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Short Report

Four high sensitivity troponin assays and mortality in US adults with cardiovascular disease: The national health and nutrition examination survey, 1999–2004

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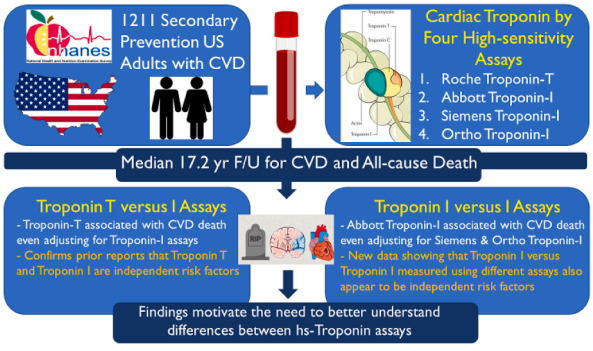
HIGHLIGHTS

- Correlations between the 4 hs-cTn assays were modest in this cohort of US adults with a prior history of CVD.
- Each assay had a similar strength of association with residual risk for all-cause and CVD death.
- Mortality associations remained significant after mutual adjustment for hs-cTn concentrations from the different assays (i.e., modeling hs-cTnT vs hs-cTnI assays and hs-cTnI vs hs-cTnI assays).
- Therefore, in secondary prevention, hs-cTn assays are not interchangeable and are independently associated with residual risk of all-cause and CVD death.
- With future more widespread use of hs-troponin testing in risk assessment, it is important that these results motivate research into understanding why the correlations between these assays are not higher (even when assays are measuring concentrations of the same troponin subunit) and how they can provide independent associations with adverse outcomes.

GRAPHICAL ABSTRACT



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ABSTRACT

Objective: High sensitivity cardiac troponin (hs-cTn) may be useful to monitor residual risk in secondary prevention. Our objective was to study the correlations and comparative associations with mortality of four hs-cTn assays in US adults with known cardiovascular disease (CVD).

Methods: We studied 1,211 adults with a history of CVD who participated in the National Health and Nutrition Examination Survey (NHANES) 1999–2004. Using stored samples, we measured hs-cTnT (Roche) and three hs-cTnI assays (Abbott, Siemens, and Ortho). Outcomes were all-cause and CVD mortality, with follow-up through December 31, 2019.

Results: Mean age was 64 years, 48 % were female, and 80 % identified as non-Hispanic White. Pearson's correlation coefficients between hs-cTn assays ranged from 0.67 to 0.85. There were 848 deaths (365 from CVD). Among adults with a history of prior non-fatal CVD, each hs-cTn assay (log-transformed, per 1-SD) was independently associated with CVD death (HRs ranging from 1.55 to 2.16 per 1-SD, all p-values <0.05) and with all-cause death (HRs ranging from 1.31 to 1.62 per 1-SD, all p-values <0.05). Associations of hs-cTnT and all-cause and CVD death remained significant after adjusting for hs-cTnI (and vice versa). Associations between hs-cTnI and CVD death remained significant after mutually adjusting for other individual hs-cTnI assays: e.g., HR 2.21 (95 % CI 1.60, 3.05) for Ortho (hs-cTnI) after adjustment for Siemens (hs-cTnI) and HR 1.81 (95 % CI 1.35, 2.43) for Ortho (hs-cTnI) after adjustment for Abbott (hs-cTnI).

Conclusion: In US adults with a history of CVD, we found modest correlations between 4 hs-cTn assays. All assays were associated with all-cause and CVD mortality. The hs-cTnT assay was associated with mortality independent of the hs-cTnI assays. Hs-cTnI assays also appeared to be independent of each other. Thus, hs-cTn assays may provide distinct information for residual risk in secondary prevention adults.

1. Introduction

Originally designed to expedite the diagnosis of myocardial infarction, high-sensitivity cardiac troponin (hs-cTn) assays have since emerged as prognostic biomarkers associated with cardiovascular disease (CVD) outcomes in a range of settings [1–3]. One of these settings is in the care of adults with a history of CVD who are being managed for secondary prevention [4–6].

