Off limits: highly sensitive troponin in the general population

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Online publish-ahead-of-print 26 May 2016

This editorial refers to ‘Troponin I and cardiovascular risk prediction in the general population: The BiomarCaRE consortium’†, by S. Blakenberg et al., on page 2428.

Risk estimates based on classical risk factors only partially explain the incidence of cardiovascular disease (CVD) in the general population, and risk estimates vary across European populations. The BiomarCaRE project aims to determine the additional value of multiple (new) biomarkers to improve risk estimation of CVD-related events in Europe. In particular, the article by Blakenberg et al. in this issue of the journal investigated the value of adding troponin I levels using a highly sensitive assay (Abbott ARCHITECT STAT) to conventional risk factors for prediction of CVD.

The investigators evaluated individual level data from 10 prospective population-based studies on a total of 74 738 participants. The investigators sought to determine cardiac troponin I (cTnI) distribution, to characterize the association of cTnI with cardiovascular outcomes, to determine the predictive value beyond the variables used in the European Society of Cardiology (ESC) SCORE (Systematic Coronary Risk Evaluation), to test a potentially clinically relevant cut-off value, and to evaluate the eligibility for statin therapy based on elevated troponin I concentrations.

Strengths

The consortium has to be congratulated for this masterpiece of an epidemiological study. BiomarCaRE is an extensive multimodular project performed in different phases, and in a very large cohort with sufficiently long follow-up periods.

The most important finding of this project is the association between cardiovascular (CV) death, CVD, and total mortality and detectable presumably still normal cTnI values using a highly sensitive cTnI assay. Median cTnI concentrations in BiomarCaRE were 2.7 ng/L (25th, 75th percentiles: 1.5, 4.6), and risk for CV death, CVD, and total mortality increased by percentiles of cTnI level.

This finding raises the suspicion for a much higher prevalence of subclinical disease in the general population than commonly anticipated. It is reasonable to speculate that highly sensitive troponin (hsTn) detects underlying structural or functional heart disease as suggested earlier from epidemiological studies. Furthermore, BiomarCaRE raises the question of whether there is a threshold of myocardial injury beyond which individual risk increases and that can be applied in clinical practice rather than for epidemiological insights. Such a convenient, ideally dichotomous cut-off is being proposed indirectly by provision of data on the strong association for prediction of CV death at cTnI concentrations above the upper quintile (>6 ng/L) that are associated with a hazard ratio (HR) of 1.87 [95% confidence interval (CI) 1.72–2.03; P < 0.001].

In addition, the clinical usefulness of such a cut-off at 6 ng/L is supported by the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER Trial). In the JUPITER trial, rosuvastatin was equally effective in preventing the occurrence of the primary endpoint [composite of non-fatal myocardial infarction (MI), non-fatal stroke, hospitalization for unstable angina, arterial revascularization, or death resulting from CV causes] across different baseline concentrations of either hsTn or brain natriuretic peptide (BNP). The primary endpoint appeared to increase across categories of hsTn, and the benefits of rosuvastatin in terms of numbers needed to treat to prevent a primary endpoint decreased from 67 in the lower tertile to 18 in the highest tertile of hsTn corresponding to 6 ng/L.

This cut-off has now been established in a large general population and not in a selected healthy reference population, but still is much lower than the general gender-independent 99th percentile value (26 ng/L) or even than the lower the 99th percentile value for females (16 ng/L) provided by the manufacturer. Obviously, the cut-off at 6 ng/L is independent of gender, providing similar prognostic information on CV outcomes and on the benefits of rosuvastatin, and obviates further differentiation by gender. This finding is very interesting as it corroborates the hypothesis
that much lower cut-offs are warranted for accurate rule-out of non-ST-segment elevation MI (NSTEMI),\textsuperscript{8} or for prediction of prognosis in acute coronary syndrome (ACS)\textsuperscript{9} using the ARCHITECT STAT hsTnI assay than those recommended by the manufacturer (Figure 1).

In the Biomarkers in Acute Cardiovascular Care (BACC) cohort\textsuperscript{8} on 1045 patients with suspected ACS, testing a rapid 1 h NSTEMI rule-out and rule-in algorithm, the optimal cut-off was determined to be $\leq 6$ ng/L at 0 and 1 h for ruling out NSTEMI with the use of the same STAT Architect hsTnI assay.\textsuperscript{8} The same cut-off at 6 ng/L was also found to discriminate best those patients at risk for death at 1 and 5 years in the BiomarCaRE study on 74 738 individuals aged 51.0 years (42–60) of the general population without prevalent CVD using a cut-off of $\leq 6$ vs. $\leq 27$ ng/L.\textsuperscript{7} In support of this, Cullen et al.\textsuperscript{9} investigated an ACS population and found an optimal prognostic performance of hsTnI at a cut-off of $\geq 6$ ng/L for women and $\geq 7$ ng/L for men using receiver operating characteristic (ROC) analyses, and $\geq 6$ ng/L for women and $\geq 9$ ng/L for men using logistic regression modelling. Therefore, Cullen et al.\textsuperscript{9} also recommended considering lowering the clinical cut-off for both sexes for prognostic purposes.

