ORIGINAL RESEARCH ARTICLE

High-Sensitive Cardiac Troponin T as an Early Biochemical Signature for Clinical and Subclinical Heart Failure

MESA (Multi-Ethnic Study of Atherosclerosis)

Editorial, see p 1506

BACKGROUND: Although small elevations of high-sensitive cardiac troponin T (hs-cTnT) are associated with incident heart failure (HF) in the general population, the underlying mechanisms are not well defined. Evaluating the association of hs-cTnT with replacement fibrosis and progression of structural heart disease before symptoms is fundamental to understanding the potential of this biomarker in a HF prevention strategy.

METHODS: We measured hs-cTnT at baseline among 4986 participants in MESA (Multi-Ethnic Study of Atherosclerosis), a cohort initially free of overt cardiovascular disease (CVD). Cardiac magnetic resonance imaging was performed at baseline. Repeat cardiac magnetic resonance was performed 10 years later among 2831 participants who remained free of interim CVD events; of these, 1723 received gadolinium-enhanced cardiac magnetic resonance for characterization of replacement fibrosis by late gadolinium enhancement. Progression of subclinical CVD was defined by 10-year change in left ventricular structure and function. Associations of hs-cTnT with incident HF, CV-related mortality, and coronary heart disease were estimated using Cox regression models.

RESULTS: Late gadolinium enhancement for replacement fibrosis was detectable in 6.3% participants without interim CVD events by follow-up cardiac magnetic resonance. A graded association was observed between higher baseline hs-cTnT categories and late gadolinium enhancement (≥7.42 ng/L versus <limit of detection [<3 ng/L]; adjusted odds ratio, 2.87; 95% confidence interval, 1.38–5.94). Higher hs-cTnT was also associated with a greater probability of an increase in LV mass >12% (highest category versus <limit of detection; odds ratio, 1.50; 95% confidence interval, 1.09–2.07), but not with decline in left ventricular ejection fraction. The risk of incident HF was greater for higher hs-cTnT (≥8.81 ng/L versus <limit of detection; adjusted hazards ratio, 5.59; 95% CI, 2.97–10.68).

CONCLUSIONS: hs-cTnT levels are associated with replacement fibrosis and progressive changes in left ventricular structure in CVD-free adults, findings that may precede HF symptoms by years. Minor elevations of hs-cTnT may represent a biochemical signature of early subclinical cardiac disease, providing an opportunity for targeted preventive interventions.

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Clinical Perspective

What Is New?

- This is the first study demonstrating, in a contemporary multi-ethnic population free of known cardiovascular disease, that a mild elevation of high sensitive cardiac troponin T (hs-cTnT) identifies subjects at highest risk for an increase in left ventricular mass and end-diastolic volume over the next 10-years.
- Higher hs-cTnT levels also associate with an increased incidence of replacement fibrosis, but with no differentiation between ischemic or nonischemic fibrosis patterns.
- hs-cTnT level remains an independent predictor for incident heart failure, coronary heart disease events and cardiovascular events, independent of underlying LVH or ejection fraction.

What Are the Clinical Implications?

- Subtle biochemical evidence of myocyte injury precedes imaging evidence of increasing LV mass and dilation, replacement fibrosis, and clinical cardiovascular events.
- Myocyte injury, measured with a high sensitive cardiac specific troponin assay, may ultimately be an important early signal used to target therapy to prevent or delay left ventricular remodeling and progression to heart failure symptoms and death.

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the industrialized world, and its impact on developing countries has made it a global epidemic.[1,2] With an aging population, incident heart failure (HF) has become an increasingly common initial presentation of CVD.[3] Once diagnosed, a rapid decline in quality of life occurs, as well as an increase in medical expenses and mortality.[4,5] Unlike the primary prevention of atherosclerotic disease, HF prevention has been more challenging beyond basic management of traditional risk factors, with heterogeneous progression of pathophysiology in asymptomatic individuals.