A number of hs-cTn assays have been developed and marketed; however, relatively little is known about their comparative prognostic performance. Emerging evidence in adults without a history of CVD suggest that hs-cTnT remains associated with cardiovascular events and death in models adjusted for hs-cTnI and vice versa [7–9]. Fewer studies have evaluated different hs-cTnI assays and compared them to hs-cTnT in a secondary prevention setting [4,5,10,11]. One such study suggested that hs-cTnT and hs-cTnI assays may also provide independent prognostic information in adults with a history of CVD [5]. However, representative data from the national US adult population are lacking and it is also unknown whether hs-cTnI assays provide prognostic information independently of the other hs-cTnI assays in secondary prevention.

To better understand these knowledge gaps, we measured hs-cTnT using the Roche assay and hs-cTnI using assays from 3 different manufacturers in secondary prevention adults with a known history of CVD participating in the 1999–2004 National Health and Nutrition Examination Survey (NHANES). The aims of the present analysis were to evaluate correlations between the 4 assays and to characterize their associations with all-cause and CVD mortality.

2. Methods

The NHANES is designed to be a nationally representative sample of the US population. Participants were selected from the US noninstitutionalized, civilian population using a complex, stratified, multistage probability cluster sampling design. We included individuals aged $\geq$20 years in NHANES 1999–2004 who self-reported a history of CVD (congestive heart failure, coronary heart disease, angina, heart attack, or stroke) and who had data on mortality linkage and available hs-cTn concentrations for all 4 assays. Persons without available stored sample for hs-cTn measurement were excluded (n = 520). The NHANES protocols and the measurement of hs-troponin in stored specimens was approved by the National Center for Health Statistics ethics review board. Written informed consent was obtained from all participants. The NHANES data, including cardiac troponin, are publicly available at the Center for Disease Control website (https://wwwn.cdc.gov/nchs/nhanes/).

Demographics and other covariables were measured in 1999–2004. Troponin was measured at the University of Maryland School of Medicine (Baltimore, Maryland, USA) between 2018 and 2020 using stored serum samples. These samples had been obtained in all consenting NHANES participants in 1999–2004 and frozen for storage. The majority (93 %) of stored serum samples used for hs-cTn measurement had never undergone a prior freeze-thaw cycle. Hs-cTnT was measured with the Roche Cobas e601 using gen 5 Elecsys assay reagents. The lower limit of quantification (LoQ) and lower limit of detection (LoD) for this assay are 6 and 3 ng/L, respectively. Coefficients of variation (CVs) were 3.1 % (at concentrations of 26 to 31 ng/L) and 2.0 % (at concentrations 2005 to 2216 ng/L). Hs-cTnI (Abbott) was measured using ARCHITECT i2000SR. The LoQ and LoD for this assay are 2.3 and 1.7 ng/L, respectively. The CVs were 6.4 % (at concentrations 8 to 16 ng/L), 3.5 % (at concentrations 169 to 314 ng/L), and 6.7 % (at concentrations 2758 to 4444 ng/L). Hs-cTnI (Siemens, TNIH) was measured using Centaur XPT. The LoQ and LoD for this assay are 2.5 and 1.6 ng/L, respectively. The CVs were 3.8 % (at concentrations 12 to 28 ng/L) and 2.6 % (at concentrations 9000 to 21,000 ng/L). Hs-cTnI (Ortho) was measured using Vitros 3600 (not currently FDA approved). The LoQ and LoD for this assay are1.23 and 0.39 ng/L, respectively. The CVs were 4.2 % (at concentrations 6 to 16 ng/L) and 2.8 % (at concentrations 17,511 to 21,403 ng/L). More details on hs-cTn measurement in NHANES are available at the Center for Disease Control website and in prior publications [9,12-14]. Vital status was ascertained through a probabilistic match between NHANES personal identifiers and linkage to death certificates from the National Death Index through December 31, 2019. Cardiovascular disease mortality was ascertained according to the recorded cause of death using International Classification of Diseases (ICD) 10 codes (I00-I78).