Thus, a single cut-off at 6 ng/L rather than a gender-specific cut-off seems appropriate and should stimulate a re-thinking about the appropriateness of gender-specific cut-offs that may confuse clinicians and complicate diagnosis of ACS in the majority of Emergency Departments or chest pain units (CPUs).\textsuperscript{10}

### Shortcomings

The use of the SCORE was selected because the ESC and the Second Joint Task Force instigated the development of a risk estimation system based on a large pool of representative European data sets that would capture the regional variation in risk across Europe.\textsuperscript{2} The SCORE risk was calculated based either on total cholesterol or on the cholesterol/HDL-cholesterol ratio plus sex, smoking, and systolic blood pressure.\textsuperscript{2} However, in contrast to the clinical endpoints studied in the BiomarCaRE, the SCORE project shifted the emphasis in risk estimation to fatal CVD events only instead of combined fatal and non-fatal events.\textsuperscript{2} Non-fatal CV events are more problematic as they are critically dependent on definitions and methods used in their ascertainment. This fundamental difference in the design of the SCORE might explain the inferior performance of SCORE to predict events other than CV death in BiomarCaRE.

Another important limitation of the SCORE is the handling of diabetes as an important risk factor. Due to non-uniformity in the ascertainment of diabetes, the SCORE Task Force decided not to include a dichotomous diabetes variable in the risk function and not to produce a separate risk score system for persons with diabetes. In the BiomarCaRE general population study,\textsuperscript{1} a total of 4655 (5.0%) patients with diabetes were included but whose risk was not reflected by the SCORE and probably whose risk was better estimated by hsTnI.\textsuperscript{11} In the Bypass Angioplasty

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**Figure 1** Graph showing 99th percentile values for the Abbott Architect STAT cardiac troponin I (cTnI) assay derived from different healthy reference populations, and optimized cut-offs for rule-out of myocardial infarction (MI) in acute coronary syndrome (ACS) cohorts, and in the general population.
Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial\(^1\) including 2368 patients with both type 2 diabetes and stable ischemic heart disease, an extensively adjusted HR for the composite endpoint (death from CV causes, non-fatal MI, or non-fatal stroke) among patients with abnormal baseline troponin T concentrations using a high sensitivity assay remained robust and significant (1.85; 95% CI 1.48–2.32; \(P < 0.001\)).

Another issue represents age-related findings in the BiomarCaRE population. According to SCORE data,\(^2\) the age range between 50 and 65 years represents the period during which risk changes most rapidly. This age group is well represented in the BiomarCaRE with a median age of 52.2 years (42.9, 60.7). Interestingly, the C-index difference for added value of cTnI to the SCORE regarding CV death was highest for the age group 45–54 years with an NRI (net reclassification improvement) of 0.014 (25th, 75th percentiles: 0.006, 0.021) but still significant for 55–64 years (NRI 0.01) and older than 65 years (NRI 0.01). Previously, epidemiological studies\(^12\) failed to show any added benefit of new biomarkers or biomarker panels. It was hypothesized that 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.\(^13\)

Two reasons may now explain partly the added value of hsTnI in this study population: (i) suboptimal performance of the ESC SCORE for prediction of CV death (the only validated outcome) for the aforementioned reasons allowing hsTnI to improve risk stratification; and (ii) evaluation of a very high number of individuals and events translating to statistically significant differences between cTnI and SCORE using C-statistics and NRI despite relatively small numerical changes.\(^13\) The need for extremely high numbers of individuals needed to treat in the general population and the lack of powerful pharmacological interventions for primary prevention represent severe obstacles. Whether routine measurement of hsTnT or hsTnI in the general population will improve risk stratification and identification of individuals who might benefit from more intense primary or secondary prevention measures is still elusive. However, data on the benefits of rosuvastatin in individuals with cTnI above the upper quintile are promising and call for prospective testing on the benefits of other pharmacological and non-pharmacological interventions in patients across the concentration range of hsTnT or hsTnI.

In addition, findings of this study highlight the need to refine and re-validate the ESC SCORE in the light of new biomarkers such as high sensitivity cardiac troponins.

**Conflict of interest:** H.A.K. reports consultancy fees and grants and lecture fees from Roche Diagnostics, and grants and lecture fees from Bayer Vital, plus lecture fees from AstraZeneca. E.G. reports consultancy fees and grants and lecture fees from Roche Diagnostics, lecture fees from AstraZeneca and Bayer Vital.

**References**


