Highly sensitive troponins knocking at the door of primary prevention

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This editorial refers to ‘High population prevalence of cardiac troponin I measured by a high-sensitivity assay and cardiovascular risk estimation: the MORGAM Biomarker Project Scottish Cohort†, by T. Zeller et al., on page 271

In this issue, Zeller et al. report on the role of detectable cardiac troponin I (cTnI) levels measured by a high-sensitivity (hs) cTnI assay for prediction of cardiovascular (CV) events and coronary death in a general Scottish population. A total of 15 340 healthy Scottish individuals, irrespective of age or gender, were studied over a follow-up period of 20 years. The level of cTnI was determined from a frozen blood sample obtained at baseline using a prototype hs assay (ARCHITECT STAT highly sensitive Troponin I immunoassay, Abbott Diagnostics) and with a contemporary-sensitivity assay from the same manufacturer (STAT troponin I immunoassay, Abbott Diagnostics). Levels of cTnI were above the limit of detection (LoD) in 74.6% of the overall population measured with the hs assay but only in 2.9% when measured with the contemporary sensitive assay. Increments of hsTnI within the normal concentration range were associated with fully adjusted hazard ratios (HRs) for CV events and coronary death. Adjusted models for prediction of CV events including myocardial infarction and stroke improved after addition of hsTnI, particularly for prediction of death. A detectable hsTnI level improved risk prediction even in individuals with non-detectable contemporary-sensitivity cTnI levels. However, the contemporary-sensitivity assay also improved risk prediction beyond the clinical risk score. If biomarkers are used as continuous variables, implementation in primary care is not practical. Therefore, the investigators determined optimal cut-offs (7 ng/L for men and 4.7 ng/L for women) for prediction of CV events from C-statistics. Implementation of gender-specific cut-offs improved risk prediction particularly among women. The data also suggest, for unknown reasons, that hsTnI is a good marker during the first decade after its measurement before its predictive power declines again.

While the USA still struggles to introduce hs assays for diagnosis of myocardial infarction, accumulating data suggest the usefulness of hs assays for prognostication of CV risk and death in numerous settings such as chronic coronary artery disease, and acute or chronic cardiac or non-cardiac disease. The study of Zeller et al. adds substantial evidence to another intriguing application of hsTn assays (Figure 1). The present study is not the first of its kind and confirms the findings of four previous reports enrolling > 20 000 participants in the general population. In the Framingham Heart Study, in a community-based population, the prognostic value of a biomarker panel including soluble ST-2, growth differentiation factor 15, and cTnI using a hs assay (Erenna cTnI, Singulex) was studied in 3428 individuals with a follow-up over 11.3 years. In multivariable-adjusted models, individuals with multimarker scores in the highest quartile had a three-fold risk of death, a six-fold risk of heart failure, and a two-fold risk of CV events. Three population-based studies focused on the usefulness of cTnT measured with a hs assay. In the Dallas Heart Study, the prevalence of detectable cTnT above the limit of blank (LoB; ≥ 3 ng/L) increased from 0.7% using a conventional generation cTnT assay to 25.0% using a hsTnT assay. After adjustment for traditional risk factors, C-reactive protein level, chronic kidney disease, and N-terminal pro-brain natriuretic peptide level, all-cause mortality increased from 1.9% to 28.4% from the lowest to the highest cTnT quintile. In the Atherosclerosis Risk in Communities (ARIC) study on 9698 participants aged 54–74 years who at baseline were free from coronary heart disease, stroke, and heart failure, measurable hsTnT levels above the LoB were detected in 66.5% of individuals. Patients with cTnT levels in the highest category (> 14 ng/L; 7.4% of the ARIC population) had significantly increased risk for coronary heart disease (HR 2.29), fatal coronary events (HR 7.59), total mortality (HR 3.96), and heart failure (HR 5.95). Even minimally elevated hsTnT values above the LoB were associated with increased risk for mortality and heart failure (P < 0.05), indicating a role for measurement of hsTn in the community. Consistently, in the Cardiovascular Health Study, hsTnT was measured in 4221 community-dwelling adults aged 65 years or older without prior heart failure. The hsTnT was above the LoB in 2794 participants.

