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Predicting myocardial infarction and other serious cardiac outcomes using high-sensitivity cardiac troponin T in a high-risk stable population

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ABSTRACT

Objectives: Previous work on high-sensitivity troponin I (hs-cTnI) has demonstrated that it may identify patients with stable cardiovascular disease (CVD) at risk for future myocardial infarction (MI). In this study, we assessed if hs-cTnT concentrations could also identify those stable CVD patients at high risk for future MI and other ischemic cardiac outcomes.

Methods: hs-cTnT (lot:153-401) was measured in specimens obtained at randomisation in the Heart Outcomes Prevention Evaluation (HOPE) study ($n=2941$ stable CVD patients, 4.5 years follow-up). The primary outcome for the HOPE study (MI, stroke, or cardiovascular death) was used to identify cutoffs by receiver operating characteristic (ROC) curve analysis and was used in conjunction with the 95th and 99th percentile upper limits to construct different concentration ranges, which were assessed using log-rank tests and multivariable Cox proportional hazard models. These different concentration ranges were then assessed for the components of the primary outcome and for heart failure (HF).

Results: The ROC derived hs-cTnT cutoff was 8 ng/L for the primary outcome. Subjects with hs-cTnT either below (8 to <14 ng/L) or slightly above the published 99th from a healthy population (14 to 21 ng/L) had similar probability for the primary outcome. Those with hs-cTnT concentrations >31 ng/L had the highest probability and greatest risk for future MI, HF, and cardiovascular death as compared to those with hs-cTnT concentrations <8 ng/L.

Conclusion: In patients with stable CVD disease hs-cTnT measurement identifies those at risk for MI as well as HF and cardiovascular death.

Introduction

The ability of high-sensitivity cardiac troponin testing to identify those individuals with known or acute cardiovascular disease at risk for an adverse cardiovascular event is beginning to be recognised [1–5]. Recent publications have further delineated the role of high-sensitivity cardiac troponin T (hs-cTnT) in both the acute and non-acute settings [4,6–12]. In addition to identifying individuals at higher risk for developing heart failure (HF), data have emerged indicating that perhaps hs-cTnT testing can identify those individuals in the stable setting at higher risk for an ischemic cardiac event [13,14]. However, these studies have focused mainly on the composite outcome that included cardiovascular death and either myocardial infarction (MI) or stroke, with limited information on the ability of hs-cTnT to detect the individual outcomes [4,13,14]. Moreover, a recent reconfiguration of the hs-cTnT assay at the low end of the analytical range (Roche Technical Bulletin - Bulletin 12-23v2 where concentrations <20 ng/L have been revised upwards due to certain lots of reagents losing signal at the low end),raises doubts on which concentrations are the most predictive of a future adverse cardiac outcome; as well as for early risk stratification for MI either in the short-term or long-term [4,15,16].

We have previously demonstrated that hs-cTnI does provide important risk stratification for MI and cardiovascular death in the Heart Outcomes Prevention Evaluation (HOPE) population at concentrations above and below the reported healthy population 99th percentile. We have also measured hs-cTnT in this population on a lot of reagent before the noted loss in signal at the low end. Thus, our objectives in this study were to assess different cutoffs based on outcomes, healthy population and general population upper limits of normal for ischemic cardiovascular outcomes over the long-term.

Methods

Study populations

The HOPE study design, population and results have previously been described [17,18]. Briefly, men and women ≥55 years ($n=9541$) who had either vascular disease or diabetes with at least one other cardiovascular risk factor (e.g., elevated total cholesterol levels, low high-density lipoprotein cholesterol (HDL-C) levels, documented microalbuminuria,

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hypertension, or cigarette smoking) without heart failure or a low ejection fraction were enrolled in the study [17]. Available baseline serum samples were measured with the hs-cTnT assay in this population ($n=2941$ patients) with this study having been approved by the Research Ethics Board.

Clinical events and hs-cTnT analysis

The main outcome was the primary outcome of the HOPE study: a composite of MI, stroke or cardiovascular death. Follow-up for these events occurred (mean 4.5 years) with adjudication by a central committee blinded to patients' status and biochemical values. Secondary analyses consisted of assessing individual cardiac outcomes: MI, cardiovascular death, and all HF (defined as HF causing death, HF hospitalisation, HF requiring open-label ACE inhibition, or development of typical symptoms, as previously reported) [19]. The hs-cTnT assay (lot 153-401; Troponin T hs (high sensitive); Roche Diagnostics) has an analytical range from 3 to 10,000 ng/L [20]. Measurements were performed on the Elecsys 2010 with the imprecision of the assay assessed at two different analytical levels; one below the published 99th percentile level for this assay (serum pool, mean 12.6 ng/L] and the other slightly above (Roche control material mean 28 ng/L). The hs-cTnT testing occurred over 4 months for the HOPE study (coefficient of variation (CV) = 26% for low serum pool and CV = 12% for Roche control material). The total imprecision of the hs-cTnT assay as determined in a multicentre evaluation ranges from 4.6% to 36.8% on concentrations ranging from 3.4 to 10.3 ng/L [21].

Statistical analysis

The HOPE cohort assessed in this study had similar characteristics as compared to the larger population [18]. Differences between subjects with and without the primary outcome in the HOPE cohort were assessed using Pearson chi-square test (categorical variables) and Wilcoxon two-sample test (continuous variables). The hs-cTnT concentrations were log-transformed and entered into logistic model for the primary outcome (MI, stroke, or cardiovascular death). Receiver operating characteristic (ROC) curve analysis was performed and the hs-cTnT concentration corresponding to the point that maximised the sensitivity and specificity was obtained. This concentration, the 95th percentile upper reference limit derived from the HOPE study (22 ng/L), and the 99th percentile from a healthy population (14 ng/L) [20,21] were compared with the log-rank test with respect to the primary outcome in one analysis with quartile analysis based on hs-cTnT concentrations being performed in an additional analysis as previous studies have employed quartile analyses [4]. This was followed with Cox proportional hazards models adjusted for age (continuous), sex (male, female), current smoker (yes, no), HDL-C (log transform) and peripheral vascular disease for the primary outcome (model 1 — same model used in previous analysis with hs-cTnI) [5].

