High-Sensitivity Cardiac Troponin I and T for Cardiovascular Risk Stratification in Adults With Diabetes

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Olive Tang,[1] Kunihiro Matsushita,[1] Josef Coresh,[1] Chiadi Ndumele,[1] John W. McEvoy,[2] A. Richey Sharrett,[1] Ron Hoogeveen,[3] Christie M. Ballantyne,[3] and Elizabeth Selvin[1]

New therapeutics for cardiovascular disease (CVD) prevention in diabetes are costly, highlighting the need for better risk stratification so that interventions may be targeted to those at the highest risk. High-sensitivity cardiac troponin I (hs-cTnI) and T (hs-cTnT) are measures of subclinical cardiac damage associated with cardiovascular risk in the general population (1,2). The troponins appear differentially associated with diabetes (3). We assessed whether hs-cTnI or hs-cTnT could improve cardiovascular and mortality risk stratification in adults with diabetes and whether elevated concentrations of either troponin (≥90th percentile) were associated with mortality risk similar to those having a history of clinical CVD.

We included 1,704 adults (ages 54–75 years) with diabetes (47.5% of whom were male, 33.8% Black, and 24.4% with CVD) in the Atherosclerosis Risk in Communities (ARIC) study who attended visit 4 (1996–1998). Diabetes status was defined based on self-reported physician diagnosis, medication use, or blood glucose (fasting ≥126 mg/dL; nonfasting ≥200 mg/dL).

hs-cTnI was measured in stored plasma using the ARCHITECT STAT High Sensitive Troponin-I assay (Abbott Diagnostics, Chicago, IL). hs-cTnT was measured in stored plasma using the Elecsys Troponin T assay (Roche Diagnostics, Indianapolis, IN). To compare hs-cTnI and hs-cTnT, we used percentile categories among those without CVD: <50th (reference), ≥50th to <75th, 75th to 90th, and ≥90th.

We examined incident CVD (N = 1,280): atherosclerotic CVD (ASCVD) (including myocardial infarction, revascularization procedure, or stroke) and heart failure (based on hospitalization, supplemented with adjudicated events after 2005) (4,5). The last date of follow-up was 31 December 2018 (median follow-up 19 years).

We used Cox regression and C-statistics to compare the prognostic value of hs-cTnI and hs-cTnT categories above and beyond a base model containing age, sex, race-center, smoking (current, former, never), BMI, systolic blood pressure, diastolic blood pressure, hypertension medication use, total cholesterol, HDL cholesterol, cholesterol-lowering medication use, estimated glomerular filtration rate with linear spline knot at 60 mL/min/1.73 m^2 (6), and preexisting CVD. The Fine and Gray method (7) was used to account for noncardiovascular mortality as a competing risk for cardiovascular mortality and all-cause mortality as a competing risk for incident CVD analyses. All protocols were approved by institutional review boards at each study center, and all participants provided written informed consent.

There were 1,102 (443 CVD) deaths. Higher levels of both high-sensitivity troponins at baseline were robustly associated with mortality risk. The 10-year cumulative mortality was 37.4% among those with hs-cTnI ≥90th percentile and no CVD and 44.6% among those with hs-cTnT ≥90th percentile and no CVD compared with 43.1% among those with preexisting CVD. After adjustment for traditional risk factors, both high-sensitivity troponins were independently associated with and significantly improved model discrimination for all-cause and cardiovascular mortality risk (Fig. 1). Neither troponin was significantly more discriminative than the other for mortality risk (all-cause, $P_{comparison} = 0.14$, and cardiovascular, $P_{comparison} = 0.07$).

Among those without CVD, there were 465 incident ASCVD and 416 incident heart failure events. Higher levels of either high-sensitivity troponin were associated with higher risk of both outcomes (Fig. 1), and both troponins similarly improved model discrimination for both outcomes (ASCVD, $P_{comparison} = 0.18$, and heart failure, $P_{comparison} = 0.29$). In a secondary analysis of middle-aged adults without CVD, there was no effect modification of diabetes status on the association of hs-cTnI or hs-cTnT with mortality or cardiovascular risk (all $P_{interaction} > 0.05$ and data not shown).

[1]*Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD*
[2]*Division of Cardiology and National Institute for Prevention and Cardiovascular Health, National University of Ireland, Galway, Galway, Ireland*
[3]*Department of Medicine, Baylor College of Medicine, Houston, TX*

