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Patterns and Determinants of Temporal Change in High-sensitivity Cardiac Troponin-T: The Atherosclerosis Risk in Communities Cohort Study

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Abstract

Background—Patterns and determinants of temporal change in highly-sensitivity troponin-T (hs-cTNT), a novel measure of subclinical myocardial injury, among asymptomatic persons have not been well characterized.

Methods—We studied 8,571 ARIC Study participants, free of cardiovascular disease, who had hs-cTNT measured at two time-points, 6 years apart (1990–1992 and 1996–1998). We examined the association of baseline 10-year atherosclerotic cardiovascular (ASCVD) risk-group (<5%, 5–

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Contributorship statement: Dr McEvoy designed the analysis plan, assisted in statistical analyses, and drafted the manuscript. Ms Chen and Ms Shen both conducted statistical analyses. Drs Lazo, Nambi, Hoogeveen, Ballantyne, Blumenthal, and Coresh contributed to critical manuscript revisions for important intellectual content. Dr Selvin designed the analysis plan, contributed to critical manuscript revisions for important intellectual content, provided access to data, and supervised the study. Drs McEvoy and Selvin had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Each author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

Supplementary information is provided in an Online Appendix.

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7.4%, 7.5%) and individual cardiac risk-factors with change across hs-cTNT categories using Poisson and Multinomial Logistic regression and with mean continuous hs-cTNT change using linear regression.

Results—Mean age was 57 years and 43% were male. Mean (SD) 6-year hs-cTNT change was higher across increasing ASCVD risk-groups; +1.2 (6.1) ng/L [$<5\%$], +2.1 (5.4) ng/L [5–7.4%], and +2.8 (8.8) ng/L [7.5%]. Major baseline determinants of temporal hs-cTNT increases were; age, male gender, hypertension, diabetes, and obesity. In addition, the relative risk (RR) of incident elevated hs-cTNT (≥ 14 ng/L) was 1.46 (95% CI 1.1–2.0) for persons with sustained hypertension compared to those who remained normotensive. Results for sustained obesity (RR 1.65 [1.19–2.29]) and hyperglycemia (RR 1.76 [1.16–2.67]) were similar. These associations were generally stronger after accounting for survival bias. However, smoking, LDL-cholesterol and triglycerides were not associated with hs-cTNT change. HDL-cholesterol was associated with declining hs-cTNT.

Conclusions—Persons in higher ASCVD risk-groups were more likely to have increases in hs-cTNT over 6 years of follow-up. The modifiable risk-factors primarily driving this association were diabetes, hypertension, and obesity; particularly when they were persistently elevated over follow-up. Future studies are needed to determine whether modifying these risk factors can prevent progression of subclinical myocardial injury.

Keywords

High-sensitivity troponin; Biomarker; Temporal change; Subclinical Myocardial Injury

INTRODUCTION

Troponin is an established biomarker of myocardial cell injury and is widely used in the clinical diagnosis of acute coronary syndrome (ACS). New highly sensitive assays could greatly expand the role of troponin testing, for example as a prognostic biomarker in asymptomatic populations.¹² Indeed, high-sensitivity cardiac Troponin-T (hs-cTNT) assays can detect troponin in a significant proportion of asymptomatic individuals without known atherosclerotic cardiovascular disease (ASCVD) and has been shown to independently predict all-cause mortality, cardiovascular death, heart failure, stroke, and sudden cardiac death.^{3–7}

As the evidence-base for this assay as a prognostic biomarker in asymptomatic ambulatory persons continues to grow, it has become increasingly important to better understand and quantify expected temporal change hs-cTNT over time. Such change likely reflects underlying progression of subclinical myocardial injury, either due to vascular or myocardial disease.²⁸ However, to our knowledge, there have been no prior studies that focus specifically on patterns and determinants of temporal hs-cTNT change in asymptomatic persons over the long term. Exploring clinical variables that are most strongly associated with temporal increases in hs-cTNT could also provide mechanistic insight into the progression of subclinical myocardial injury. This line of investigation may yield targets for pharmacologic interventions designed to reduce myocardial injury, as well as informing the utility of change in hs-cTNT as a surrogate-endpoint biomarker in trials and other

clinical studies.⁹ Thus, we sought to characterize hs-cTNT change in an asymptomatic community-based population over 6-years of follow-up, hypothesizing that hs-cTNT change would differ based on global cardiac risk and modifiable risk factors.

METHODS

Study Population

The Atherosclerosis Risk in Communities (ARIC) Study is a community-based prospective observational cohort of 15,792 participants sampled from four U.S. communities (Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis, Minnesota; and Washington County, Maryland). Full recruitment details are previously published.¹⁰ Institutional review boards at each clinical site reviewed the study and informed consent was obtained from all participants. We measured Hs-cTNT at two time points, 6 years apart: visit 2, which took place from 1990 to 1992 and visit 4, which took place from 1996 to 1998. Of the 11,656 persons who attended both the baseline (visit 2, 1990–1992) and follow-up (visit 4, 1996–1998) examinations, we excluded all persons who had coronary heart disease, stroke, or heart failure at or prior to visit 4 (n=1,619), or who were missing variables of interest (n=1,466). Thus, 8,571 persons were included in our main analysis sample (online appendix and eFigure 1).

