlipidemia	-0.42146	0.0084	0.66	0.48	0.90
Diabetes mellitus	0.38059	0.0130	1.46	1.08	1.97
Prior CABG	0.30039	0.0963	1.35	0.95	1.92
cTn ratio $\geq 70 \times$ ULN	0.48707	0.1198	1.628	0.88	3.0
Male	-0.24611	0.1214	0.78	0.57	1.07

Abbreviations as in Tables 2 and 3.

depicted. The hazard of mortality increased from 1.02 at 3-fold to 1.67 at 20-fold troponin elevation. Although in this report, cTn $\geq 70 \times$ ULN in the Kaplan-Meier curve was associated with an increase in mortality, in the multivariate analysis, cTn elevation was not associated independently with increase in mortality.

Our findings thus extend these previous observations. Moreover, these previous studies were performed largely in an era when the dominant forms of PCI were balloon angioplasty and atheroablation, anticoagulation was achieved predominantly using unfractionated heparin, and use of aggressive and prolonged oral and parenteral antiplatelet therapy were uncommon. The present study thus demonstrates that despite substantial changes in PCI technology and pharmacology—with a resulting shift in the mechanism of ischemic complications from dissection and abrupt vessel closure to microembolization and side branch occlusion—only large periprocedural infarcts are unequivocally associated with an increase in long-term mortality.

However, cTn has replaced or will replace CK-MB as the preferred marker of myocardial injury, for well-documented reasons. The increased sensitivity of cTn may allow better differentiation among devices in clinical trials. For example, scaffolds with thicker struts may result in greater elevations in a sensitive biomarker, reflecting more marked effects on small side branches. To date there is no evidence that such differences will have any effect on clinical outcomes.

Many studies have shown that pre-procedural cTn elevations are associated with a worse prognosis. This has been shown diverse settings such as apparently

healthy subjects, patients with chronic pulmonary disease, and patients with sepsis. Tricoci et al. (17) investigated whether a threshold elevation of cTn in the periprocedural setting, in conjunction with pre-defined ancillary criteria such as those proposed by the universal definition of MI in 2012, was associated with mortality. They also included same analysis by using the SCAI definition. The rates of PCI-related MI criteria were 2.0% by the third universal definition and 1.2% by the SCAI criteria. One-year mortality was 3.3% with the third universal definition (hazard ratio: 1.96; 95% confidence interval: 1.24 to 3.10) and 5.3% with the SCAI criteria (hazard ratio: 2.79; 95% confidence interval: 1.69 to 4.58; $p < 0.001$). In the present study, we do not have the ancillary criteria to obtain the rates of PCI-related MI criteria by the third universal definition; we have, however, included the SCAI definition using the CK-MB $>10 \times$ ULN threshold; in this study, the mortality rate in patients with CK-MB $>10 \times$ ULN was much higher, 9.1% in patients with cTn $<70 \times$ ULN and 10.4% in those with cTn $>70 \times$ ULN. This large difference in mortality rate may be due to the difference in the studied populations.

STUDY LIMITATIONS. First, despite the large number of patients included, the number of deaths was small. Second, it may be that troponin elevations affect nonfatal clinical complications, which may be important. Third, we cannot exclude that a higher cTn threshold of $70 \times$ ULN or more would be predictive. Fourth, cTn cutoff values and assay types are site specific. This information was not systematically collected and therefore not available for inclusion in

this report. Last, only biomarker data are available, not clinical (i.e., chest pain post-PCI, etc.) and angiographic (i.e., side branch occlusion, etc.) data, which are also known to be prognostic.

CONCLUSIONS

Following elective PCI in patients in stable condition treated with second-generation DES, CK-MB and cTn elevations remain common. Although mortality was increased with even small elevations of CK-MB after PCI, only elevations $\geq 10 \times$ ULN were associated with increased 1-year mortality in our categorical analyses. In contrast, cTn elevation was not independently associated with mortality at 1 year.

ADDRESS FOR CORRESPONDENCE: Dr. Hector M. Garcia-Garcia, Division of Interventional Cardiology, MedStar Washington Hospital Center, 110 Irving Street, NW, Washington, DC 20010. E-mail: hector.m.garciagarcia@medstar.net.

