Editorial

Torrent of Troponin

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“The River Eddy Whirls”
—The Lady of Shalott, Lord Alfred Tennyson (1842)

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n this issue of Circulation: Cardiovascular Interventions, Herrmann et al1 report data from a contemporary registry from the Mayo clinic. The study examined the relationship between the magnitude of periprocedural myonecrosis with percutaneous coronary intervention (PCI), measured simultaneously with contemporary troponin T (TnT) and creatine kinase-myocardial band (CK-MB), with 3-month postprocedural survival and determine whether there was a threshold value for TnT at which prognosis was significantly affected. Importantly they only included patients with normal baseline biomarker levels.

Of the 5268 patients (43%), 1142 (22%) patients after PCI developed TnT or CK-MB elevation >1× upper limit of normal (ULN). Post PCI elevations tended to be small; the peak level was 0.05 ng/mL (median; interquartile range, 0.02–0.15) for TnT and 10.8 ng/mL (median; interquartile range, 7.3–19.5) for CK-MB. This should be no surprise to the field and highlights the critical role of making sure that the baseline TnT value is normal before the procedure.2

Three-month mortality was 0.9% in patients with and 0.4% in those without any level of postprocedural TnT elevation (P=0.01). The optimal TnT cutoff value for 3-month mortality prediction was 0.25 mg/mL, that is, 25× ULN, but this level was found in only 7% of patients. In respect of prognostic bioequivalence, a cutoff value of 25× ULN for TnT and 5× ULN for CK-MB provided similar information.

In a multivariate model that adjusted for the Mayo Clinic risk scores, postprocedural TnT elevation remained associated with 3-month all-cause death (hazard ratio [HR] per doubling of TnT, 1.24 [1.08–1.43]; P=0.003) and cardiovascular death (HR per doubling of TnT, 1.26 [1.04–1.54]; P=0.02). Although any level of elevation of CK-MB was associated with higher 3-month mortality, independent of the Mayo risk score, there was no significant correlation with cardiovascular mortality (HR per doubling, 1.30 [1.05–1.60]; P=0.069).

How do we interpret these results? First the findings of this study are important with contemporary troponin elevation being related to 3-month cardiovascular mortality. However the cut point for the TnT value, which barely reached statistical significance, is so high that it is associated with so few events that it renders it nonuseful for either clinical or trial purposes and it will vary with the characteristics of the patients in the study. The study also raises the question whether CK-MB should be abandoned given that it was not related to cardiovascular death.

Patients with postprocedural TnT elevation had more complex coronary artery disease and were more likely to have multivessel PCI or intervention on a saphenous vein graft. This raises the intriguing possibility that a normal baseline TnT is not really obtained with the relatively insensitive contemporary TnT assay. Similarly, postprocedural thrombolysis in myocardial infarction (MI) flow <3 was more common in patients with elevated TnT levels.

Potential Limitations of the Study

There are several important limitations of the study. The numbers of events are small, for patients with TnT elevation there were only 9 cardiac deaths. Relying on such a small number of events is likely to be misleading. The authors focus on total mortality and this is germane in studies where a large number of deaths cannot be ascribed to cardiovascular causes. Here, we really want to determine whether periprocedural elevation of biomarkers are related to cardiovascular morbidity/mortality and not to some other cause such as cancer or pulmonary disease, which would be related to baseline elevation of troponins and not to a complication of PCI such as loss of a coronary artery side branch. Appropriately all deaths without known cause were considered cardiovascular for the purposes of the present analysis. Despite, >50% of deaths were because of noncardiac causes (11/20) and many others were unlikely to be related to a complication of PCI but were related to high-risk characteristics such as refractory ventricular tachycardia. Also in a recent study, procedural complications accounted for only 8.2% of post-PCI in-hospital deaths and most deaths were attributed to pre-existing or unrelated postprocedural disease processes.3

