Making it More Sensitive
The New Era of Troponin Use

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About a decade ago, the prevailing wisdom was that conventional risk factors explained only approximately half of the risk for a myocardial infarction or stroke. Consequently, efforts to identify novel risk factors were undertaken to improve cardiovascular risk prediction. The hypothesis that inflammation is a central contributor to atherothrombosis has stimulated sustained efforts to characterize the specific molecules and pathways that may be involved and to identify biomarkers in humans that enable detection of underlying inflammation. Ridker et al1 pioneered this work and reported that biomarkers in humans that enable detection of underlying molecules and pathways that may be involved and to identify biomarkers in humans that enable detection of underlying inflammation. Ridker et al1 pioneered this work and reported that biomarkers in humans that enable detection of underlying inflammation are a central contributor to atherothrombosis. The hypothesis that inflammation is a central contributor to atherothrombosis has stimulated sustained efforts to characterize the specific molecules and pathways that may be involved and to identify biomarkers in humans that enable detection of underlying inflammation.

The currently used universal definition of myocardial infarction recommends the use of a robust and precise troponin assay with a coefficient of variation of ≤10% at the threshold concentration representing the 99th percentile of a reference population. This demand to optimize diagnosis of myocardial infarction according to the guidelines stimulated the development of newer, more sensitive troponin assays over the past few years. The introduction of such contemporary and highly sensitive troponin assays that meet the recommendations of the universal definition has enabled a significant improvement in the detection of troponin release, particularly early after an ischemic event.9 Application of these assays in specific study populations as well as in unselected chest pain cohorts has proven to substantially facilitate early diagnosis of myocardial infarction.10–14

With the introduction of assays that allow for reliable troponin I detection at very low levels, the known strong potential of elevated troponin for risk stratification in patients with acute coronary syndrome can be translated to patients with stable disease. Omland et al17 observed that even minor troponin elevations are associated with poorer outcome in patients with stable coronary artery disease.

The availability of different generations of troponin assays in respect to their improved sensitivity requires a well-defined classification system. The introduction of troponin assays that provide such high precision should be characterized as contemporary sensitive assays. A second criterion should be the proportion of troponin detection in a general population, with highly sensitive troponin assays allowing measurements in at least half of the population. The next generation of super-sensitive troponin assays covers the complete reference range, with detectability in ≥95% of a general population. The Figure provides an overview of the proposed troponin nomenclature and potential clinical application; secondary prevention includes both stable and acute coronary syndrome.
Another aspect in the era of sensitive troponin assays merits consideration. Conventional troponin testing resulted in troponin-negative or -positive patients with clear therapeutic options. Use of sensitive or highly sensitive troponin assays provides much more information than a Boolean variable; their results must be interpreted as continuous values rather than as dichotomous information. Especially in settings other than diagnosis of myocardial infarction, few guidelines exist for interpretation of the measured troponin concentration. Accordingly, the established diagnostic troponin cutoff representing the 99th percentile of a reference concentration. Accordingly, the established diagnostic troponin cutoff representing the 99th percentile of a reference concentration.

In the current issue of Circulation, Saunders et al report the association between troponin T assayed with a highly sensitive test kit and incident heart failure, fatal and nonfatal coronary events, and overall mortality. Their study extends current knowledge described earlier from analyses of the Cardiovascular Health Study (which addresses the relationship between highly sensitive troponin T and incident heart failure as well as overall mortality in the elderly) and the Dallas Heart Study (which describes the association between highly sensitive troponin T [detected in 25% of the population] and overall mortality in younger individuals aged 35 to 65 years with a limited number of end points). The present findings of the ARIC Study now provide data on the middle-aged population with an age range of 54 to 74 years, resulting in detection of 66.5% of the individuals. Surprisingly, 7.4% of the ARIC population had troponin T levels >0.014 μg/L, which should represent the 99th percentile of the general population. Although those individuals had been at highest risk for future events, those individuals with minimal elevated troponin T above the detection limit of 0.003 μg/L were at increased risk for incident heart failure and overall mortality. Although the current data may result in improved cardiovascular risk prediction by an impressive net reclassification of 0.179 for overall coronary heart disease risk prediction, there is a need for better understanding of the manner in which troponin level predicts risk according to different decades among women and men separately. This is of particular importance because troponin concentrations, particularly in the low ranges, correlate moderately to strongly with age, and differ between men and women. Furthermore, we need to elaborate on whether the prediction metrics of a single troponin determination assayed with a highly sensitive test are similar or superior to a 3-marker score that had been defined in the European MONICA, Risk, Genetics, Archiving, and Monograph (MORGAM) consortium with the use of the FINRISK and Prospective Epidemiological Study of Myocardial Infarction (PRIME) cohorts in a derivation and validation approach. Incorporation of a composite biomarker score including the noninterdependent variables troponin I (assayed with a contemporary sensitive assay), C-reactive protein, and the N-terminal fragment of B-type natriuretic peptide significantly improved risk assessment.

Far greater importance is now placed on the manner in which biomarkers might improve clinical decision making. In the present study, the most significant reclassification affected ≈17.9% of men destined for coronary heart disease risk during long-term follow-up. Potentially, some of the difference in net reclassification between men and women is attributable to the higher troponin detection and incident cardiac event rates in men. With this number of subjects in primary prevention settings, these proportions could portend significant resource implications if it were to be shown subsequently that treatment on the basis of this biomarker profile could improve outcomes, as has been claimed for C-reactive protein in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial. Such studies are clearly warranted, given the long shadow cast by circulating troponin in middle-aged individuals, with an enduring association with long-term cardiovascular disease risk. In light of the strong association with prevalent structural heart disease and incident fatal and nonfatal cardiac events, it appears plausible that even the determination of very low troponin concentrations assayed with a highly sensitive troponin test might discriminate those individuals in the general population who could benefit from a primary prevention therapy irrespective of the presence of classic risk factors. As such, those medications addressing the renin-angiotensin mechanisms might be attractive candidates. Although the application of highly sensitive troponin testing in the population might make available a pathway to more personalized medication, much more remains to be done, including the performance of biomarker-guided trials.

Disclosures

None.

References


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