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In that study, hscTnT was measured again 2 or 3 years after initial assessment. Increases in the hscTnT level of ≥ 50% during this period identified individuals at increased risk of death or heart failure, with decreases in the hscTnT level associated with lower risk, suggesting that risk might be monitored by serial hsTn. An exploratory analysis from the Cardiovascular Health Study demonstrated that individuals who were physically active at baseline had a low probability of developing elevated cTnT levels during follow-up.8

A strength of the present study is the application of state-of-the-art statistical evaluation using categorical NRI (net reclassification improvement) and IDI (integrated discrimination improvement) for reclassification and discrimination, respectively, and fully adjusted Cox proportional hazard analysis for risk prediction. Previously, epidemiological studies9 failed to show any added benefit of new biomarkers or biomarker panels as C-statistics do not allow the unmasking of a superior performance of a new test if performance of the comparator is already moderate with an area under the curve (AUC) > 0.75.10

The study of Zeller et al. differs from the previous trials in several important aspects. Unlike the others, the Scottish population included all age groups and both genders. Secondly, the study used a new prototype hsTnI assay (ARCHITECT STAT highly sensitive Troponin I immunoassay, Abbott Diagnostics) with a very high analytical sensitivity. Data from head-to-head comparison among 19 different assays showed that this prototype assay yielded 96% measurable values above the LoD, the highest rate among hsTn assays.11 Thus, this assay would be designated a level 4 (third-generation hs assay, detection ≥ 95% measurable normal values below the 99th percentile) according to the scorecard definition proposed by Apple.12 In the Scottish population, detectable rates of cTnI were considerably higher than those reported previously with hsTnI4 or hsTnT5,7 despite the fact that the cut-off was set at the LoD and not at the LoB as with the previous general population trials.

The reasons why detectable cTn values that are still below the 99th percentile value of a healthy reference population are strong independent indicators of incident future risk for CV events and death in a general population without overt cardiovascular disease are not fully understood. It has been speculated that chronic cTn elevations reflect physiological cell turnover, modified by individual, presumably genetically determined factors, and possibly influenced by superimposed mechanisms causing ultrastructural and subclinical changes.3 Supporting evidence comes from the Dallas Heart Study that demonstrated a strong association between the level of cTn and the presence and degree of underlying structural heart disease.5

However, there are also some imperfections of this study. First, methodological differences prohibit generalization of the present population study to other populations because event rates (coronary death was 4.6% over 20 years in the Scottish study vs. 1.7% CV death over 6.4 years in the Dallas Heart Study vs. 1.2% over 9.9 years in the ARIC Study vs. 2.5% over 11.8 years in the Cardiovascular Health Study) were higher in the Scottish population. In addition, the clinical risk score used in this population was the ASSIGN score, a clinical risk

**Figure 1** More sensitive cardiac troponin (cTn) assays enable detection of pathologies at earlier stages and pathophysiological processes that escaped identification by generations of less sensitive assays, thereby expanding their possible use from diagnosis of a large myocardial infarction (top) to screening of asymptomatic individuals in the general population (bottom). AMI, acute myocardial infarction; AVNRT, atrioventricular nodal re-entrant tachycardia; CKD, chronic kidney disease; ESRD, end-stage renal disease; NSTEMI, non-ST-elevation myocardial infarction; PAH, pulmonary arterial hypertension. This figure has been taken from the 2nd edition of the ESC Textbook and Acute Cardiac Care (Oxford University Press), and was adapted.
stratification score derived and validated in > 13,000 individuals from the same population. The score takes into account social deprivation and family history of CV disease, and uses a quantitative measure of smoking, i.e. number of cigarettes. When tested against the Framingham cardiovascular risk score in the same database, discrimination of risk was marginally better than the Framingham risk score. Limitations are that the score is based on a Scottish population only, is not well validated, and does not take into account obesity and body mass index. To generalize and to pool data for a more comprehensive understanding and interpretation and for broader acceptance among clinicians, a more common denominator such as the SCORE from the European Society of Cardiology or the Framingham Risk score would have been more useful.

Finally, the investigators measured cTn only using a prototype hsTn assay along with a contemporary-sensitivity cTnI assay from the same manufacturer. One issue that needs to be clarified is the discrepancy between the analytical characteristics, i.e. LoD and 99th percentile values provided for the prototype assay in this report that differ greatly from previously published data on the same assay. In the latter comparative analysis of 19 cTn assays in a single reference population, rates of measurable cTn concentration above the LoD in a healthy reference population were reported to be 96% as compared with 74.6% measured in the Scottish population.

Finally, provision of data on other commercially available more sensitive or hsTn assays would have facilitated adoption of such a novel use, as findings with one hsTn assay cannot be generalized to another.

In conclusion, the findings of the study of Zeller et al. strongly suggest that hsTn measurements might eventually become a screening tool for future risk estimation in primary care. Although we hear hsTn knocking heavily on the door of population screening, there are still some unresolved issues that need to be addressed before we can open the door.

Conflicts of interest: H.A.K. holds a patent on cTnT jointly with Roche Diagnostics, and receives honoraria and research grants from Roche Diagnostics. E.G. receives speaker’s honoraria and research grants from Roche Diagnostics.

References