High-Sensitivity Cardiac Troponin for Screening Large Populations of Healthy People: Is There Risk?

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Imagine a biomarker that is able to diagnose acute myocardial infarction (MI)⁴ with high clinical sensitivity and within 2 h of the onset of ischemic symptoms. Imagine that the same biomarker can rule out an MI with almost 100% negative predictive value by using multiple measurements taken over a 2- to 3-h period. Imagine that the biomarker can also risk-stratify symptomatic and stable acute coronary syndrome (ACS) patients for both short-term (during admission) and long-term (over 6 months to 2 years) major adverse cardiac events by using the same measurements. Imagine thinking, beyond ACS, that the biomarker can also identify nonischemic pathologies that have caused the myocardial injury, thus identifying these individuals as belonging to a group at higher risk than ACS patients. The story gets better—no hype. Imagine this biomarker can stand alone—without the cumbersome weight of a multiple-biomarker strategy—as a predictor of major adverse cardiac events in individuals within the general population. So what is this biomarker, and is it being used in clinical practice? What is the evidence to convince laboratory scientists and clinicians that they should drop everything and add this test to their laboratory test menu?

In the year 1995 the first cardiac troponin assay, for cardiac troponin T (cTnT), was cleared [510(k)] by the US Food and Drug Administration (FDA) as an aid for the diagnosis of MI. In 1996, the FDA cleared cTnI. I often wonder why it took 20 years for this cardiac-specific marker to get to the market. Once these markers were FDA cleared, and with the rapid development and availability of immunoassays for both cTnT and cTnI, data regarding their clinical utility quickly accumulated in the evidence-based literature (1). In 1999, the clinical chemistry community, followed by the cardiology community in 2000, recommended cardiac troponin as the definitive biomarker to aid in the diagnosis of MI. The year 2007 saw the establishment of the universal definition of MI, which was predicated on an increasing (or decreasing) pattern of cardiac troponin in patients presenting with symptoms of ischemia and at least 1 concentration greater than the 99th-percentile reference value. This was a very short time span over which to change the diagnostic criteria for such an important diagnosis, and during this period the new cardiac troponin markers virtually eclipsed the use of the older enzyme marker, creatine kinase MB. Now, only 4 years after universal consensus on the use of cardiac troponin as the sole biomarker for MI, this protein is again causing a stir, this time resurfacing in a high-sensitivity (hs) assay format. What distinguishes these new hs assays from their predecessors is the ability to measure very low cTnT and cTnI concentrations (1–20 ng/L, well below the limit of detection of the sensitive and contemporary assays used in clinical practice today) with an excellent imprecision (CV ≤10%) at and below the assay’s 99th-percentile value. This added sensitivity allows hs cardiac troponin assays to reliably measure concentrations in almost 100% of healthy individuals (2). Contemporary assays can typically measure cardiac troponin values in only 10% to 20% of individuals from the general, apparently healthy population. No longer do we have to imagine.

Studies are now starting to address the role of hs cardiac troponin in primary prevention. A review of this literature supports the use of hs cardiac troponin as a necessary tool to assist clinicians in all cardiovascular evaluations. deFillipi et al. from the Cardiovascular Health Study reported on their findings for 4221 community-dwelling adults ≥65 years of age without prior heart failure (HF). They found that both baseline concentrations and changes in serial measurements of hs-cTnT were significantly associated with incident HF and cardiovascular death during the 11.8-year follow-up period (3). A baseline hs-cTnT concentration ≥12.94 ng/L had an adjusted hazard ratio (HR) of 2.48 for HF and 2.91 for cardiovascular death. A subsequent increase in hs-cTnT of >50% was associated...
with a greater risk of HF (HR, 1.61) and cardiovascular death (HR, 1.68). A graded relationship between increasing hs-cTnT concentrations >3.0 ng/L and increased risk of both HF and cardiovascular death was observed, although approximately 83% of the study observations were well below the 99th percentile of healthy individuals. These data confirmed that higher hs-cTnT concentrations were associated with multiple traditional risk factors. Neither N-terminal pro–brain natriuretic peptide (NT-proBNP) nor hs C-reactive protein (hs-CRP) added significantly to risk assessment.

