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EDITORIAL COMMENT

The Devil Is Always in the Details*

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Myocardial infarction (MI) is a commonly used endpoint in clinical trials evaluating the efficacy and safety of cardiovascular drugs and devices. Periprocedural MIs (PMIs), also known as type 4a MIs, contribute to the MI endpoint and can account for a substantial number of events. In the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38) study, for example, approximately 40% of MIs occurred periprocedurally (1). How a PMI is defined influences the number of MI events that may be adjudicated by a clinical events committee (CEC).

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In this issue of *JACC: Cardiovascular Interventions*, Spitzer et al. (2) develop algorithms to identify PMI events in the RAC (RESOLUTE All-Comers) trial using 3 definitions currently used in percutaneous coronary intervention trials and demonstrate that PMI definitions and the criteria used to identify PMI events (i.e., event triggers) are not interchangeable.

The RAC trial was a prospective, multicenter, randomized, noninferiority trial comparing the Medtronic Resolute Zotarolimus-Eluting Coronary Stent System (Medtronic, Minneapolis, Minnesota) with the Abbott XIENCE V Everolimus-Eluting Coronary Stent System (Abbott Vascular, Santa Clara, California) in 2,292 subjects at 17 Western European sites. The primary endpoint was target lesion failure, defined as a composite of cardiac death, MI not clearly attributable to a nontarget vessel, and clinically indicated target lesion revascularization at 12 months (3). Follow-up occurred out to 5 years. According to the instructions for use, "data from the RAC trial were used to support the pre-market approval (PMA) of the Resolute Integrity stent" (4).

The 3 definitions used for the PMI algorithms were: 1) the World Health Organization extended definition (WHO-ED); 2) the 2012 third universal definition of MI (TUD) of the Joint European Society of Cardiology, American College of Cardiology, American Heart Association, and World Health Federation Task Force for the Universal Definition of Myocardial Infarction; and 3) the Society for Cardiovascular Angiography and Interventions (SCAI) definition of clinically relevant MI after coronary revascularization (5-7). **Table 1** summarizes these definitions and their criteria. The WHO-ED was developed out of necessity during CEC adjudication of the RAC trial when, after 70% of the patients were recruited, it "became evident that CK [creatine kinase] and CK-MB, the study criteria for MI," were not available "in a sizeable proportion of patients because of biomarker collection compliance issues" (8). The WHO-ED was thus created to allow PMI adjudication even when biomarker data are incomplete and to allow a bridge to the historical control data from the Medtronic ENDEAVOR clinical program (which used CK and CK-MB) (5).

As Spitzer et al. (2) note, these definitions are fundamentally different, with distinct preferred biomarkers (CK, CK-MB, cardiac troponin), thresholds (>2, >3, >5, and >10 times the upper limit of normal), and different clinical, electrocardiographic (ECG), imaging, and angiographic criteria required to define PMI. Given these differences, it is not surprising that the number of PMI events for any given dataset varies with these definitions.

The investigators identify 5 triggers (i.e., on the basis of investigator reports, monitor findings, electronic case report forms, ECG and angiographic core laboratory findings, and CEC reviews) to detect potential PMI events. These triggers generally led to

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TABLE 1 Differences Among the World Health Organization Extended Definition, the Universal Definition of Type 4a Myocardial Infarction, and the Society for Cardiovascular Angiography and Interventions Definition