Assessment of Risk Factors

Risk factor values from visit 2 were used for the primary analysis. Participants self-reported alcohol use and smoking status. Plasma lipid concentrations and body mass index (BMI) were measured using standardized protocols. Blood pressure (BP) was recorded as the mean of the last 2 of 3 seated measurements. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or the use of medications prescribed for hypertension. Left ventricular hypertrophy (LVH) was assessed using resting 12-lead electrocardiograms and defined by Cornell criteria.

Glucose was measured using the hexokinase method and HbA1c was measured in stored whole-blood samples, both at visit 2.¹¹ Diagnosed diabetes was defined as a self-reported physician diagnosis of diabetes or current use of diabetic medications. C-reactive protein was measured in 2012–13 in stored serum samples drawn at visit 2 (Roche Diagnostics). Glomerular filtration rate was estimated using serum creatinine and the CKD-EPI 2009 equation.¹² Categories of 10-year estimated ASCVD risk ($<5\%$, 5–7.4%, and $\geq 7.5\%$), a surrogate measure for overall risk-factor burden, were calculated using visit 2 variables as per 2013 American Heart Association/American College of Cardiology risk assessment guidelines.¹³

Measurement of Cardiac Troponin T using a Highly Sensitive assay (hs-cTnT)

Cardiac troponin T was measured at 2 time points, 6 years apart, using the same highly sensitive (precommercial) sandwich immunoassay method (Roche Elecsys T, Roche Diagnostics, Indianapolis, IN). We measured hs-cTnT in stored serum samples collected at visit 2 using a Roche Elecsys 2010 Analyzer (Roche Diagnostics, Indianapolis, Indiana) at the University of Minnesota in 2012–2013. Samples had been stored since collection at

–70°C. Coefficients of variation (CVs) were 6.0% at a mean cTnT concentration of 25 ng/L and 3.7% at a concentration of 1940 ng/L.⁸ We measured hs-cTnT in stored plasma samples from visit 4 using the same assay implemented on a Cobas e411 analyzer (Roche Diagnostics, Indianapolis, Indiana) at Baylor College of Medicine in 2010. Plasma samples had been stored since collection at –80°C. CVs were 6.9% and 2.6% at mean cTnT concentrations of 29 ng/L and 2378 ng/L.¹⁴ Finally, a formal calibration study evaluating heterogeneity across specimen type and laboratory has been conducted and no significant differences were observed (N=200 paired samples).¹⁵

Statistical Analyses

We evaluated the associations between baseline (visit 2) risk factors and the outcome of change in hs-cTnT over 6 years, modeled using two approaches; mean change as a continuous outcome (calculated as visit 4 hs-cTnT level minus visit 2 hs-cTnT) and proportional change within pre-defined categories: “undetectable” (hs-cTnT <5 ng/L), “detectable” (hs-cTnT ≥ 5 and <14 ng/L), or “elevated” (hs-cTnT ≥ 14 ng/L).⁴⁷ With respect to our hs-cTnT categories, while the hs-cTnT assay can measure concentrations of troponin as low as 3 ng/L³, values <5 ng/L are measured with less precision. Thus, 5 ng/L is a typical lower threshold used to define reliable detection and was used as the cut-off for our ‘detectable’ category. To evaluate hs-cTnT change over time across these hs-cTnT categories, we defined the following binary outcomes; a) “Incident detectable” (progression from <5 ng/L at baseline to ≥ 5 ng/L at the follow-up visit); and b) “Incident elevation” (progression from <14 ng/L at baseline to ≥ 14 ng/L at the follow-up visit).

The continuous outcome of mean absolute hs-cTnT change was modeled using multivariate linear regression. In these continuous outcome analyses, we included measurable outcomes values between 3 and 5 ng/L and unmeasurable hs-cTnT levels were assigned a value of half the lower limit of measurement (1.5 ng/L).¹⁶ For the categorical troponin change outcomes, we used multivariable Poisson regression models to estimate the relative risks (cumulative incidence ratios) for each of the above binary troponin change outcomes. For all outcomes we constructed two models: 1) ASCVD risk factor categories alone; and 2) an individual cardiac risk-factor model. The latter cardiac risk factor model was adjusted for: age (years), race (black, white), gender, body mass index ≥ 30 kg/m² (vs. <30 kg/m²), C-reactive protein ≥ 2 mg/L (vs. <2 mg/L), smoking (current; former; never), hypertension (yes, no), LVH (yes, no), diagnosed diabetes (yes, no), LDL-cholesterol (mg/dL), HDL-cholesterol (mg/dL), triglycerides (mg/dL), current use of cholesterol-lowering medication (yes or no), estimated glomerular filtration rate <60 mL/min/1.73m² (vs. ≥60 mL/min/1.73m²), and alcohol use (current; former; never).