For all analyses we used survey weights to generate estimates representative of the 1999–2004 US adult population. After log-transformation to approximate a normal distribution and using only concentrations above the assay limit of blank, we generated weighted Pearson correlation coefficients and sunflower plots (a type of scatterplot used to illustrate data density) between the 4 hs-cTn assays.

To evaluate associations with all-cause and CVD mortality, we used Cox regression with hs-cTn concentrations modeled per 1 SD increase on

the log scale. We also modeled the hs-cTn assays as restricted cubic splines (with 4 knots at 5th, 35th, 65th and 95th percentiles). To put the different assays on equal footing and since hs-troponin concentrations below the LoD have been reported to contain prognostic information [15], we included concentrations below the LoD for each assay in all Cox models [12]. The proportionality assumption was assessed using Schoenfeld residuals. Using the Wald Test we generated multiplicative interaction p-values in groups defined by age (<60 vs ≥60 years), sex, and race/ethnicity. Due to multiple testing, we considered $p<0.01$ significant for these interactions. We followed STROBE Reporting Guidelines. All analyses were conducted using Stata version 17.0 between March 2023 and May 2023.

3. Results

We studied 1211 adult NHANES participants with a self-reported prior history of CVD. The weighted mean age was 64.1 years, 48 % were female, 80 % identified as non-Hispanic White, and 9.9 % identified as non-Hispanic Black (**Supplement, eTable 1**). The Pearson's correlations ranged from $r = 0.67$ for hs-cTnT versus Siemens hs-cTnI to $r = 0.85$ for Abbott hs-cTnI versus Siemens hs-cTnI (**Supplement, eFigure 1**).

There were 848 deaths (365 cardiovascular) during a median follow-up of 17.2 years (maximum, 20.8 years). All 4 hs-cTn assays were robustly and independently associated with all-cause and CVD mortality (Fig. 1 **and Supplement eTable 2**). The magnitude (slope) of associations between each assay and all-cause and CVD mortality were similar overall (Fig. 1 **and Supplement eFigure 2**). There were no significant differences according to age-, sex-, or race/ethnicity, with interaction p-values all ≥0.01 for all-cause and CVD mortality (**Supplement eTable 2**).

Hs-cTnT was independently associated with all-cause and CVD mortality after individual adjustment for each of the hs-cTnI assays (Table 1). Except for the Siemens assay, hs-cTnI concentrations were independently associated with all-cause and CVD mortality after adjustment for hs-cTnT. The Ortho hs-cTnI assay remained significantly associated with all-cause and CVD mortality after adjustment for the Siemens hs-cTnI or the Abbott hs-cTnI assay. The Abbott hs-cTnI was also significantly associated with all-cause mortality after further adjustment for each of the other hs-cTnI assays. The Siemens hs-cTnI assay was no longer significantly associated with CVD or all-cause mortality after adjustment for the Abbott or Ortho hs-cTnI assays.

4. Discussion

In a general population of US adults with a self-reported prior history of CVD, we found robust and independent associations of hs-cTnT and three hs-cTnI assays with all-cause and CVD mortality. The prognostic value for mortality was consistent across population subgroups defined by age, sex, and race/ethnicity. Associations of hs-cTnT with death