It might not be surprising that in a tertiary referral hospital such as the Mayo Clinic, multiple interventions may be done on a variety of critically or terminally ill individuals with elevated troponins whose longevity may be limited. Including such patients in one sense may be reasonable since when critical illness is present, elevations of TnT identify patients at high risk. Despite this logic, criticisms related to patient selection may blunt the importance of the principles involved which are whether elevations of TnT post PCI are of clinical cardiovascular importance.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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The contemporary TnT is egregiously insensitive in detecting some baseline elevations and unfortunately high-sensitive TnT was not available, which is better at detecting baseline elevations. The study used a cut point for TnT of <0.01 ng/mL, which is a strength of the study because it makes sure that at least the 99th percentile upper reference limit (URL) value is used at baseline. Only a prior Mayo study has done this in the past. To not do this, renders less importance to the prognostic impact of baseline samples. The frequency of marked elevations is small when the baseline value is at the 99th percentile value. Most of the prognostic information is in the baseline value and with higher sensitivity assays, the results seen in this study may disappear and patients with postprocedural elevation of troponins will likely be those with worse coronary artery disease. It is known that elevated troponin values are associated with worse coronary anatomy in patients with acute coronary syndromes and those with stable coronary artery disease as well. And there are data to suggest that the more extensive the coronary artery disease, the greater the extent of the high-sensitive troponin elevations.

When data indicating the potent prognostic value of elevated high-sensitivity troponin values found in the Heart Outcomes Prevention Evaluation study (HOPE) and Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trials are added, it maybe that with better baseline measurements, that even the significance of these marked elevations will be obviated. It is unfortunate high-sensitive troponin measurements were not available in this study.

**Comparison With the Society for Cardiovascular Angiography and Interventions Definition**

The threshold level found in the current study is lower than the clinically relevant level defined as an event associated with a worsened prognosis set by the Society for Cardiovascular Angiography and Interventions definition of periprocedural MI. This requires isolated elevation ≥10× for CK-MB using the local laboratory URL without sex-specific differences or troponin ≥70× URL. And if there are new Q waves or new left bundle-branch block, the CK-MB level required is ≥5× URL and for troponin is ≥35× URL.

Biomarker increases should not be used in isolation as they may increase with successful procedures and optimal stent deployment and if the baseline TnT is not elevated, there will be few large biomarker elevations (eg, troponin ≥70× URL). If so, there will be few periprocedural MIs identified and opportunity may be lost to improve patient outcomes.

The attempt to make a close correlation between diagnosis and prognosis defy the reality that is present clinically. It is clear that a substantial amount of cardiac injury may be well tolerated in many patients with normal cardiac function who undergo successful PCI. A similar amount of injury may be less tolerated when there is poor ventricular function and less than ideally successful procedures. Thus, attempts to find a magic number where diagnosis and prognosis are similar are unlikely to be fruitful and even if successful, this value would vary depending on the TnT assay use. In addition, the concept that any given diagnosis must have prognostic importance or may be flawed. Clearly having cardiac injury is not a good thing and most often it has prognostic importance in the right clinical situation. However, in the absence of the development of additional disease and assuming a good result has been obtained, it is unclear that this search is one that will be productive, especially if one adheres to the concept that one needs a normal baseline value as has been documented previously.

In several studies the increase of troponin related to 3× URL of CK-MB ranged from 20 to 60× URL reflecting the heterogeneity of the assays involved. In the small gadolinium-enhanced Myocardial Injury following Coronary Artery Surgery versus Angioplasty (MICAISA) study, categorization of a type 4a MI associated with a 3× elevation of CK-MB required a troponin elevation of ≥40× 99th percentile. In the Evaluation of Drug Eluting Stents and Ischemic Events (EVENT) registry, troponin levels had to be elevated 20× URL to be equivalent to the 1-year mortality (5.8%) associated with 3× elevation of CK-MB. In the Early Glycoprotein Ib/IIa Inhibition in Non-ST-Segment Elevation Acute Coronary Syndrome (EARLY ACS) and Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein Ib/IIa Inhibitors (SYNERGY) trials there was a significant increase in 1-year mortality with an increase of 10× URL of troponin (HR, 1.07; 95% confidence interval, 1.02–1.11; P=0.004). An elevation of troponin >60× URL had a similar adjusted 1-year mortality risk (5%) as 3× CK-MB elevation. Thus, the concept that a given threshold can be defined to cover all assays as suggested by the Society for Cardiovascular Angiography and Interventions criteria is unlikely to be correct.

