Cardiac biomarkers of necrosis provide clinicians with important “messages” from the heart. They are released into the interstitium of the myocardium after loss of the integrity of cardiac myocyte membranes. The pattern of the rise and fall of an individual biomarker (ie, its release kinetics) depends on its intracellular location in the myocyte, molecular weight, and clearance from the interstitium of the myocardium and ultimately the circulation. Cardiac biomarkers play an integral role in the clinical diagnosis of myocardial infarction (MI). Referring to the spontaneous occurrence of MI in patients, the World Health Organization required that at least 2 of the following be present to fulfill the criteria for MI: a history of ischemia-type chest discomfort, evolutionary changes on serially obtained ECG tracings, and a rise and fall in serum cardiac markers.

Several dramatic advances have occurred in the biomarker component of the diagnosis of MI. Analytes with greater specificity for the myocardium were introduced into clinical medicine, with creatine kinase-MB replacing total creatine kinase and subsequently cardiac-specific troponins replacing creatine kinase-MB as the biomarker of choice for diagnosing MI. Assay technology improved as clinical chemists moved from enzymatic activity assays for CK to highly specific immunoassays that can detect progressively smaller concentrations of cardiac troponins in the peripheral circulation. Although ST-elevation MI (STEMI) is easily identified on the 12-lead ECG, we now recognize that many patients previously diagnosed with unstable angina are more properly diagnosed as having non–ST-elevation MI (NSTEMI) on the basis of the detection of elevated levels of cardiac troponins in their blood. Cardiac biomarkers are used as a rough guide to the extent of myocardial necrosis. The higher the peak biomarker level after STEMI, the larger the infarct and the higher the risks of complications and death. The higher the biomarker level is at presentation with NSTEMI, the worse the prognosis, but the therapeutic implications are not straightforward. Interpretation of the peak biomarker level is more complicated after reperfusion. In patients with STEMI, rapid washout of the biomarker from the interstitium causes a higher and earlier peak biomarker level (ie, many multiples above the upper reference limit), a useful noninvasive indicator of epicardial reperfusion. The same process probably occurs to some degree in patients with NSTEMI, but issues of the exact position on the release kinetics curve (ie, time from onset of NSTEMI to percutaneous coronary intervention [PCI]) vary much more than in STEMI, rendering interpretation of the pattern of biomarker levels more complicated.

It is also appreciated that MI can occur in a variety of settings. Some are readily recognized clinically (spontaneous MI related to plaque rupture); others are less cut clear (eg, sudden unexpected cardiac death before blood samples are obtained); and others occur in association with procedures on the coronary circulation (PCI, coronary artery bypass graft surgery). In the latest iteration of a universal definition of MI, a task force codified MI into 5 types (Table 1).

Type 4a, MI associated with PCI, has generated considerable controversy, not so much about whether the biomarker release truly reflects myocyte necrosis as about the mechanism and the prognostic implications. Discussions about MI after PCI are important not only to inform clinical practice but also to place the findings in proper perspective for the purposes of diagnostic coding, epidemiological considerations, insurance considerations, interpretation of clinical trials, and performance “scorecards.” The topic of scorecards often leads to emotionally charged arguments because of the potentially adverse consequences for operators if PCI in their hands is perceived as being associated with high rates of MI, an especially excoriating situation for operators who are willing to take on high-risk PCI procedures.

Let us begin with a few high points with regard to the state of play of a type 4a MI as assessed with cardiac-specific troponins:

1. Elevations of cardiac troponins occur more frequently than elevations of creatine kinase-MB after elective PCI. The pattern of release may be even more important than the level of the biomarker. Early elevations (2 to 10 hours) may reflect a composite of myocyte necrosis and reperfusion. Later elevations that may be less flow dependent may carry prognostic significance even if they are lower than those biomarker elevations seen early.
2. Postprocedural cardiac troponin elevation in high-risk patients with NSTEMI is associated with abnormal tissue-level perfusion.10,11

3. Patients demonstrating postprocedural elevation in cardiac troponin I have evidence of irreversible myocardial ischemia, accompanied by presumably new ST elevation, new left bundle-branch block, or presumably new major obstruction in a coronary artery by angiography and/or pathologic, but death occurring before blood samples could be obtained or before the appearance of cardiac biomarkers in the blood.