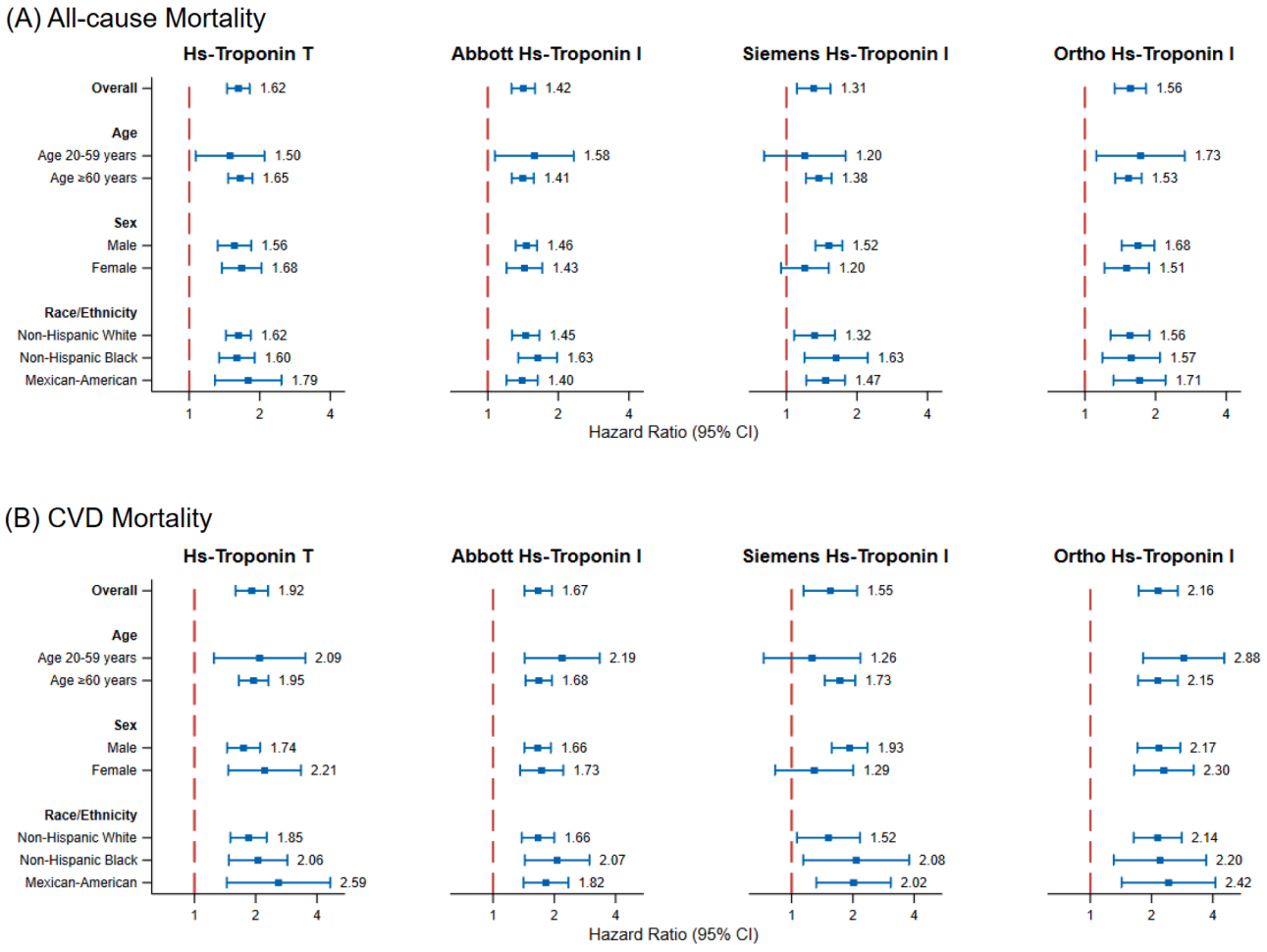

Fig. 1. Adjusted* HR (95 %CI) of log-transformed high-sensitivity cardiac troponin (per 1-SD) with all-cause (panel A) and cardiovascular mortality (panel B), overall and according to age, sex, race/ethnic groups. *Hs-troponin modeled as a continuous (per 1 SD increase on the log scale) exposure, and model adjusted for age, sex, race/ethnicity, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, cigarette smoking status, diabetes mellitus, family history of CVD, body mass index, use of blood pressure medications, use of cholesterol-lowering medications, and eGFR. CVD, cardiovascular disease; SD, standard deviation; eGFR, estimated glomerular filtration ratio.