PERSPECTIVES

WHAT IS KNOWN? Periprocedural events have a significant association with hard clinical outcomes when they reflect substantial loss of myocardium.

WHAT IS NEW? In the Cox multivariate analysis, in which cTn and CK-MB ratios post-procedure were forced into the model, age, prior MI, lesion complexity, hyperlipidemia, and CK-MB ratio ($\geq 10 \times$ ULN) post-procedure were associated with increased 1-year mortality.

WHAT IS NEXT? However, cTn has replaced or will replace CK-MB as the preferred marker of myocardial injury, for well-documented reasons. The increased sensitivity of cTn may allow better differentiation among devices in clinical practice; its threshold is yet unknown.

REFERENCES

- Byrne RA, Serruys PW, Baumbach A, et al. Report of a European Society of Cardiology-European Association of Percutaneous Cardiovascular Interventions task force on the evaluation of coronary stents in Europe: executive summary. *Eur Heart J* 2015;36:2608-20.
- White H. Avatar of the universal definition of periprocedural myocardial infarction. *J Am Coll Cardiol* 2013;62:1571-4.
- Prasad A, Herrmann J. Myocardial infarction due to percutaneous coronary intervention. *N Engl J Med* 2011;364:453-64.
- Moussa ID, Klein LW, Shah B, et al. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization. *J Am Coll Cardiol* 2013;62:1563-70.
- Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2019;40:237-69.
- Windecker S, Serruys PW, Wandel S, et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet* 2008;372:1163-73.
- von Birgelen C, Basalus MWZ, Tandjung K, et al. A randomized controlled trial in second-generation zotarolimus-eluting resolute stents versus everolimus-eluting XIENCE V stents in real-world patients. *J Am Coll Cardiol* 2012;59:1350-61.
- von Birgelen C, Sen H, Lam MK, et al. Third-generation zotarolimus-eluting and everolimus-eluting stents in all-comer patients requiring a percutaneous coronary intervention (DUTCH PEERS): a randomised, single-blind, multicentre, non-inferiority trial. *Lancet* 2014;383:413-23.
- Serruys PW, Silber S, Garg S, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *N Engl J Med* 2010;363:136-46.
- Camenzind E, Wijns W, Mauri L, et al. Stent thrombosis and major clinical events at 3 years after zotarolimus-eluting or sirolimus-eluting coronary stent implantation: a randomised, multicentre, open-label, controlled trial. *Lancet* 2012;380:1396-405.
- Lindsey JB, Marso SP, Pencina M, et al. Prognostic impact of periprocedural bleeding and myocardial infarction after percutaneous coronary intervention in unselected patients. *J Am Coll Cardiol Intv* 2009;2:1074-82.
- Garcia-Garcia HM, McFadden EP, Farb A, et al. Standardized end point definitions for coronary intervention trials. *Eur Heart J* 2018;39:2192-207.
- Ishibashi Y, Muramatsu T, Nakatani S, et al. Incidence and potential mechanism(s) of post-procedural rise of cardiac biomarker in patients with coronary artery narrowing after implantation of an everolimus-eluting bioresorbable vascular scaffold or everolimus-eluting metallic stent. *J Am Coll Cardiol Intv* 2015;8:1053-63.
- Ioannidis JPA, Karvouni E, Katritsis DG. Mortality risk conferred by small elevations of creatine kinase-MB isoenzyme after percutaneous coronary intervention. *J Am Coll Cardiol* 2003;42:1406-11.
- Stone GW, Mehran R, Dangas G, Lansky AJ, Kornowski R, Leon MB. Differential impact on survival of electrocardiographic Q-wave versus enzymatic myocardial infarction after percutaneous intervention: a device-specific analysis of 7147 patients. *Circulation* 2001;104:642-7.
- Novack V. Troponin criteria for myocardial infarction after percutaneous coronary intervention. *Arch Intern Med* 2012;172:502.
- Tricoci P, Newby LK, Clare RM, et al. Prognostic and practical validation of current definitions of myocardial infarction associated with percutaneous coronary intervention. *J Am Coll Cardiol Intv* 2018;11:856-64.

KEY WORDS cardiac troponin, CK-MB, drug-eluting stent, percutaneous coronary intervention, mortality