4. Two types of post-PCI MI have been proposed.13 Type 1 (proximal type) is related to the epicardial obstruction that occurs during the procedure. This typically is either direct or indirect side-branch occlusion. Type 2 (distal type) is a result of downstream microvascular obstruction. It occurs as a consequence of embolization of atherothrombotic material that produces microvascular plugging, platelet activation, neutrophil activation, and release of active peptides that contribute to vasospost-tional stimulation.13,14

When one considers the fact that the risk factors for post-PCI MI include those that are patient related, lesion related, and procedure related, it is not surprising that the detection of a type 4a MI has been interpreted differently by many investigators.13,15,16 On one side of the argument are proponents who advocate that there is a clear, graded relationship between the amount of biomarker released and long-term risk of death.15 An important implication of this argument is that drugs and devices that reduce peri-procedural MI are desirable, making the prevention of periprocedural MI a valid end point for clinical trials. Others have argued that the relationship between the extent of biomarker release and long-term risk of death is not so clearcut and that biomarker release is not an independent predictor of adverse outcomes after successful PCI.16 An important component of this argument is that biomarker release in the setting of PCI is a reflection of increased baseline risk in the patients in whom it occurs. The long-term risk in such patients may be dictated by their large atherosclerotic burden rather than the specific peri-PCI MI.16 In clinical practice, there is likely to be a contribution from both of these arguments in the general topic of post-PCI MI, but the relative importance in a given patient is less clear.

Building on their experience with measurement of cardiac troponins in the setting of PCI, investigators from the Mayo Clinic report an important observation in this inaugural issue of Circulation: Cardiovascular Interventions.17 The Mayo Group previously reported that in 2352 patients referred for elective or urgent PCI, those who had an elevated baseline cardiac troponin T (cTnT) (<0.03 ng/mL) had a 12-month rate of death or MI of 11.1%, compared with 4.7% in those without a baseline cTnT elevation (P < 0.05).18 After adjustment for baseline risk factors, baseline cTnT was a significant predictor of outcomes after PCI (hazard ratio, 1.14; 95% confidence interval [CI], 1.07 to 1.22; P < 0.001). In their present report, the Mayo Group analyzed 5487 patients undergoing elective PCI using a cTnT assay with an upper limit of normal <0.01 ng/mL.17 In patients with normal pre-PCI cTnT levels, post-PCI elevation of cTnT occurred frequently (43%), but the magnitude of the rise was minor (interquartile range, <0.01 to 0.04).17

Table 1. Classification of MI

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Spontaneous MI related to ischemia caused by a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection</td>
</tr>
<tr>
<td>Type 2</td>
<td>MI secondary to ischemia caused by either increased oxygen demand or decreased supply, e.g., coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension</td>
</tr>
<tr>
<td>Type 3</td>
<td>Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, new left bundle-branch block, or presumably new major obstruction in a coronary artery by angiography and/or pathologic, but death occurring before blood samples could be obtained or before the appearance of cardiac biomarkers in the blood</td>
</tr>
<tr>
<td>Type 4a</td>
<td>MI associated with PCI</td>
</tr>
<tr>
<td>Type 4b</td>
<td>MI associated with stent thrombosis as documented by angiography or autopsy</td>
</tr>
<tr>
<td>Type 5</td>
<td>MI associated with coronary artery bypass graft surgery</td>
</tr>
</tbody>
</table>

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Table 2. Classification of the Different Types of MI According to Multiples of the 99th Percentile of a Control Group of the Applied Cardiac Biomarker

<table>
<thead>
<tr>
<th>Multiples ×99%</th>
<th>MI Type 1 (Spontaneous)</th>
<th>MI Type 2 (Secondary)</th>
<th>MI Type 3* (Sudden Death)</th>
<th>MI Type 4a** (PCI)</th>
<th>MI Type 4b (Stent Thrombosis)</th>
<th>MI Type 5† (CABG)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–2×</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>2–3×</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>3–5×</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>5–10×</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>&gt;10×</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

*Biomarkers are not available for this type of MI because the patients died before biomarker determination could be performed.
†For the sake of completeness, the total distribution of biomarker values should be reported. The areas marked with X represent biomarker elevations below the decision limit used for these types of MI. Regardless of the specific end-point definition chosen in a clinical trial, all data should be provided. All boxes in the table should be completed, including those with an X.

