Definitions of Periprocedural Myocardial Infarction as Surrogates for Catheterization Laboratory Quality or Clinical Trial End Points

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A consensus on what constitutes a clinically meaningful periprocedural myocardial infarction (PMI) remains highly debated. We evaluated the accuracy of 2 PMI definitions currently implemented for quality outcome assessment and clinical trial end points. Patients who underwent elective percutaneous coronary intervention with normal baseline troponin-I and creatine kinase-MB were included. PMI was defined according to either the 2007 Task Force (National Cardiovascular Database Registry [NCDR] CathPCI Registry) definition or the updated 2012 Task Force definition. Multivariate analysis was performed for the end point of 1-year all-cause death or myocardial infarction (MI). Of the 7,333 patients included, 31.9% and 2.1% were identified as having a PMI by NCDR or 2012 definition, respectively. Mean age was 66 ± 11 years; 66.8% were men, 1.4 ± 0.9 stents implanted per patient, 84.5% bivalirudin use, and 29.7 type C lesions. Death or MI occurred in 5.6% of NCDR and 6.6% of 2012 defined patients. Neither biomarker was independently associated with death or MI for either definition (NCDR odds ratio 1.1, 95% confidence interval 0.9 to 1.5, p = 0.34; 2012 Task Force odds ratio 1.4, 95% confidence interval 0.7 to 3.0, p = 0.38). Only a modest correlation exists for either definition to predict death or MI, which did not improve for the 2012 definition. In conclusion, PMI definitions currently used for catheterization lab quality metrics and those used for clinical trial end points have poor discrimination for adverse events. Although the 2012 definition drastically reduced the number of PMIs defined, it did not decrease the predictive accuracy over the NCDR definition. **(Am J Cardiol 2014;113:1326−1330)**

Numerous studies have looked at the influence of creatine kinase-MB fraction (CK-MB) and cardiac troponin (cTn) elevation postpercutaneous coronary intervention (PCI) on subsequent mortality, as well as degree of elevation required for significance, with varying results.[1−5] Despite this well-published topic, a consensus on the clinical significance of periprocedural myocardial infarction (PMI) and how it should be reported in clinical trials remains highly debated. The incidence of PMI varies considerably based on the threshold of the biomarker used and can range from <5% to >30%.[2,6,7] The definition of what constitutes a PMI has been updated because it was first introduced in 2007.[8] Realizing the lack of correlation between PMI and clinical outcomes, along with the development of more sensitive cTn assays, the definition was updated by the Joint European Society of Cardiology (ESC), the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), and the World Heart Federation (WHF) Task Force in 2012.[9] Because catheterization laboratories are now graded on their performance and adherence to established guidelines and self-monitoring of periprocedure-related complications, it is important to understand how these recommendations are made and their applicability in clinical practice. The present analysis evaluates the accuracy of PMI definitions currently used by the National Cardiovascular Database Registry (NCDR) CathPCI Registry[1] and the 2012 Joint Task Force[2] to predict death or myocardial infarction (MI) at 1 year in a large, referral-based, tertiary care center. We also evaluated the optimal biomarker threshold at which PMI should be addressed.

Methods

From April 2003 to September 2012, 12,806 patients with normal baseline cardiac biomarkers underwent elective PCI at our institution. Of them, 7,330 had complete data for 1-year follow-up and were included. Patients with cardiogenic shock and those without available biomarkers 48 hours after the procedure were excluded. Clinical and demographic data were prospectively collected and patients underwent clinical follow-up for 12 months. Outcomes included all-cause death, defined as death from any cardiac or noncardiac cause, and MI, defined as an increment of CK-MB twice the upper limit of normal, along with symptoms and/or electrocardiographic changes suggestive of myocardial ischemia. Outcomes were evaluated based on the following prespecified definitions: (1) PMI as defined by the NCDR CathPCI Registry, which incorporates the 2007 Joint ESC/ACCF/AHA/WHF Task Force definition[8] of cTn or CK-MB fraction elevation values >3 × ninety-ninth percentile upper limit of normal and (2) PMI as defined by the updated 2012 Joint ESC/ACCF/AHA/WHF Task Force[9] as cTn or CK-MB >5 × ninety-ninth percentile upper limit of normal in addition to the presence of ischemic symptoms, new ischemic electrocardiographic changes, or angiographic

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Table 1
Baseline characteristics

Variable	Population (n = 7,330)
Age (yrs)	65.5 ± 10.9
Men	4,900 (67)
Body mass index (kg/m^2)	29.9 ± 6.3
European-American	5,037 (69)
Systemic hypertension*	6,368 (87)
Hypercholesterolemia‡	6,575 (90)
Diabetes mellitus	2,657 (37)
Smoker (any)	3,937 (54)
Previous MI	1,764 (25)
Previous coronary artery bypass graft surgery	1,563 (21)
Previous PCI	2,374 (34)
History of chronic renal insufficiency†	884 (12)
History of congestive heart failure	834 (12)
Left ventricular ejection fraction	50 ± 14
Asymptomatic at admission	3,719 (51)
Canadian cardiovascular society score III or IV	2,676 (39)
Baseline CK-MB	0.9 ± 2.52
Baseline troponin I	0.02 ± 0.03

Data are presented as mean ± SD or n (%); percentages have been rounded.