Criteria	WHO Extended Definition	Universal Definition	SCAI Definition
Symptoms of ischemia	>20 min	≥20 min	–
Choice of biomarker	CK, CK-MB, and troponin	Troponin	CK-MB
Baseline biomarkers	• Normal (and no acute MI in progress) • Stable or falling • Elevated biomarkers and acute MI in progress (i.e., biomarkers continue to rise)	• ≤99th percentile URL (normal); and • Stable or falling Note: "If a single baseline cTn value is elevated, it is impossible to determine whether further increases are due to the procedure or to the initial process causing the elevation" (8).	• Normal baseline CK-MB (or baseline cTn) • Elevated CK-MB (or cTn) in whom biomarker levels are stable or falling • Elevated CK-MB (or cTn) in whom biomarker levels have not been shown to be stable or falling (i.e., biomarkers continue to rise)
Timing of biomarker measurement	Is there >1 measurement of the same biomarker post-PCI (within 48 h)?	Before procedure, repeated 3–6 h later, and optionally, further remeasurement 12 h thereafter	Ideally twice within 24 h, then 8–12 h if no symptoms or angiographic complications and **not necessary** if ECG is normal at 1–4 h
Biomarker elevation	**PCI** **Baseline biomarkers of myocardial damage (CK and CK-MB and troponin <1 × URL) and no acute MI in progress (periprocedural <48 h post-PCI):** • New pathologic Q waves in ≥2 contiguous ECG leads AND ○ Any CK-MB >1 × URL ***or*** ○ In the absence of CK-MB: troponin >1 × URL ***or*** ○ In the absence of CK-MB and troponin: CK >1 × URL ***or*** ○ In the absence of CK-MB and troponin and CK: CEC decision upon clinical scenario • Appropriate cardiac enzyme data: ○ CK ≥2 × URL confirmed by: ▪ CK-MB >1 × URL ***or*** ▪ In the absence of CK-MB, troponin >1 × URL ***or*** ▪ In the absence of CK-MB and troponin: CEC decision upon clinical scenario **OR** ▪ In the absence of CK: CK-MB >3 × URL **OR** ▪ In the absence of CK and CK-MB: troponin >3 × URL **In patients with baseline biomarkers of myocardial damage: CK and/or CK-MB >1 × URL or acute MI in progress (MI, reinfarction [extension] <48 h post-PCI):** • If CK (or CK-MB) from index MI has not yet reached its maximal level: ○ Recurrent thoracic chest pain or ischemia equivalent >20 min (or new ECG changes consistent with MI) **AND** ○ Appropriate cardiac enzyme data: ▪ A rise in CK within 24 h of the index event >2 × URL (confirmed by either CK-MB or troponin >1 × URL) and ≥50% above the previous level ***or*** ▪ In absence of CK: a (post-PCI) rise in CK-MB within 24 h of the index event >3 × URL and ≥50% above the previous level ***or*** ▪ In absence of CK and CK-MB: a (post-PCI) rise of troponin within 24 h of the index event >3 × URL and ≥50% above the previous level	>5 × 99th percentile URL within 48 h if normal baseline or ≥20% if baseline elevated	In patients with normal baseline CK-MB (or if CK-MB measurements are absent and baseline cTn is normal): • Isolated CK-MB ≥10 × local laboratory ULN or troponin ≥70 × ULN within 48 h • If new Q waves or new LBBB, CK-MB ≥5 × ULN or troponin ≥35 × ULN If CK-MB (or cTn) level is elevated and stable or falling: • CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level If CK-MB (or cTn) level is elevated and continues to rise: • CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression (not defined) plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension (not defined)

(Continued on the next page)

TABLE 1 Continued

Criteria	WHO Extended Definition	Universal Definition	SCAI Definition
	• If elevated CK (or CK-MB) following the index MI has peaked **AND** CK level has returned <URL then any new rise in: ○ CK >2 × URL (confirmed by either CK-MB >URL or troponin >URL) ***or*** ○ In the absence of CK: CK-MB >3 × URL ***or*** ○ In the absence of CK and CK-MB, troponin >3 × URL • If CK (or CK-MB) following the index MI has peaked AND CK level has NOT returned <URL: ○ A rise in CK ≥50% above the previous level and >2 × URL confirmed by either CK-MB >URL or troponin >URL ***or*** ○ In absence of CK, when CK-MB has NOT returned <URL, a rise in CK-MB ≥50% above the previous level and >3 × URL ***or*** ○ In absence of CK, when CK-MB and troponin have not returned <URL, a rise in troponin ≥50% above the previous level and >3 × URL		
Associated features			
Ischemic ST-segment changes	• ST-T-wave changes • New Q waves • New LBBB	• New ST-segment elevation defined with sex cutoffs • New horizontal or down-sloping ST-segment depression ≥0.5 mm in 2 contiguous leads and/or T-wave inversion ≥1 mm in 2 contiguous leads with prominent R wave or R/S ratio >1 • New Q waves • New LBBB	• New ST-segment elevation or depression • New Q waves • New LBBB
Angiographic complications			
Embolization	No	Yes	No
Loss of patency of major artery or side branch	No	Yes	No
Persistent slow flow or no reflow	No	Yes	No
New regional wall motion abnormality	No	Yes	No
Imaging evidence of new loss of viable myocardium	No	Yes	No
Myocardial injury	–	• Biomarkers ≤5 × 99th percentile URL with associated features • >5 × 99th percentile URL in absence of ischemic, angiographic, or imaging findings	–
Myonecrosis without clinically relevant MI	–	–	Biomarkers less than cut points as above without Q waves, symptoms or signs of ischemia (not defined), or heart failure