For the continuous change outcome, we conducted a sensitivity analysis that adjusted for visit-2 hs-cTnT in the cardiac risk-factor model. In addition, to better define the longitudinal impact of hypertension, hyperglycemia, and obesity on subclinical myocardial injury, we also analyzed these variables as time-varying categorical exposures measured at the three study visits encompassing ARIC visits 2 through 4 (Supplemental appendix). Furthermore, we included a sensitivity analysis evaluating the association between our exposures of interest and declining troponin, defined categorically (Supplemental Appendix).

Finally, we conducted sensitivity analyses designed to address the survival bias that is inherent to repeat assessment of biomarkers over time (e.g. unhealthy individuals are less likely to have repeat troponin measurement at the 6-year follow-up visit due to intervening deaths between visits 2 and 4). These competing-risks sensitivity analyses required a different analytic sample (N=9,651) than our main analysis sample of 8,571 participants (eTable1) and were performed for the categorical troponin change outcomes only. For these analyses, we performed multinomial logistic regression evaluating the odds of either incident detectable or incident elevated troponin levels that were conditional on the competing outcomes of ASCVD death (coronary heart disease, heart-failure or stroke death) or non-ASCVD death between visit 2 and visit 4, in persons who were free of prevalent coronary heart disease, heart-failure or stroke at or prior to visit 2 (eTable1).

RESULTS

Differences in baseline demographics and cardiac risk factors, according to categories of hs-cTNT change, are shown in Table 1. In general, persons who had hs-cTNT <5 ng/L at both visits were younger, more likely to be female, and more likely to have a lower overall burden of cardiac risk factors than persons who moved in to higher hs-cTNT categories at follow-up or who remained in the elevated category over the 6-year period. For example, the 10-year estimated ASCVD risk score at baseline was 3.2% in persons with hs-cTNT <5 ng/L at both visits, compared to 5.6% for those who increased from <5 ng/L to 5 ng/L at follow-up, and 12.9% for those who had hs-cTNT 14 ng/L at both the baseline and follow-up visits.

Distribution of 6-year hs-cTNT change

A significant proportion of ARIC participants changed hs-cTNT categories between visit 2 and visit 4 (eTable 2). For example, of those in the “detectable” category (5–13ng/L, n=2,464) at baseline, 22.9% decreased to undetectable levels (<5ng/L) and 13.7% increased into the “elevated” (14ng/L) range after 6 years. However, approximately 63.4–72.4% of participants within each baseline category remained in the same hs-cTNT category at follow-up. In the study population overall, the mean absolute change in hs-cTNT was an increase of 1.87 ng/L between baseline and 6-year follow-up. This was equivalent to a mean annualized change of +0.31 ng/L per year. The standard deviation of 6-year hs-cTNT change was 7.06 ng/L, reflecting high variability in hs-cTNT change relative to the mean increase (6-year coefficient of variation=377%).

Persons in the intermediate and high ASCVD risk score categories at baseline had higher absolute and relative increases in hs-cTNT over 6 years compared to persons in the low ASCVD risk score category (Table 2, eFigure 2). As levels <5ng/L are measured with less reliability, we also performed analyses of continuous 6-year change in hs-cTNT that were limited to persons with baseline hs-cTNT levels 5ng/L. The results of this analyses were quantitatively and qualitatively similar to the sample overall (eTable 3). Crude 6-year and annualized hs-cTNT changes, stratified by age, sex, ethnicity, and major cardiac risk factor categories, are shown in eTable 4.

Potential determinants of 6-year hs-cTNT change

In the ASCVD risk category model, we found that persons in the highest category of ASCVD risk were more likely to demonstrate increased follow-up hs-cTNT (Table 3). The relative risks (RRs) for incident elevated hs-cTNT (progression from <14 ng/L at baseline to 14 ng/L at the follow-up visit) were 2.71 (95% CI 1.99, 3.70) for those with ASCVD risk of 5.0 to 7.4% and 4.94 (95% CI 3.87, 6.31) for those with ASCVD risk ≥7.5%, compared to low risk persons (ASCVD risk <5%). In addition, the association of baseline ASCVD risk score with mean 6-year increase in hs-cTNT was roughly linear (Figure 1).

In the fully adjusted individual cardiac risk factor model, persons with baseline hypertension demonstrated larger increases in hs-cTNT values over the 6-years of follow-up, with evidence for a linear association (Figure 2a). A similar trend was seen for obesity, however absolute 6-year hs-cTNT change plateaued in those with BMI over 35 kg/m² (Figure 2b). Indeed, of the modifiable cardiac risk factors, hypertension, BMI and diabetes were consistently and independently associated with higher follow-up hs-cTNT, by all of the hs-cTNT outcomes (continuous change and both categorical change outcomes [Table 3]). Importantly, when we further adjusted for baseline visit-2 hs-cTNT in the continuous models, these associations were stronger (eTable 5).

Reduced kidney function was associated with incident elevated categorical hs-cTNT change and, in the continuous model, with larger increases in hs-cTnT over follow-up. Black study participants were also more likely to develop incident elevated hs-cTNT, but not other hs-cTNT outcomes. In contrast, lipid parameters, hs-CRP, and smoking were not independently associated with temporal hs-cTNT increases in the primary model. Indeed, there was inconsistent evidence that smoking may be associated with reduced follow-up hs-cTNT, by the incident detectable but not the incident elevated categorical outcomes.