* History of systemic hypertension diagnosed and/or treated with medication or currently being treated with diet and/or medication by a physician.

† Chronic renal insufficiency; defined as creatine clearance <60 ml/min.

‡ Included patients with a previously documented diagnosis of hypercholesterolemia; the patient might be treated with diet or medication; a new diagnosis can be made during this hospitalization with elevated total cholesterol >160 mg/dl; did not include elevated triglycerides.

Table 2
Procedural and periprocedural characteristics

Variable	Population (n = 7,330)
Heparin	796 (11)
Bivalirudin	6,195 (85)
Glycoprotein IIb/IIIa inhibitors	358 (5)
Length of stay (days)	2 ± 2.5
Troponin I maximum	1.6 ± 15.61
CK-MB maximum	2.9 ± 11.27
Variable (lesion based)	
No. of lesions	12, 068
Target coronary vessel	
Left main	221 (2)
Left anterior descending	4,522 (38)
Left circumflex	2,832 (24)
Right	3,769 (31)
Saphenous vein graft	663 (6)
Procedural characteristics	
Angiographic success	11,776 (98)
Rotational atherectomy	424 (4)
Cutting balloon angioplasty	759 (6)
Direct stenting	2,639 (36)
Predilation	3,790 (34)
Type C lesion	3,467 (30)
Dissection	57 (0.5)
No reflow	21 (0.2)
Stents implanted per patient	1.4 ± 0.9
Total stent length (mm)	19.6 ± 6.7
Stent diameter (mm)	3.1 ± 1.2
Drug-eluting stent	9,201 (78)
Bare-metal stent	1,711 (15)

Data are presented as n (%) and mean ± SD.

findings consistent with procedural complication. Cardiac biomarkers were available on all patients and were measured for baseline before the procedure at 6 to 8 and 12 to 24 hours after the procedure, and thereafter if still increasing. Our institution currently utilizes a highly sensitive fourth-generation troponin I (Dimension Vista, Siemens Healthcare Diagnostics Inc., Newark, Delaware) with a value of >0.045 ng/ml indicative of myocardial necrosis. This corresponds to a 10% coefficient of variation at a troponin I concentration of <0.04 ng/ml. The upper limit of normal for the CK-MB immunoassay used in our laboratory is 3.6 ng/ml. Temporal changes in the troponin assay sensitivities and the ninety-ninth percentile upper limit of normal were standardized for evaluation.

Data were collected by trained research personnel by way of chart review. Data were subsequently entered into the registry by dedicated data center personnel. Neither data collection personnel nor data entry personnel was aware of the study's objective. One-year outcomes were available on all patients and assessed by electronic health records as well as mail or telephone contact with patients or their physician. The basis for each clinical event was adjudicated by independent physicians not involved in the clinical procedure. All patients provided written, informed consent for PCI, and the institutional review board at MedStar Washington Hospital Center approved the study.

PCI was performed according to the standard clinical practice, whereas interventional strategy and choice of pharmacologic therapy were at the discretion of the operator. All patients were pretreated with aspirin 325 mg and received a 300- or 600-mg dose of clopidogrel, 60 mg of prasugrel, or 180 mg of ticagrelor before PCI. Choice of anticoagulant was based on the operator's preference as dictated by the clinical scenario. When bivalirudin was used, an initial bolus of 0.75 mg/kg followed by an intravenous infusion of 1.75 mg/kg/hour was administered. For unfractionated heparin, a bolus of 40 U/kg was administered with subsequent bolus dosing to achieve an activated clotting time of >250 seconds. Glycoprotein IIb/IIIa inhibitors were also administered at the physician's discretion according to the guidelines. Angiographic success was defined as postprocedural stenosis <30% and thrombolysis in MI flow grade 3.

Categorical variables are presented as frequencies and continuous variables as mean ± SDs. Variables found to correlate with the 1-year outcomes of death or MI on univariate analysis include age, diabetes mellitus, chronic kidney disease, history of coronary artery bypass grafting, history of PCI, type C lesion, glycoprotein IIb/IIIa inhibitor, number of implanted stents, rotational atherectomy, predilation, and saphenous vein graft intervention. Troponin I and CK-MB were also included in the model as continuous variables. Logistic regression was subsequently performed to identify independent predictors of the primary outcome. The results are presented as adjusted odds ratios with their 95% confidence interval and p values. Receiver operating characteristic curves were generated to assess the accuracy of the two definitions in predicting the primary outcome, as well as to assess for an optimal biomarker threshold for