In the same issue of JAMA, de Lemos et al. (4) from the Dallas Heart Study reported on a study of a cohort of 3546 individuals between 30 and 65 years of age from a multiethnic population. They found the prevalence of measurable hs-cTnT to be 25%, with significantly different rates in men (37.1%) and women (12.9%), and between participants <40 years old (14%) and those >60 years of age (57.5%). An increased hs-cTnT value was associated with structural heart disease, including left ventricular hypertrophy and left ventricular systolic dysfunction, as well as with chronic kidney disease. During a median follow-up of 6.4 years, all-cause mortality increased from 1.9% to 28.4% across groups of increasing hs-cTnT concentrations, with 95% of individuals having concentrations lower than the 99th-percentile value (14 ng/L). After adjustment for traditional risk factors, hs-CRP, and NT-proBNP, the hs-cTnT concentration remained independently associated with all-cause mortality (HR, 2.8 in the group with concentrations >14 ng/L). The authors conclude that the presence of measurable cTnT at concentrations lower than what can be measured with current assays points to a greater burden of cardiovascular risk and may represent a biomarker of “end organ” cardiovascular damage. They also point out, as has been discussed previously, that the added diagnostic sensitivity of the hs assays early after presentation comes at the price of reduced clinical specificity when applied to patients with a suspicion of MI.

In the largest multiple biomarker study to date, Blankenberg et al. reported results for 2 disease-free cohorts [7915 men and women from the FINRISK97 population and 2551 men from the Belfast Prospective Epidemiology Study of Myocardial Infarction (PRIME)], in which 30 novel biomarkers from different pathophysiological pathways were evaluated (5). No single biomarker improved risk estimation for incident cardiovascular events over a 10-year follow-up, when baseline values were used after adjustment for risk factors. hs cardiac troponin assays, however, were not evaluated in these studies. Unique to the study was the development of a biomarker score that included NT-proBNP, hs-CRP, and a contemporary cTnI, which added to the conventional risk model by improving the 10-year risk estimation for cardiovascular events (HR, 1.36). The authors noted that even using a contemporary cTnI assay in their multibiomarker group score substantially improved predictive ability, compared with that of another community-based study that did not include cardiac troponin.

Finally, preliminary observations have been published from the Minnesota Heart Survey, an ongoing population-based surveillance study of risk factors for coronary heart disease that has examined 7 biomarkers in a nested case–control study of 137 cardiovascular deaths and age- and sex-matched controls with 5–12 years of follow-up (6). After adjustments were made for traditional risk factors, the odds ratios (ORs) for predicting cardiovascular mortality were independently significant for hs-cTnI (Singulex assay) (OR, 6.7), NT-proBNP (OR, 5.6), and hs-CRP (OR, 1.8) in this community sample (6).

What do we take away from these recent population-based and non-ACS studies? Any multiple-biomarker study in the year 2011 and beyond that does not include an hs cardiac troponin assay in its investigation for the prediction of (first) cardiovascular events or death should be reviewed as deficient. Measuring hs-cTnI or hs-cTnT is (and should be until proved otherwise) the standard to test all other biomarkers in patients from a community population with or without known coronary artery disease. The use of hs cardiac troponin assays, I think, will assume a spot as a biomarker in primary prevention and will eventually become a risk factor alongside the conventional Framingham risk factors, such as smoking, hypertension, and hyperlipidemia. hs troponin fits the role described in the Institute of Medicine’s statement for “efforts to make sure the right patients get the right treatment.” Future studies will define the optimal role for screening young adults, for assessing the risk of future events, and for potential early intervention and therapies to improve both short- and long-term outcomes.

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**References**