Of the risk factors examined here, high HDL cholesterol levels and the absence of either diabetes or obesity were associated with lower follow-up concentrations of hs-cTnT. Smoking was not associated with declining troponin in these models (eTable 6).

Sensitivity analyses accounting for survival bias

We further evaluated risk-factors for categorical 6-year hs-cTNT change, using multinomial logistic regression models that incorporated ASCVD deaths and non-ASCVD deaths occurring after visit 2 and before visit 4 (and thus precluding a second measurement of hs-cTNT) among those free of coronary heart disease, stroke or heart-failure prior to visit 2. In these sensitivity analyses, the impact of age, sex, hypertension and diabetes on troponin change appeared stronger in these competing risk models. In addition, HDL-cholesterol was more consistently associated with falling hs-cTNT levels over time.

Blood pressure, BMI, and glycemic control as time-varying exposures

Persistent elevation BP at ARIC visits 2, 3 and 4 were independently associated with graded increases in follow-up hs-cTNT values (Table 5). Specifically, compared to the “BP optimal at all visits” group, the RRs of incident detectable hs-cTNT (progression from <5 ng/L at baseline to ≥5 ng/L at the follow-up visit) were 1.05 (95% CI 0.92, 1.21) for the “BP not

optimal at one visit” group, 1.14 (95% CI 1.01, 1.32) for the “BP not optimal at 2 or more visits” group, 1.15 (95% CI 1.00, 1.32) for the “BP elevated at one visit only” group, and 1.17 (95% CI 1.01, 1.35) for the “BP elevated at 2 or more visits” group. Similar trends were observed for incident elevated hs-cTNT and absolute change outcomes. In addition, both fasting glucose and BMI, also analyzed as time-varying exposures, demonstrated an association with increased temporal change in hs-cTNT, with the strongest association seen for those who consistently remained in the highest categories of these risk factors over time (Table 5). The findings for these time-varying exposures were robust, with evidence for stronger associations in the competing risk regression models that accounted for interval deaths between visit 2 and visit 4 (precluding the ability to obtain a repeat hs-cTNT level in these persons, eTable 7)

DISCUSSION

In this large community-based cohort study, comprised of asymptomatic subjects who remained free of known cardiovascular disease, including silent MI by ECG, we found that hs-cTNT increased 1.9 ng/L, on average, over 6 years of follow-up. However, the range of hs-cTNT change was wide (SD 7.1 ng/L), with marked variability between subjects. Nonetheless, different patterns of change were noted in subcategories of the study sample and we demonstrate that, for example, baseline cardiovascular risk-group (as assessed by 10-year predicted ASCVD score¹³) appears to be a strong determinant of hs-cTNT change. These data also provide reference ranges for expected hs-cTNT change among clinically relevant sub-groups (based on age, sex, and major cardiac risk factor status) that may be applied to persons with similar demographics to our study sample (Supplement eTable 2)¹⁷.

In this study, the strongest individual risk factors associated with increased follow-up hs-cTNT were older age, male gender, hypertension, diabetes, and obesity. In addition, persons with persistent elevations in the latter three modifiable risk factors had far higher risk for temporal increases in hs-cTNT than persons who had inconsistent elevations in these risk factors. Notably, in contrast to the known pattern of higher baseline hs-cTNT levels in blacks compared to whites¹⁷, race was not consistently associated with hs-cTNT change after adjustment.

Pathophysiological mechanisms of long-term subclinical hs-cTNT change

Cardiac troponin T is a highly specific cardiac biomarker and temporal increases in hs-cTNT have been attributed to progressive myocardial injury.²⁸ Nonetheless, it is possible that changes in hs-cTNT reflect a range of heterogeneous underlying processes. One factor contributing to hs-cTNT change could be subclinical myocardial infarction events.¹⁸¹⁹ Indeed, Meune et al. have demonstrated that hs-cTNT levels below the 99th percentile can help identify symptomatic hospitalized persons with acute coronary syndromes.²⁰ However, our sample was asymptomatic and ambulatory. Alternatively, hs-cTNT change could reflect progression of structural myocardial disease. For example, hypertension is a common cause of LVH, a well-established mechanism of myocardial injury.²¹ In addition, microvascular disease may also be an important cause of hs-cTNT change and may be particularly relevant

in persons with diabetes.¹⁴²² In some cases, the etiology of hs-cTNT change may be multifactorial.