Table 1
Adjusted* HR (95 %CI) for log-transformed high-sensitivity cardiac troponin (per 1 SD) with all-cause mortality with and without mutual adjustment for the other hs-troponin assays.

	Roche Hs-cTnT Hazard Ratio (95 % CI)	Abbott Hs-cTnI Hazard Ratio (95 % CI)	Siemens Hs-cTnI Hazard Ratio (95 % CI)	Ortho Hs-cTnI Hazard Ratio (95 % CI)
All-cause mortality				
Model 1	1.62 (1.45, 1.81)	1.42 (1.26, 1.59)	1.31 (1.11, 1.54)	1.56 (1.34, 1.82)
Model 1 plus Roche hs-cTnT†	–	1.18 (1.03, 1.34)	1.08 (0.92, 1.25)	1.27 (1.09, 1.48)
Model 1 plus Abbott hs-cTnI†	1.46 (1.27, 1.67)	–	0.94 (0.77, 1.15)	1.33 (1.11, 1.60)
Model 1 plus Siemens hs-cTnI†	1.56 (1.39, 1.77)	1.49 (1.25, 1.77)	–	1.52 (1.24, 1.86)
Model 1 plus Ortho hs-cTnI†	1.43 (1.27, 1.61)	1.20 (1.04, 1.38)	1.04 (0.86, 1.26)	–
CVD mortality				
Model 1	1.92 (1.59, 2.30)	1.67 (1.43, 1.95)	1.55 (1.14, 2.10)	2.16 (1.73, 2.69)
Model 1 plus Roche hs-cTnT†	–	1.32 (1.11, 1.57)	1.17 (0.87, 1.57)	1.65 (1.33, 2.05)
Model 1 plus Abbott hs-cTnI†	1.59 (1.32, 1.91)	–	0.90 (0.64, 1.26)	1.81 (1.35, 2.43)
Model 1 plus Siemens hs-cTnI†	1.78 (1.44, 2.19)	1.81 (1.39, 2.37)	–	2.21 (1.60, 3.05)
Model 1 plus Ortho hs-cTnI†	1.47 (1.23, 1.75)	1.17 (0.94, 1.46)	0.97 (0.68, 1.39)	–

* Model 1- association of each hs-cTn assay (columns 2 to 5) with events after adjusting for age, sex, race/ethnicity, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, cigarette smoking status, diabetes mellitus, family history of CVD, body mass index, use of blood pressure medications, use of cholesterol-lowering medications, and eGFR.

† These models report the association of each hs-cTn exposure with mortality, after adjustment for the variables in Model 2 and concentrations from one other hs-cTnassay (i.e., these models contain 2 hs-cTn assays).

SI conversion factor: To convert hs-cTn to micrograms per liter, divide by 1000. CVD, cardiovascular disease; SD, standard deviation; eGFR, estimated glomerular filtration ratio.

remained significant after adjustment for hs-cTnI concentration (and vice versa), confirming that troponin T and I are independent risk factors for death in secondary prevention. Similarly, associations of the Abbott and Ortho hs-cTnI assays with death also remained significant after mutual adjustment for the other hs-cTnI assays.

Hs-cTn may be an important tool to measure residual CVD risk in secondary prevention [4–6]. The current NHANES results are important as this cohort is designed to be representative of the diverse US adult population and because of the ability to test for any differences in important subgroups (including by sex and race/ethnicity). In addition, the strengths of associations between the various hs-cTn assays and events in this secondary prevention NHANES analysis are very similar to prior reports [8,9], providing construct validity to our results. Routine monitoring of hs-cTn in adults with a history of CVD also has potential to inform the intensity of secondary prevention treatment and the allocation of newer therapeutics. For example, a report from the LIPID (Long-Term Intervention With Pravastatin in Ischaemic Disease) study suggested that the intensity of lipid lowering therapy can reduce circulating cardiac troponin levels and that these reductions are associated with lower risk for recurrent CVD events [16]. Similar results were reported in WOSCOPS (West of Scotland Coronary Prevention Study) [17].