Corresponding author: Elizabeth Selvin, eselvin@jhu.edu

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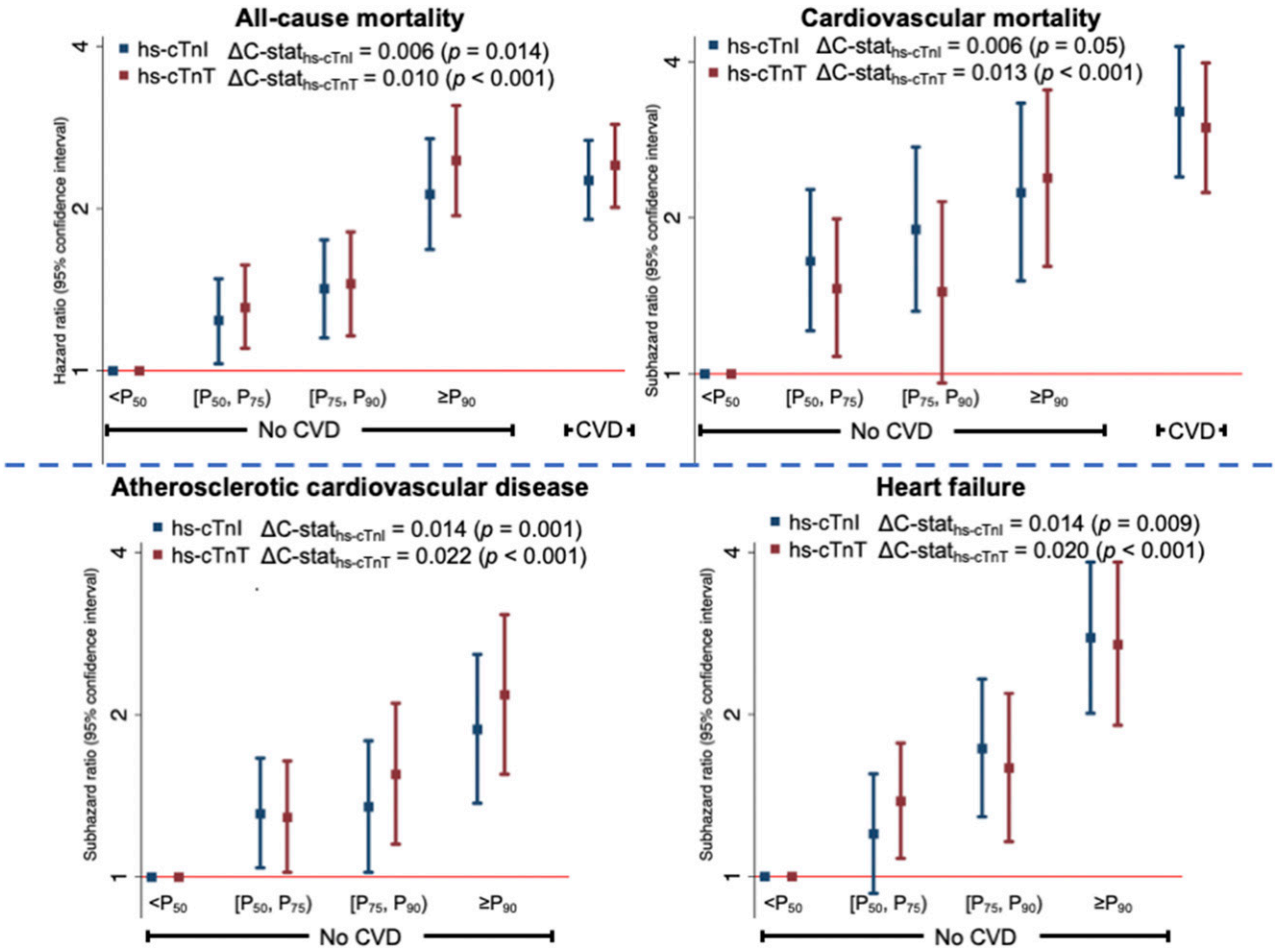

Figure 1—Relative (hazard ratios and 95% CIs) risks of mortality (N = 1,704) and incident CVD (N = 1,288) by troponin categories among middle-aged adults with diabetes. Changes in C-statistics (ΔC-stat) are in comparison with a base model including age, sex, race-center, smoking (current, former, never), BMI, systolic blood pressure, diastolic blood pressure, hypertension medication use, total cholesterol, HDL cholesterol, cholesterol-lowering medication use, estimated glomerular filtration rate with linear spline knot at 60 mL/min/1.73 m^2, and preexisting CVD. The base model C-statistics were as follows: 0.6998 for all-cause mortality, 0.6764 for cardiovascular mortality, 0.6305 for incident ASCVD, and 0.6365 for incident heart failure. P refers to percentiles of troponin among those without preexisting CVD (e.g., P$_{50}$ refers to the 50th percentile).

There was evidence that hs-cTnI and hs-cTnT may be differentially associated with certain clinical characteristics, such as diabetes, and have differential risk associations in certain populations (3,8). Risk stratification in diabetes is of particular importance given the growing availability of costly cardioprotective antihyperglycemic therapies. Our findings suggest that a single measurement of hs-cTnI or hs-cTnT in middle age could be used for risk stratification. We demonstrated that high concentrations of hs-cTnI or hs-cTnT in this general population identify high-risk subgroups with elevated mortality risk, approaching risks observed among those with existing CVD.

As with any observational study, there is potential for residual confounding; however, the extensive measurements in ARIC have allowed us to control for the major cardiovascular risk factors and evaluate the independent association of each troponin with cardiovascular outcomes beyond traditional risk factors. Few prior studies have had simultaneous measurements of both hs-cTnI and hs-cTnT, allowing for analyses comparing the two biomarkers. Our study also benefitted from comprehensive surveillance and adjudication of CVD events.

In a general population of middle-aged adults with diabetes, subclinical levels of both hs-cTnI and hs-cTnT were robustly associated with long-term mortality and cardiovascular risk. Those persons with high-sensitivity troponin values >90th percentile had risks on par with risks of persons with a history of clinical CVD. Our findings suggest that hs-cTnI or hs-cTnT can be used to improve risk stratification in diabetes to help guide clinical management.

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Author Contributions. O.T. and E.S. designed the study and drafted the manuscript. O.T. conducted the analyses. O.T., K.M., J.C., C.N., J.W.M., A.R.S., R.H., C.M.B., and E.S. provided data interpretation and meaningful contributions to the revision of the manuscript. O.T. and E.S. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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