Our findings are supportive of the hypothesis that structural heart problems and myocardial disease may play a more prominent role in long-term increases in hs-cTNT than macrovascular coronary artery events. Specifically, we found that common risk factors that are related to myocardial hypertrophy (hypertension, diabetes, and obesity²³²⁴) were the most strongly associated with increases in hs-cTNT during the 6 year follow-up period. In keeping with this hypothesis, LVH was another independent determinant of increasing hs-cTNT levels. Similarly, persistent elevations in these three modifiable risk factors were the strongest determinants of temporal troponin elevation. This suggests that chronic elevations in these factors may drive subclinical myocardial injury; a finding with potential implications for heart failure prevention. However, risk factors for epicardial coronary disease (hyperlipidemia, hsCRP and smoking), were not as strongly associated with hs-cTNT change. While low HDL-cholesterol was associated with hs-cTNT increase in our analysis, we note that HDL is often considered a non-causal risk factor for ASCVD and is typically confounded by other variables.²⁵

While hs-cTNT increases over time have been associated with adverse clinical outcomes⁵⁶, to our knowledge, only one prior analysis has evaluated actual determinants of hs-cTNT change²⁶. This analysis included primary and secondary prevention subjects and found that male gender, BMI, and lower HDL-cholesterol were independently associated with increasing hs-cTNT over 5 years follow-up. We confirm these findings and extend them, both by examining multiple types of hs-cTNT change outcomes and by conducting sensitivity analyses addressing survival bias; showing that hypertension, diabetes, and reduced kidney function are additional determinants of temporal increases in hs-cTNT.

Clinical Utility of hs-cTNT change

Hs-cTNT is approved for use in Europe and it is likely that this assay will be approved for future clinical use in the U.S.²⁷. However, while hs-cTNT has clear application in the work-up of acute chest pain admissions¹⁹, the use of hs-cTNT as an ASCVD risk stratification biomarker in asymptomatic persons is also very promising¹. Accordingly, we provide reference ranges for annualized hs-cTNT change in asymptomatic persons and our findings suggest that 'one size' does not fit all when interpreting change in this biomarker. For example, average change in hs-cTNT over time can be expected to differ by 10-year ASCVD risk groups.

Research utility of hs-cTNT change

Hs-cTNT is an attractive candidate for use as a surrogate marker for efficacy or harm in cardiology trials. It is cardiac specific, it is associated to the risk of CHD, CHF and death, and the values of this biomarker vary widely over time²⁸. Our findings suggest that change in hs-cTNT may have particular use in capturing beneficial myocardial and CVD effects of treatments aimed at improving blood pressure, glycemic control, or BMI. In contrast, effects of interventions aimed a lipid parameters may be less well captured by monitoring hs-cTNT. It is worth noting that statin therapy has been demonstrated to reduce hs-cTNT levels over

one year in the LIPID study⁹. However, this high risk group also had reduced recurrent ACS events during the study period, and it is unclear whether this effect could have been seen in a primary prevention cohort.

Limitations

We only had hs-cTNT measurements from two points in time, and, in such, were unable to determine more granular trends in hs-cTNT change that would have been possible with more interval hs-cTNT testing. ARIC data do not allow clear determination of the actual underlying causes of troponin elevation in this cohort. While we use the term “myocardial injury” throughout, troponin release may be due to cardiomyocyte cell death or other mechanisms.²⁹ Importantly, while values $\geq 14\text{ng/L}$ have known prognostic implications³⁴, it is inherently arbitrary, as clear reference ranges for this assay have not yet been established in primary prevention and other clinical settings.¹⁷ Finally, as these data are observational, there is a possibility that residual confounding could bias our results.

Conclusion

This study quantifies expected change in hs-cTNT among different demographic subgroups and identifies key clinical exposures associated with progression of subclinical myocardial injury over a 6 year period. Hypertension, obesity and diabetes were most strongly associated with increases in hs-cTNT over time; and persistent elevations in these modifiable risk factors, in particular, were the most strongly associated with incremental increases in subclinical myocardial injury. Studies are needed to determine whether modifying these risk factors can prevent progression of subclinical myocardial injury.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

ACS	Acute Coronary Syndrome
ASCVD	Atherosclerotic Cardiovascular Disease
BMI	Body-Mass Index
BP	Blood Pressure

eGFR	estimated glomerular filtration rate
Hs-cTNT	high-sensitivity cardiac Troponin-T
HbA1c	Glycated Hemoglobin
HDL	High Density Lipoprotein
hsCRP	high-sensitivity C Reactive protein
LDL	Low Density Lipoprotein
LVH	left ventricular hypertrophy

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Highlights

- This is the first study to focus on long-term temporal change in hs-cTNT
- Expected hs-cTNT change in asymptomatic persons differs by demographics
- Major risk factors for hs-cTNT change are hypertension, diabetes, & obesity
- These results provide insights into myocardial injury and heart failure prevention
- Hs-cTNT may also be useful for monitoring therapies or as a surrogate marker

Figure 1.

Association of 10-year predicted cardiovascular risk at baseline (ASCVD risk score) with both 6-year change in cardiac troponin T measured using a highly sensitive assay (hs-cTnT in ng/L) and with percent increase in hs-cTnT from baseline level.

Restricted Cubic splines of hs-cTnT change with background distributional histogram of ASCVD scores, truncated at the 1st and 99th percentile of ASCVD score. The shaded area around the regression line represents the 95% confidence interval.

ASCVD=10 year atherosclerotic cardiovascular disease risk.

Figure 2.

Association of blood pressure (a) and body-mass index (b) at baseline with both 6-year change in cardiac troponin T measured using a highly sensitive assay (hs-cTNT in ng/L) and with percent increase in hs-cTNT from baseline level.

Restricted Cubic splines of hs-cTNT change with background distributional histogram of (a) systolic blood pressure and (b) BMI. The shaded area around the regression line represents the 95% confidence interval.