A secondary analysis, with an additional cutoff (i.e., 31 ng/L) [22,23] was also performed for the primary outcome and for MI, HF or cardiovascular death. In this analysis Harrell's *c*-statistic [24] and Net Reclassification Improvement (NRI) [25] were calculated using leave-one-out cross validated predicted 4.5-year risk based on full and reduced Cox proportional hazards regression models. Full model (used in the PEACE study) [4] included hs-cTnT (continuous and log transformed), age (continuous), sex (male, female), current smoker (yes, no), and ramipril use (yes, no) (model 2). Reduced model included the covariates only. For Harrell's *c*-statistic [24], among the usable pairs a pair of two patients was concordant if the predicted 4.5-year risk was higher for the patient with the earlier event time and a pair was discordant if the predicted 4.5-year risk was lower for the patient with the earlier event time. Usable pairs were those that included at least one non-censored patient. NRI(>0) and NRI(3) correspond to, respectively, NRI with no categories and NRI with three categories of predicted 4.5-year risk: <6%, 6–20%, and >20%. For NRI(>0), a patient was "reclassified up" if their predicted 4.5-year risk based on full model was higher than the risk based on reduced model and "reclassified down" if their predicted 4.5-year risk based on full model was lower than the risk based on reduced model. For NRI(3), a patient was "reclassified up" if their risk category based on full model was higher than the risk category based on reduced model and "reclassified down" if their risk category based on full model was lower than the risk category based on reduced model. Kaplan–Meier estimates of 4.5-year survival were used to calculate NRI as described in Pencina et al. [25]. Analyses were performed in SAS version 9.1 (SAS Institute, Cary, NC).

Results

In the HOPE cohort, the hs-cTnT concentrations were detected (≥3 ng/L) in 69% of this population at baseline (Fig. 1) and were significantly higher in those with the primary outcome versus those without (Table 1). Increasing concentrations of hs-cTnT, as indicated by quartile analysis, demonstrated a higher probability for the primary outcome (Fig. 2a). However, in Cox analysis after adjusting for age, sex, diabetes, smoking, HDL-C and peripheral vascular disease (model 1), only those subjects in the highest quartile (hs-cTnT≥10.92 ng/L) had significantly higher risk for the primary outcome as compared to those in the lowest quartile (hazard ratio (HR) = 1.65 (95%CI:1.27–2.16); $p=0.002$).

ROC curve analysis for the primary outcome identified 8 ng/L as the hs-cTnT concentration that optimised the sensitivity and specificity. Cox analyses for 8 ng/L, 14 ng/L, and 22 ng/L as cutoffs were performed for the primary outcome resulting in the following HRs (after adjusting for variables in model 1): hs-cTnT ≥8 ng/L HR = 1.47 (95%CI:1.20–1.78), $p<0.001$; hs-cTnT ≥14 ng/L HR = 1.34 (95%CI:1.07–1.69), $p=0.012$; hs-cTnT ≥22 ng/L HR = 1.97 (95%CI:1.44–2.69), $p<0.001$.

To explore if concentration ranges translated to different risks, the population was further broken down into the following 4 groups based on the three cutoffs: <8 ng/L; 8 to <14 ng/L, 14 to 21 ng/L and >21 ng/L. Both the 8 to <14 ng/L and 14 to 21 ng/L groups displayed a similar probability for the primary outcome, with the group of hs-cTnT>21 ng/L at the highest probability for the primary outcome (Fig. 2b).

As the 8 to <14 ng/L and 14 to 21 ng/L groups had similar probability for the primary outcome, cox analyses were then performed based on the following three hs-cTnT concentration categories: <8 ng/L; 8 to 21 ng/L, and >21 ng/L for the primary composite outcome as well as the individual cardiac outcomes (i.e., MI, HF, cardiovascular death) (model 2; see Table 2). Inclusion of hs-cTnT to these models increased the c-statistic and the NRI for MI, HF and CV death (Table 3). Specifically, addition of hs-cTnT improved risk prediction for both patients with events and patients without events for all outcomes. Patients with MI had the greatest improvement in risk prediction (NRI(3) for events, 6.1%; NRI(3) total, 6.4%) compared with other outcomes. The total net improvement for HF was 7.3% (NRI(3) for events, 2.6%; NRI(3) for non-events, 4.7%). For the composite outcome of MI, stroke, and CV

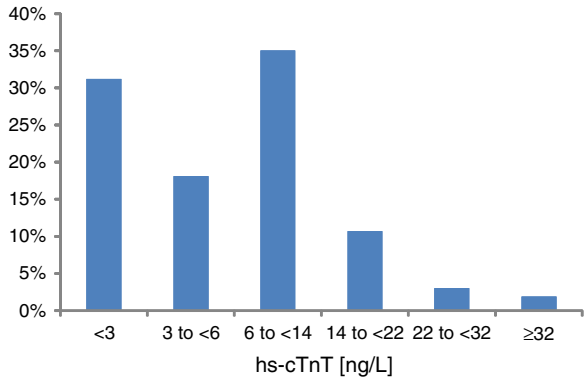

Fig. 1. Distribution of hs-cTnT in the HOPE cohort.