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CEC = clinical events committee; CK = creatine kinase; CK-MB = creatine kinase–myocardial band; cTn = cardiac troponin; ECG = electrocardiographic; LBBB = left bundle branch block; MI = myocardial infarction; PCI = percutaneous coronary intervention; SCAI = Society for Cardiovascular Angiography and Interventions; ULN = upper limit of normal; URL = upper reference limit, defined as 99th percentile of normal reference range; WHO = World Health Organization.

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requests for additional source documents to create adjudication packets for the CEC to review.

The investigators also highlight the following 6 specific issues considered in developing the PMI algorithms: 1) the interchangeability of upper reference limit and upper limit of normal units; 2) whether the biomarkers were stable, rising, or falling and collection of biomarkers was incomplete; 3) presence of MI at baseline; 4) use of ECG data specifically for the WHO-ED and the SCAI definition and presuming that ECG changes were present when tracings were missing; 5) the hierarchical use of biomarkers; and 6) the presence or absence of MI at baseline when no cardiac biomarkers were available post-procedure. The resulting algorithms appear to represent the selected definitions adequately.

Of the 2,509 procedures included in this analysis, 382, 234, and 216 were associated with PMI triggers according to the TUD, the WHO-ED, and the SCAI definition, respectively. A total of 636 PMI triggers were identified, only 38 (6%) of which were common to all definitions; 478 unique triggers were also identified, including 240 (37.7%), 91 (14.3%), and 147 (23.1%) using the TUD, the WHO-ED, and the SCAI definition, respectively. Concordance between 2 definitions was highest between the TUD and WHO-ED (14.0%) but was similar between the TUD and the SCAI definition (2.4%) and between the WHO-ED and the SCAI definition (2.5%).

More importantly, additional analyses demonstrated that when clinical presentation and ECG data were unavailable, the number of triggers increased by 40% for all definitions combined, because these data caused some elevated biomarkers to no longer support PMI. Hence, missing data increase the number of triggers and potential PMI events. Similarly, an analysis using only the peak post-procedural value of a biomarker (instead of all post-procedural values) increased the number of triggers from 636 to 867, except for the SCAI definition, for which the number of triggers was similar (214 with peak value vs. 216 with all available values). In summary, when clinical presentation, ECG data, and all post-procedural cardiac biomarker data are available, the number of triggers for PMI decreases with all 3 definitions.

How the data are collected throughout a clinical trial is critical. Although the investigators suggest that "the SCAI definition may be preferred for large [randomized controlled trials] due to its simplicity and less costs involved, as well as in strategy trials comparing [percutaneous coronary intervention] versus [coronary artery bypass grafting]," we recommend a different approach. The U.S. Food and Drug Administration's Center for Drug Evaluation and Research generally uses the TUD but recognizes that collecting data to facilitate analyses (preferably pre-specified) with alternative MI definitions (such as that of SCAI) may be reasonable and can confirm consistency of signals.

In summary, MI is a commonly used endpoint in clinical trials. PMIs contribute to the MI endpoint and in some cases can account for a substantial fraction of the events. How a PMI is defined can influence the number of MI events that are adjudicated by the CEC. Although Spitzer et al. (2) demonstrate that the TUD, the WHO-ED, and the SCAI PMI definition and their event triggers are not interchangeable, more importantly, they demonstrate that missing data increase the number of triggers and potential number of PMI events for each of the definitions. We encourage early (before study initiation) interaction with the U.S. Food and Drug Administration to discuss the proposed trial and supporting documentation, because the devil is always in the details. We also recommend using the 2014 American College of Cardiology and American Heart Association's "Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials" for regulatory submissions that are based on work by the Standardized Data Collection for Cardiovascular Trials Initiative (10).

Rigorous collection of clinical, ECG, angiographic, imaging, and laboratory results may improve the correct identification of PMI.

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