Characteristics of the study population at baseline (1990–1992) according to categories of baseline and 6-year follow-up (1996–1998) cardiac troponin T measured using a highly sensitive assay (hs-cTnT), n=8,571

Table 1

Baseline hs-cTnT Level	<5 ng/L		5–13 ng/L			14 ng/L	
	<5 ng/L	5 ng/L	<5 ng/L	5–13 ng/L	14 ng/L	<14 ng/L	14 ng/L
6-year follow-up hs-cTnT							
Number (%)	3,791 (44.2)	2,095 (24.5)	564 (6.6)	1,563 (18.2)	337 (3.9)	61 (0.7)	160 (1.9)
Age, years	54.8	57.1	56.5	58.6	59.2	58.2	59.8
Male %	23.6	47.3	37.4	63.6	78.6	63.9	76.9
Black %	19.2	18.9	23.9	22.6	24.9	23.0	37.5
Current smoker %	23.0	16.9	15.8	12.4	13.1	14.8	18.8
Current drinker %	61.0	59.9	56.0	59.4	56.7	57.4	44.4
Systolic blood pressure mmHg	116.1	120.3	119.1	123.2	127.4	120.6	129.9
Hypertension medication %	19.9	25.4	27.5	30.3	40.9	37.7	49.4
Hypertension %	25.7	33.6	34.8	40.2	51.3	44.3	58.8
LVH by EKG %	0.9	1.4	1.8	2.8	2.4	1.6	6.9
BMI, kg/m ²							
Normal weight (<25)	39.5	29.0	33.5	26.4	23.4	29.5	19.4
Overweight (25 - 30)	38.0	42.4	41.1	43.3	38.0	37.7	33.1
Obese (> 30)	22.4	28.6	25.4	30.4	38.6	32.8	47.5
Total cholesterol, mg/dL	209.6	206.5	211.7	207.6	202.5	211.8	206.1
LDL-cholesterol, mg/dL	130.9	131.6	134.4	134.3	130.7	139.5	134.9
HDL-cholesterol, mg/dL	54.5	49.4	52.6	47.2	43.9	46.1	44.5
Triglyceride, mg/dL	120.9	127.5	123.5	130.4	139.6	131.0	133.6
Lipid Medicines %	4.6	4.8	5.5	6.2	6.2	3.3	4.4
hs-CRP, mg/L	3.8	3.7	3.6	3.6	3.6	6.9	5.1
Fasting Glucose, mg/dL	103.8	110.4	108.3	113.4	126.3	124.9	134.3
HbA1c, %	5.5	5.6	5.6	5.7	6.1	5.9	6.4
Serum creatinine, mg/dL	1.1	1.1	1.1	1.2	1.2	1.2	1.3
Proportion with eGFR <60 mL/min/1.73m ² (%)	0.5	0.9	1.1	1.5	2.7	3.3	6.9

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Baseline hs-cTnT Level	14 ng/L		5–13 ng/L		<5 ng/L		
6-year follow-up hs-cTnT	14 ng/L	<14 ng/L	14 ng/L	5–13 ng/L	<5 ng/L	5 ng/L	<5 ng/L
ASCVD score (median)	12.9	8.8	10.5	7.8	4.6	5.6	3.2

Estimates are mean (SD) or % unless otherwise indicated.

Table 2

Absolute and relative change in cardiac troponin T measured with a highly sensitive assay (hs-cTNT), overall and according to categories of 10-year cardiovascular risk (ASCVD risk score), n=8,571

	Visit 2 hs-cTNT, Mean (SD) in ng/L 1990–1992	Visit 4 hs-cTNT, Mean (SD) in ng/L 1996–1998	6-year absolute change, Mean (SD) in ng/L	Annualized absolute change, Mean (SD) in ng/L	Relative Change, % of baseline level (SD)
Overall	3.97 (4.64)	5.84 (7.77)	+1.87 (7.06)	+0.31 (1.23)	+95% (331%)
ASCVD score category					
Low <5%	2.98 (3.34)	4.18 (6.55)	+1.20 (6.14)	+0.20 (1.03)	+78% (238%)
Intermediate 5–7.5%	3.95 (3.50)	6.09 (6.13)	+2.14 (5.43)	+0.36 (0.91)	+107% (276%)
High >7.5%	5.55 (6.22)	8.34 (9.46)	+2.78 (8.83)	+0.46 (1.59)	+116% (459%)

Table 3

Risk Factor models for 6-year change in hs-cTNT, both by categorical change and continuous change outcomes, n=8,571