Elevation of CK-MB post PCI has been associated with 2-year mortality but not TnT elevations. The Randomized, Two-Arm, Non-Inferiority Study Comparing Endeavor Resolute Stent With Abbot Xience-V Stent (RESOLUTE-AC) studies showed no relation of 3× elevation of CK-MB with 2-year cardiovascular mortality. However in a study of 23,604 patients from Korea, 5× URL increase in CK-MB was associated with an increase in mortality at 2.9 years (HR, 1.33; 95% confidence interval, 1.03–1.71). Also in the Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON), cardiovascular mortality was increased at 180 days if CK-MB rose ≥3× (2 samples) or ≥5× (1 sample) URL (adjusted HR, 2.4; 95% confidence interval, 1.6–3.7).17

**Third Universal Definition of MI**

In the universal definitions of MI, the diagnosis of MI is based on pathophysiology, that is, myocyte necrosis in the setting of ischemia and there is no requirement for the diagnosis of MI to be related to mortality. The 2007 universal definition of a periprocedural MI (type 4a MI) had been controversial with data challenging the idea that type 4a MIs are prognostically important. The 2007 universal definition required increases of cardiac biomarkers ≥3× 99th percentile URL with troponin preferred. Because myocardial injury occurs commonly after PCI, the definition resulted in large numbers of patients being defined as having had a procedure-related MI, with ~15% of patients undergoing PCI having an MI, with higher rates in patients undergoing complex procedures. Some of this was because of the fact that many studies did not adhere to the need for a normal baseline or defined that...
with some other criteria other than the 99th percentile URL.\textsuperscript{19} Therefore, the universal definition has not been embraced enthusiastically by the interventional community either in clinical practice or in trials.

In the 2012 universal definition, the biomarker cut point level was raised to an elevation of TnT values \( \geq 5 \times \) 99th percentile URL and associated ischemic features or angiographic complications were added.\textsuperscript{20} The definition states that troponins should be measured before PCI to assess whether the baseline is stable.\textsuperscript{20} If the baseline is not stable or values are not falling, increasing biomarker values cannot be interpreted as being related to PCI. Several studies have shown that only elevation of pre-PCI biomarkers and not post-PCI levels affects survival.\textsuperscript{2,4,21} If biomarker values are not elevated \( \geq 5 \times \) 99th percentile URL, then the term myocardial injury should be used.

The increase from \( 3 \times \) to \( 5 \times \) 99th percentile from the 2007 definition was chosen arbitrarily, giving the increased sensitivity of troponin assays and also the fact that many less sensitive assays are still in use. It was to improve the specificity of the diagnosis of post-PCI MI that the 2012 universal definition of MI that in addition either (1) symptoms suggestive of myocardial ischemia, (2) new ischemic ECG changes, (3) angiographic findings consistent with a procedural complication with loss of a major artery or side branch, embolization, or (4) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required. It is unfortunate that their use was not included in the current study.

Conclusions

Herrmann et al\textsuperscript{1} report data from a large carefully collected registry of patients undergoing PCI. A prognostically important level was defined for post-PCI TnT elevation with a threshold of \( 25 \times \) ULN for TnT, which occurred in \( 7 \% \) of patients in the study. This was the optimal cutoff value to identify patients at increased risk for cardiovascular death within 3 months after PCI, although this risk is largely conferred by adverse baseline and procedural characteristics. It seems rational that the cut point for troponin should be much higher than for CK-MB but it is unlikely that these criteria with the present assay can be applied to any other assay in clinical use, including the high-sensitivity TnT assay.

The number of events in this study is extremely small (9 cardiac deaths and 11 noncardiac deaths), probably because of the excellent procedures performed, perhaps lower risk patients, and high rates of evidence-based medicine. It likely reflects reality, that is, post-PCI values of TnT are not often associated with increases in mortality. Indeed, it is likely that more sensitive baseline values might have obviated even these modest findings still further. Elevation of troponin levels is often not related to the procedure and therefore coupling a rise in troponins with complications of PCI may obscure the causality of adverse outcomes. Larger studies with ascertainment of complications of PCI to improve the specificity of the diagnosis and with focus on cardiovascular deaths with different high-sensitivity troponin assays are required to inform us further about whether there are any troponin thresholds that contain prognostic information after PCI and if so to define the mechanisms. At present, it seems that the baseline value which is indicative of the extent and severity of the coronary artery disease, even in this study, has much more importance. Perhaps these patients may benefit from more aggressive therapy such as high dose statins. Even if some post-PCI threshold can be defined, it is not at all clear that insisting that prognostic and diagnostic criteria be the same in general and applicable to all TnT assays will be a reasonable strategy.

Disclosures

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