Cardiac Troponins and the Future of Precision Medicine

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There is an increasing emphasis across the fields of medicine on managing individual patients in ways that are tailored to the patient’s unique characteristics—an approach termed personalized or individualized medicine. Although these terms are relatively new, the concept of personalized medicine has a long history, with Sir William Osler (1849–1919) famously quoted as saying that “the good physician treats the disease; the great physician treats the patient who has the disease.” Because physicians have practiced personalized medicine in this classic sense since long before the introduction of modern advanced testing, the term precision medicine has been proposed to better reflect the incorporation of new scientific and technological advances in the practice of personalized medicine, including the use of genetic information and biomarkers.

An important principle of using biomarkers to understand disease is that the same biomarker may provide different information depending on the clinical context, the timing of measurement(s), the sensitivity and precision of the assay, and the question being asked. The most established clinical use for cTn is to aid in the diagnosis of acute myocardial infarction (MI), with contemporary criteria for MI diagnosis requiring serial cTn measurements showing a rise and/or fall in cTn and at least 1 value above the 99th percentile upper reference limit of the assay. However, these criteria do not apply in the context of periprocedural MI, which represent a specific, and highly contentious, subset of MI. Percutaneous coronary intervention (PCI)–related MI, in particular, is a definition in evolution, with criteria having been revised multiple times in successive Universal Definitions of MI and with different criteria suggested by different organizations.

The advent of new high-sensitivity cTnT (hs-cTnT and hs-cTnI) assays, allowing the measurement of very low cTn levels that were undetectable with previous assays, has added one more layer of complexity to the use of cTn in suspected MI, but it has also opened up the field to potential applications beyond acute coronary syndromes. There is now abundant evidence that among patients with stable coronary artery disease (CAD) small elevations of troponins, detectable with hs-cTnT and hs-cTnI assays, identify patients at risk for death and heart failure (more so than MI). This suggests that cTn may be useful for risk stratification in patients with chronic CAD, either in the outpatient setting or when measured before invasive cardiac procedures. Furthermore, this stable baseline measurement seems to be much more informative for long-term outcomes than postprocedural measurements.

The logical question that follows is whether interventions intended to improve clinical outcomes in patients with stable CAD, such as coronary revascularization and secondary prevention medical therapies, modify the relationship between baseline (preprocedural) cTn and outcomes. This would substantiate a role for troponin measurement as a precision-medicine tool for guiding therapy in stable CAD. A second important question specific to PCI, given the risk of transient ischemia and cTn increase because of the procedure itself, is whether postintervention cTn levels should factor into the long-term risk prediction equation. The answers to these questions are far from obvious. Theoretically, PCI may reduce long-term risk in some initially higher-risk patients (with higher baseline cTn), thus attenuating the relationship between baseline cTn and outcomes. Conversely, PCI could worsen long-term prognosis in some initially lower-risk patients (with lower baseline cTn) in which significant procedure-related myocardial injury occurs, again attenuating the relationship between baseline cTn and outcomes, as well as implicating postprocedural cTn measurement in risk prediction.

Previous studies addressing these questions have suggested that baseline cTn levels in patients with stable CAD remain associated with clinical outcomes after PCI, whereas postprocedural cTn increases are associated only...
with short-term complications but not with long-term outcomes.\textsuperscript{9-11} The article by Zanchin et al\textsuperscript{4} adds to this body of evidence, reporting the association between cTnT levels measured with a highly sensitive assay and clinical outcomes in a single-center cohort study of patients with stable CAD undergoing elective PCI. The key finding of this retrospective study is that preprocedural hs-cTnT levels $>$99th percentile upper reference limit were associated with all-cause mortality within 1 year after PCI, an association that persisted after multivariable adjustment. In contrast, an analysis (admittedly exploratory) of postprocedural cTn elevation versus baseline cTn did not demonstrate incremental value from the postprocedural measurement.

Several limitations of the study by Zanchin et al\textsuperscript{4} merit comment. First, the number of all-cause death events at 1 year was small (59 deaths among 2029 study participants), and thus the authors’ finding that the association between cTnT and mortality was limited to hs-cTnT values $>$99th percentile upper reference limit is limited by the lack of sufficient power to investigate dose–response relationships between lower levels of cTnT and outcomes. Lack of power also precluded a more substantial analysis comparing pre- versus postprocedural hs-cTnT and outcomes. Although the exploratory analysis presented in the article is compatible with previous findings demonstrating that periprocedural injury is much less important than baseline troponin status, it should not be interpreted as conclusive. Heart failure events were not systematically recorded during follow-up and were thus not available for analysis, an important limitation given the known association between hs-cTnT and heart failure in stable CAD.\textsuperscript{9} In spite of these limitations, the study by Zanchin et al\textsuperscript{4} represents a welcome addition to a growing body of evidence supporting the theory that preprocedural cTn (likely reflective of preexisting chronic myocardial injury) is more relevant than immediate postprocedural cTn (reflective of periprocedural injury) for long-term risk assessment in patients undergoing elective PCI.

Before preprocedural hs-cTn measurement is elevated to the pantheon of useful precision-medicine tools, an additional step is required: evidence that specific therapies provide incremental benefit for patients with chronic CAD and elevated troponins. Do such data yet exist? The answer to date is unfortunately no. For example, in a substudy of the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, prompt coronary revascularization in patients with elevated baseline cTnT did not result in a significant reduction in the rate of the composite end point of death from cardiovascular causes, MI, or stroke.\textsuperscript{13} Moreover, medical therapies such as angiotensin-converting enzyme inhibitors did not lower risk among patients with stable CAD and elevated troponins.\textsuperscript{14} Finally, statin therapy seems equally beneficial across strata defined by troponin levels.\textsuperscript{15} Thus, although elevated preprocedural troponin levels clearly identify patients at increased risk for long-term complications, and seem to do so better than postprocedural levels, it is not yet clear what clinicians should do differently based on this information.

Advances in precision medicine are likely to have transformative effects on the way medicine is practiced in the 21st century,\textsuperscript{2} and we anticipate that cTn measured with highly sensitive assays will have increasingly important roles to play in patient-level risk assessment and therapeutic targeting in the future. However, many questions remain unanswered, ranging from the intricacies of clinical use and adequacy of contemporary cut-off values,\textsuperscript{16} to the cellular and molecular mechanisms of cTn release from the cardiac myocyte in health and disease,\textsuperscript{17} to the critically important therapeutic implications. A broad research agenda that spans the spectrum of basic and translational studies, through to substudies of clinical trials investigating novel therapies and their effect among subgroups with and without troponin elevation, will be needed to fully define the role of high-sensitivity cTnT assays in precision cardiovascular medicine.

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References


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