	Adjusted RR (95% CI) [*] for categorical hs-cTNT change		Adjusted β (95% CI) in ng/L [†]
	Incident Detectable (Baseline <5ng/L, Follow-up 5ng/L)	Incident Elevated (Baseline <14ng/L, Follow-up 14ng/L)	Continuous 6-year hs-cTNT change outcome
Model 1- ASCVD Risk Categories[‡]			
Low (<5%)	1 (reference)	1 (reference)	0 (reference)
Intermediate (5–7.4%)	1.61 (1.43,1.81)	2.71 (1.99,3.70)	0.77 (0.59,0.95)
High (7.5%)	2.02 (1.84,2.23)	4.94 (3.87,6.31)	1.22 (1.08,1.37)
Model 2- Cardiac Risk factors[‡]			
Age, per 10 years	1.60 (1.48,1.73)	2.04 (1.71,2.43)	0.77 (0.50,1.04)
Male (vs. female)	1.86 (1.68,2.06)	4.88 (3.75,6.35)	1.34 (0.99,1.69)
Black (vs. white)	1.06 (0.94,1.20)	1.36 (1.06,1.75)	0.04 (–0.36,0.45)
HDL-cholesterol, per 10mg/dL	0.95 (0.92,0.98)	0.92 (0.84,1.00)	–0.09 (–0.21,0.02)
LDL-cholesterol, per 10mg/dL	0.99 (0.98,1.00)	0.97 (0.95,1.00)	–0.02 (–0.06,0.02)
Triglycerides, per 10mg/dL	1.00 (0.99,1.00)	1.00 (0.98,1.02)	–0.01 (–0.03,0.03)
Cholesterol medication (vs. none)	0.94 (0.76,1.15)	0.94 (0.62,1.42)	–0.26 (–0.94,0.43)
Hypertension (vs. not) [§]	1.15 (1.05,1.27)	1.62 (1.32,1.99)	0.37 (0.03,0.70)
LVH (vs. no LVH)	1.19 (0.82,1.72)	1.57 (0.87,2.82)	2.99 (1.79,4.18)
Diagnosed Diabetes (vs. not) [§]	1.30 (1.08,1.56)	2.31 (1.74,3.07)	0.85 (0.20,1.49)
BMI 30kg/m ² (vs. <30kg/m ²)	1.23 (1.10,1.36)	1.53 (1.23,1.90)	0.68 (0.31,1.05)
eGFR <60 mL/min/1.73m ² (vs. >60 mL/min/1.73m ²)	1.16 (0.72,1.85)	2.20 (1.12,4.30)	3.88 (2.40,5.35)
hsCRP 2mg/L (vs. <2mg/L)	1.00 (0.91,1.09)	0.92 (0.74,1.13)	–0.05 (–0.38,0.27)
Smoking			
Current vs. never	0.77 (0.68,0.88)	0.81 (0.60,1.10)	0.07 (–0.36,0.50)
Former vs. never	0.95 (0.86,1.05)	0.89 (0.71,1.12)	–0.22 (–0.57,0.14)
Alcohol Drinking			
Current vs. never	0.99 (0.88,1.12)	0.95 (0.71,1.25)	0.04 (–0.36,0.45)
Former vs. never	0.98 (0.85,1.13)	1.03 (0.75,1.42)	–0.30 (–0.79,0.19)

^{*} Risk Ratios (RR) estimated using Poisson regression.

[†] The β -coefficient should be interpreted as the adjusted absolute difference in hs-cTNT change between each category and the reference category. Baseline hs-cTNT for the undetectable group was assigned values of 1.5ng/L for the analysis of continuous change (modelled by robust linear regression).

[‡] Model 1- univariable model including only ASCVD risk score categories. Model 2- Fully adjusted for all included risk factors. **Significant values (P<0.05) are presented in bold.**

[§] Hypertension was defined as being on anti-hypertensive medication or a systolic BP >140mmHg.

Diagnosed diabetes was defined as medication use for diabetes or a self-reported physician diagnosis.

Table 4

Sensitivity analysis accounting for ASCVD deaths and non-ASCVD deaths: Risk Factor models for 6-year change in hs-cTNT, by categorical change, n=9,651

	Adjusted OR (95% CI) * for categorical hs-cTNT change	
	Incident Detectable (n=2095: Baseline <5ng/L, Follow-up 5ng/L)	Incident Elevated (n=407: Baseline <14ng/L, Follow-up 14ng/L)
Model 1- ASCVD Risk Categories[†]		
Low (<5%)	1 (reference)	1 (reference)
Intermediate (5–7.4%)	2.06 (1.77–2.39)	2.81 (2.05–3.85)
High (7.5%)	3.21 (2.82–3.64)	5.37 (4.18–6.89)
Model 2- Cardiac risk factors[‡]		
Age, per 10 years	2.30 (2.06–2.56)	2.21 (1.83–2.67)
Male (vs. female)	2.98 (2.60–3.43)	5.68 (4.31–7.48)
Black (vs. white)	1.10 (0.94–1.29)	1.42 (1.09–1.85)
HDL-cholesterol, per 10mg/dL	0.91 (0.87–0.95)	0.91 (0.84–1.00)
LDL-cholesterol, per 10mg/dL	0.98 (0.96–0.99)	0.97 (0.94–1.00)
Triglycerides, per 10mg/dL	0.99 (0.98–1.00)	1.00 (0.98–1.02)
Cholesterol medication (vs. none)	0.91 (0.69–1.18)	0.99 (0.64–1.54)
Hypertension (vs. not) [‡]	1.28 (1.13–1.46)	1.70 (1.37–2.11)
LVH (vs. no LVH)	1.43 (0.85–2.43)	1.74 (0.92–3.29)
Diagnosed Diabetes (vs. not) [‡]	1.68 (1.28–2.20)	2.75 (2.01–3.77)
BMI 30kg/m ² (vs. <30kg/m ²)	1.44 (1.25–1.66)	1.64 (1.30–2.07)
eGFR <60 mL/min/1.73m ²		
(vs. >60 mL/min/1.73m ²)	1.33 (0.67–2.64)	2.37 (1.12–5.02)
hsCRP 2mg/L (vs. <2mg/L)	0.99 (0.87–1.12)	0.89 (0.72–1.11)
Smoking		
Current vs. never	0.66 (0.56–0.77)	0.83 (0.60–1.14)
Former vs. never	0.93 (0.82–1.07)	0.89 (0.70–1.13)
Alcohol Drinking		
Current vs. never	0.99 (0.85–1.16)	0.92 (0.68–1.23)
Former vs. never	0.96 (0.80–1.16)	1.01 (0.72–1.41)