Our results match those of the secondary prevention PEACE (Prevention of Events With Angiotensin-Converting Enzyme Inhibitor Therapy) study cohort [5], as well as reports from primary prevention cohorts, demonstrating the prognostic independence of hs-cTnT vs hs-cTnI [7–9]. It has been speculated that these independent associations may relate to reduced correlation between the hs-cTnT and hs-cTnI assays due to factors like skeletal muscle disease [18,19] or to differences in the relationship of renal dysfunction and concentrations of hs-cTnT vs hs-cTnI [20].

We also found surprisingly low correlations between hs-cTnI assays from three different manufacturers. We have recently described similar results in a primary prevention sample of NHANES participants [9], but we are not aware of any prior analyses comparing multiple hs-cTnT and hs-cTnI assays in a secondary prevention sample. While, in theory, the three hs-cTnI assays are measuring the same sub-unit of the troponin protein complex (and should therefore have Pearson correlation efficients approaching 1.0), the assays differ with respect to binding sites of capture and detection antibodies, which may be relevant because troponin-I is often fragmented in circulation [21]. Indeed, modest concordance across hs-troponin assays has been previously noted in acutely symptomatic patients with suspected MI [22–24]. Hs-troponin assays are also heterogeneously affected by heterophile-antibodies, macro-troponin, and spuriously elevated results (so-called 'fliers') [25–30]. These considerations, along with the independent associations of each of the hs-troponin I assays with events, suggests that there may be fundamental differences in what is being measured by these hs-troponin I assays. Before their deployment as markers of residual risk in secondary prevention adults, a better understanding of these differences and their mechanisms is needed.

There are limitations to this study. This is an observational analysis and we cannot exclude the possibility of residual confounding explaining the association between hs-cTn and events. History of CVD was self-reported, which may have resulted in misclassification. CVD death was classified based on ICD codes and we did not have information on non-fatal cardiovascular events. Results might also differ in a more contemporary cohort.

Our results highlight the importance of hs-cTn as a biomarker to monitor residual risk in secondary prevention. Furthermore, hs-cTn assays are not directly interchangeable and are independently associated with mortality risk. These findings also motivate new lines of investigation into better understanding the differences between the hs-cTnT and the various hs-cTnI assays.

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CRediT authorship contribution statement

John W. McEvoy: Conceptualization, Validation, Writing – original draft. **Dan Wang:** Data curation, Formal analysis, Validation, Writing –

review & editing. **Olive Tang:** Writing – review & editing. **Michael Fang:** Writing – review & editing. **Chiadi E. Ndumele:** Writing – review & editing. **Josef Coresh:** Writing – review & editing. **Robert H. Christenson:** Data curation, Formal analysis, Project administration, Validation, Writing – review & editing. **Elizabeth Selvin:** Funding acquisition, Supervision, Project administration, Validation, Writing – original draft.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Robert Christenson reports financial support was provided by Roche Diagnostics Corp. Robert Christenson reports financial support was provided by Fujirebio Diagnostics Inc. Robert Christenson reports financial support was provided by Beckman Coulter Inc. Robert Christenson reports financial support was provided by Siemens Healthcare Diagnostics GmbH. Robert Christenson reports financial support was provided by Ortho-Clinical Diagnostics Inc. Robert Christenson reports financial support was provided by Becton Dickinson and Company. Robert Christenson reports financial support was provided by Abbott Diagnostics. Robert Christenson reports financial support was provided by Mitsubishi Chemical Corporation. Robert Christenson reports financial supportwas provided by HORIBA Scientific. Robert Christenson reports financial support was provided by Pixcell Medical. Robert Christenson reports financial support was provided by QuidelOrtho Corporation. Robert Christenson reports financial support was provided by Siemens Healthineers. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2023.100631.

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