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The 30-day death rate was 0.3% versus 2.3% in those patients with pre-PCI cTnT <0.01 versus ≥0.01 ng/mL, respectively.\textsuperscript{17} The long-term (60-month) risk of death or MI, although higher in patients with a post-PCI cTnT elevation, appeared to be driven largely by the presence of a pre-PCI cTnT elevation. In a Cox model for long-term risk of death, an isolated post-PCI cTnT elevation was associated with a hazard ratio of 1.31 (95% CI, 0.98 to 1.75; \( P = 0.065 \)) compared with a pre-PCI cTnT elevation with a hazard ratio of 1.79 (95% CI, 1.35 to 2.39; \( P < 0.001 \)).\textsuperscript{17} Given that there were only a total of 31 deaths, it is probably not entirely correct to state that an isolated post-PCI cTnT elevation was not predictive of long-term risk of death; the power of this study was limited. The absolute risk of death from minor, isolated cTnT elevations appears to be lower than when there is a pre-PCI cTnT elevation, reflecting spontaneous rather than procedure-induced myocardial injury. However, as suggested by the observation in their Figure 4 of a pattern of increased long-term death with isolated post-PCI cTnT elevation (compared with no post-PCI elevation), additional investigation of the prognostic implications of isolated post-PCI elevations in those with stable coronary artery disease is warranted.

How do we incorporate this new report with the existing literature and controversy over type 4a MIs? Jeremias et al\textsuperscript{19} report in \textit{Circulation} data from 2382 patients with stable coronary artery disease undergoing PCI in the Evaluation of Drug-Eluting Stents and Ischemic Events (EVENT) registry. Among these patients with stable coronary artery disease, 142 (6%) had a cardiac troponin level above the upper limit of normal before the procedure. In multivariate analyses adjusted for patient, lesion, and procedural factors, baseline cardiac troponin elevation was independently associated with the composite of death or MI by hospital discharge (odds ratio, 2.1; 95% CI, 1.2 to 3.8; \( P = 0.01 \)) and 1-year follow-up (odds ratio, 2.0; 95% CI, 1.2 to 3.3; \( P = 0.005 \)).\textsuperscript{19} In an accompanying editorial, Cavender and Ohman\textsuperscript{20} suggest that knowledge of the pre-PCI biomarker status may inform clinicians about the optimum combination of anticoagulant and antiplatelet therapies when weighing the benefits and risks for an individual patient.

Biomarker elevations in the setting of PCI indeed are a message from the heart. Understanding and decoding that message requires an integrated assessment of patient factors (risk scores are helpful\textsuperscript{21}), with particular attention to whether the biomarker was elevated before PCI\textsuperscript{19}; information from the catheterization report, focusing on lesion characteristics (native, saphenous vein graft) and procedure-related factors (eg, side-branch occlusion, dissection, no reflow); and post-PCI data, including the timing and magnitude of biomarker elevations and whether there are new ECG abnormalities.

The latest report from the Mayo Group suggests that isolated, minor post-PCI cTnT elevations do not appear to convey a significant short- (or long-) term risk and do not warrant prolongation of hospitalization.\textsuperscript{17} Clinicians must bear in mind, however, that large releases of biomarkers, especially in higher-risk patients with an acute coronary syndrome, are unlikely to be as benign as that described in the elective PCI patients from Mayo. The latest American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions PCI guideline integrates available data and advocates measurement of biomarkers 8 to 12 hours after PCI.\textsuperscript{22} Because clinical trialists may use various definitions for post-PCI MI, the current recommendation is that clinical trial reports should include a grid that classifies MI by type and pattern of biomarker elevation and should tabulate the type of MI seen in each treatment group (Tables 2 and 3).\textsuperscript{8} Adherence to these recommendations will add clarity to our clinical practice and trial findings. This rapidly evolving area is likely to have a new wrinkle added when ultrasensitive cardiac troponin assays are introduced into clinical practice.\textsuperscript{23–25}

### Disclosures

None.

### References


### Table 3. Sample Clinical Trial Tabulation of Randomized Patients by Types of MI

<table>
<thead>
<tr>
<th>Types of MI</th>
<th>Treatment A, No. of Patients</th>
<th>Treatment B, No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI type 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI type 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI type 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI type 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI type 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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17. Miller WL, Garratt KN, Burritt MF, Lennon RJ, Reeder GS, Jaffe AS. Baseline troponin level: key to understanding the importance of post-PCI troponin elevations. Eur Heart J. 2006;27:1061–1069.
Biomarker Release After Percutaneous Coronary Intervention: A Message From the Heart
Elliott M. Antman and David A. Morrow

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