High-Sensitivity Cardiac Troponin I for Predicting Death in a Female Emergency Department Population

To the Editor:

The Third Universal Definition of Myocardial Infarction has indicated that “sex-dependent values may be recommended for high-sensitivity troponin assays” (1). This statement is supported by several reference-interval studies that reported that women had lower concentrations and 99th percentile cutoffs with the high-sensitivity assays than men (2, 3). Despite these findings, it is unclear whether this information—gained only from the use of high-sensitivity assays—would be important for diagnostic or prognostic purposes in the female population. Presently, only Roche Diagnostics’ high-sensitivity cardiac troponin T (hs-cTnT)1 assay and Abbott Diagnostics’ high-sensitivity cardiac troponin I (hs-cTnI) assay have been approved by regulatory bodies. These assays are in clinical use throughout the world (outside the US). Roche has discontinued the fourth-generation cTnT assay in jurisdictions where the cTnT assay has achieved regulatory approval; therefore, prospective comparisons of the readjusted hs-cTnT assay (in 2012) and the fourth-generation assay for assessing sex-specific clinical performance are no longer possible in many regions. Nevertheless, studies that assess both high-sensitivity and sensitive cTnI assays with respect to health outcomes in the female population are essential if sex-specific cutoffs are to be used. To this end, we performed a large prospective observational study of emergency department (ED) patients to assess whether an incremental benefit for predicting hospital death for women at presentation (compared with men) exists when a high-sensitivity cardiac troponin assay is used, vs. a sensitive cardiac troponin assay.

After ethics approval was obtained, every adult patient who presented to the ED at the Hamilton General Hospital and Juravinski Hospital and had a cTnI test (ARCHITECT STAT TnI; Abbott Diagnostics) and results over a period of 3 months also had the same sample measured with a hs-cTnI assay (ARCHITECT STAT hsTnI; Abbott Diagnostics), with the result blinded to the treating physician. During the study, commercial QC materials and the same patient pool material were also measured with both the cTnI and hs-cTnI assays on 3 different platforms. As expected, the imprecision (CV) values of the results for the pools were greater for the cTnI assay than for the hs-cTnI assay [19% for the ci8200 cTnI pool (n = 264; mean = 0.032 μg/L) vs. 4.8% for the hs-cTnI pool (n = 147; mean = 43.2 ng/L); 17% for the ci16200#1 cTnI pool (n = 197; mean = 0.032 μg/L) vs. 5.4% for the hs-cTnI pool (n = 103; mean = 40.8 ng/L); 12% for the ci16200#2 cTnI pool (n = 183; mean = 0.035 μg/L) vs. 4.7% for the hs-cTnI pool (n = 117; mean = 41.0 ng/L)]. After completion of the study, medical records were reviewed for all patient encounters in the ED (i.e., a new encounter of the same patient would be recorded if troponin measurements in the ED were 3 days apart) to ascertain if death occurred in the ED or after admission to the hospital from the ED (i.e., hospital death). For the present study, we carried out nonparametric analyses with the Mann–Whitney U-test (StatsDirect v.2.7.9; StatsDirect Ltd.) and ROC curve analyses [95% CIs calculated via the binomial exact method (MedCalc v.12; MedCalc Software)] with the ED-presentation cTnI and hs-cTnI results only for the ED encounters for which an ED disposition was recorded (i.e., 61 patient visits were not assessed because the patients left after receiving medical advice, after being seen, or after being triaged but not seen, or because the field was missing).

cTnI was measured at presentation for 5206 ED visits, with hs-cTnI detectable [limit of detection (LoD) > 1.2 ng/L] (2) in 93.3% (95% CI, 92.6%–94.0%) of EDTA-containing plasma samples [2552 samples (49%) from female patients]. The female population was older than the male population: a median of 73 years [interquartile range (IQR), 58–83 years] for females and 67 years (IQR, 54–79 years) for males (P < 0.001). There was no difference in the prevalence of hospital death between females (4.6%; 95% CI, 3.8%–5.5%) and males (5.2%; 95% CI, 4.5%–6.2%; P = 0.305), nor was there a difference between the sexes in the performance of the cTnI assay, as assessed by ROC curve analysis for death [area under the ROC curve (AUC) for females, 0.766 (95% CI, 0.749–0.782); AUC for males, 0.741 (95% CI, 0.724–0.757)]. With respect to the hs-cTnI assay, ROC curve analysis yielded a significantly higher AUC for women (0.793; 95% CI, 0.777–0.809) than for men (0.748; 95% CI, 0.731–0.764) (Fig. 1). Further analysis revealed no difference in hs-cTnI concentration between females with a hospital death (median, 35 ng/L; IQR, 12–92 ng/L) and males with a hospital death (median, 33 ng/L; IQR, 14–102 ng/L; P = 0.795). hs-cTnI concentrations in patients without the outcome, however, were significantly lower in the female population (median, 6 ng/L; IQR, 0.032 ng/L).

1 Nonstandard abbreviations: hs-cTnT, high-sensitivity cardiac troponin T (assay); hs-cTnI, high-sensitivity cardiac troponin I (assay); ED, emergency department; LoD, limit of detection; IQR, interquartile range; AUC, area under the ROC curve.
3–17 ng/L) than in the male population (median, 8 ng/L; IQR, 3–23 ng/L; P < 0.001).

Several studies that used the Abbott hs-cTnI assay demonstrated lower hs-cTnI concentrations in women, but with different derived 99th percentiles for the studies, mainly because of different selection criteria for classifying healthy individuals [i.e., 99th percentiles of 4.8 ng/L (4), 6.1 ng/L (3), 15 ng/L (2), 26.3 ng/L, and 48.3 ng/L (5)]. If the lowest reported 99th percentile that achieved a CV value of <10% (4.8 ng/L; CV, 9%) (4) is applied, the rate of detection of death is 94% (110 of 117 patients) with the hs-cTnI assay, compared with only 69% (81 of 117 patients) with the cTnI assay, with a cutoff of >0.01 μg/L (LoD, 0.01 μg/L). This result represents a 25% increase (95% CI, 2%–48%; P = 0.036) in the rate of predicting death when the hs-cTnI assay is used at this cutoff, compared with use of the LoD for the current sensitive cTnI assay. Lowering the hs-cTnI cutoff to a concentration corresponding to a 20% CV (2.0 ng/L) (5) or the LoD (1.2 ng/L) identified all 117 deaths in the female population.

These findings suggest that the increased analytical sensitivity of the hs-cTnI assay may be especially useful for the female population. A limitation to the present analysis is the limited clinical information and the incomplete information about cause of death; however, the large observational study assessing hs-cTnI performance in predicting death in the female population at ED presentation is noteworthy.

The lowest reported 99th percentiles for females (4.8 ng/L) [Tan et al. (4)] and males (13.0 ng/L) [Koerbin et al. (3)] are indicated by the solid arrows; the manufacturer’s reported 99th percentiles for females (15.6 ng/L) and males (34.2 ng/L) are indicated by the dashed arrows.

**Fig. 1.** ROC curves for death for hs-cTnI concentration at ED presentation in the male and female populations.

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Peter A. Kavsak2,3*
Colleen Shortt2
Greg Pond2
Andrew Worster2,3

2 McMaster University and
3 Hamilton Health Sciences
Hamilton, Ontario, Canada

* Address correspondence to this author at: Juravinski Hospital and Cancer Centre 711 Concession St. Hamilton, Ontario L8V 1C3 Canada E-mail kavsakp@mcmaster.ca

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