* Conditional Odds Ratios (OR) estimated using Multinomial Logistic regression among persons free of ASCVD at or prior to visit 2. There were 638 competing ASCVD deaths and 304 non-ASCVD deaths among those eligible for the incident elevated outcome and 338 competing ASCVD deaths and 174 non-ASCVD deaths for the incident detectable hs-cTNT outcome.

[†] Model 1- univariable model including only ASCVD risk score categories. Model 2- Fully adjusted for all included risk factors.

[‡] Hypertension was defined as being on anti-hypertensive medication or a systolic BP >140mmHg. Diagnosed diabetes was defined as medication use for diabetes or a self-reported physician diagnosis.

Significant values (P<0.05) are presented in bold.

Table 5

Association of time-varying exposures to elevated BP, BMI and glucose with hs-cTNT change outcomes (categorical and continuous), main analysis sample n=8,571*

	Adjusted RR (95% CI) [†] for categorical hs-cTNT change		Adjusted β (95% CI) in ng/L [†]
	Incident Detectable (Baseline <5ng/L, Follow-up 5ng/L)	Incident Elevated (Baseline <14ng/L, Follow-up 14ng/L)	Continuous 6-year hs-cTNT change outcome
Blood Pressure (BP)*			
BP optimal (<120/80 mmHg) at all visits (ARIC visits 2,3, and 4)	1.00 (reference)	1.00 (reference)	0 (reference)
BP not optimal (>120/80, <140/90) at one visit	1.05 (0.92,1.21)	0.88 (0.62,1.24)	-0.23 (-0.69,0.23)
BP not optimal at 2 or more visits	1.14 (1.01,1.30)	0.82 (0.59,1.13)	-0.29 (-0.73,0.15)
BP elevated (>140/90) at one visit only	1.15 (1.00,1.32)	1.10 (0.80,1.52)	0.10 (-0.38,0.58)
BP elevated at 2 or more visits	1.17 (1.01,1.35)	1.46 (1.07,2.00)	0.66 (0.15,1.18)
Body Mass Index (BMI)*			
BMI optimal (<25kg/m ²) at all visits (ARIC visits 2,3, and 4)	1 (reference)	1 (reference)	0 (reference)
BMI not optimal (25–30) at one visit	0.97 (0.79,1.19)	1.65 (1.03,2.63)	0.29 (-0.39,0.97)
BMI not optimal at 2 or more visits	1.03 (0.91,1.17)	1.00 (0.72,1.38)	-0.14 (-0.57,0.28)
BMI elevated (≥ 30) at one visit only	1.14 (0.93,1.39)	1.31 (0.82,2.08)	-0.09 (-0.78,0.60)
BMI elevated at 2 or more visits	1.25 (1.09,1.43)	1.65 (1.19,2.29)	0.50 (0.04,0.97)
Glycemic control*			
FG optimal (<100 mg/dL) at all visits (ARIC visits 2,3, and 4)	1 (reference)	1 (reference)	0 (reference)
FG not optimal (100–125) at one visit	0.92 (0.81,1.05)	0.87 (0.60,1.25)	-0.18 (-0.64,0.28)
FG not optimal at 2 or more visits	0.99 (0.88,1.11)	1.09 (0.81,1.48)	-0.03 (-0.44,0.38)
FG elevated (≥ 126) at one visit only	1.10 (0.88,1.37)	0.86 (0.50,1.48)	0.19 (-0.60,0.99)
FG elevated at 2 or more visits	1.00 (0.81,1.24)	1.76 (1.16,2.67)	1.49 (0.74,2.24)

* The BP analysis excluded 203 persons with missing BP variables and the study population for this analysis was 8386. The BMI analysis excluded 212 persons with missing BMI variables and the study population for this analysis is 8368. The Fasting glucose analysis excluded 818 persons with missing glucose variables or fasting less than 8 hours and the study population for this analysis is 7753.

[†] Fully adjusted as per Model 2 in table 1 (including hypertension treatment status for the BP analysis and diabetes status for the glycemic analysis, but removing baseline BMI from BMI time varying analysis). See supplementary appendix for further details on time-varying exposure categories.

Significant values (P<0.05) are presented in bold. FG=Fasting Glucose.