The concept of preclinical HF stages was introduced as a strategy to identify individuals at risk for future HF, in whom closer monitoring and attention to prevention are warranted.[6] The presence of stage B preclinical HF findings, which includes electrocardiographic and imaging measures of left ventricular hypertrophy (LVH) and dysfunction, predicts progression to HF and death.[7,8] We and others have shown that high-sensitive cardiac troponins I and T (hs-cTnI, hs-cTnT), biomarkers that can detect small amounts of myocyte injury, are associated with structural cardiac abnormalities that define a stage B HF phenotype, most notably LVH.[9–12] Moreover, small elevations in hs-cTnT and hs-cTnI predict progression to incident HF and CV death among asymptomatic individuals in the general population.[9–13] However, the extent to which hs-cTn levels identify individuals at risk for progression of structural cardiac abnormalities is unknown. Moreover, it is not known whether low levels of hs-cTn represent an early biochemical signature of myocyte cell loss with replacement fibrosis, indicative of an ongoing dynamic process resulting in subsequent pathophysiologic changes in cardiac structure and function. Such insight could provide targeting of preventive therapy years before detection of structural heart disease (ie, in advance of imaging-based stage B preclinical HF) and development of symptoms by allowing early differentiation of individuals with similar traditional risk factor profiles who are at highest risk for CVD progression and death.

Therefore, the purpose of this study was to determine whether hs-cTnT identifies an early phenotype for subclinical cardiac disease as assessed by serial cardiac magnetic resonance (CMR), and CVD outcomes in a prospective, ethnically diverse general population cohort free from CVD at baseline.

METHODS

Study Population

Details of the MESA (Multi-Ethnic Study of Atherosclerosis) design have been previously described.[14] In short, 6814 men and women, 45 to 84 years of age and of 4 self-reported race/ethnicities (non-Hispanic white, black, Hispanic, and Chinese) who were free of known CVD (including a history of HF) were enrolled in 6 participating centers in the United States. On entry, all participants underwent extensive evaluations, including questionnaires, physical examination, and laboratory tests. For these analyses, we included individuals who had a complete CMR evaluation done at examination 1; for further analyses of changes in subclinical CVD, we included those participants with complete CMR at examinations 1 (2000–2002) and 5 (2010–2012) and who remained free of interim clinically overt CVD, as described below. All participants provided informed consent for participation. MESA was approved by the Institutional Review Boards of the University of Washington and the participating sites; the measurement of hs-cTnT and this analysis were approved by the Institutional Review Board of the University of Maryland, Baltimore.

Biomarker Assay Measurements

hs-cTnT was measured in ethylenediaminetetraacetic acid plasma collected at baseline (examination 1). Sequential biomarker measures of amino-terminal B-type natriuretic peptide (NT-proBNP) were also performed on blood samples collected at examinations 1 and 3 (2003–2005). NT-proBNP had already been measured in 5597 participants at baseline (examination 1)[15] and 4996 participants at examination 3 but was measured in all additional participants at both time points with available plasma who were without a previous measure. All hs-cTnT at examination 1, plus additional NT-proBNP levels at examinations 1 and 3, were measured at the University of Maryland using the Cobas e601 (Roche Diagnostics). A 250 μl ethylenediaminetetraacetic acid plasma sample previously unthawed or only thawed once was used for analysis. For hs-cTnT, the interassay

coefficients of variation (CVs) observed for the MESA cohort measurements were 3.6% at 28 ng/L and 2.0% at 2154 ng/L. The Cobas e601 instrument used in this study is superior for low-end measurement of hs-cTnT because of an additional wash step that improves the assay's signal-to-noise ratio compared with the Cobas e411. This instrument translates into better performance; by comparison, the 10% CV is 4.3 ng/L for e601 compared with 8 ng/L for e411, and the LoQ (20% CV) is 5.6 ng/L for e411 and 2.5 ng/L on the e601 (A. Sanger, personal communication, June 6, 2015). Thus, measurements at the 3 ng/L, defined as the limit of detection (LOD) as the lowest reported value from the instrument, were well within the reportable range for the hs-cTnT used in this study. Details for NT-proBNP have previously been reported.[15] In total, 4986 (99.7%) of participants with CMR completed at examination 1 had hs-cTnT measured at examination 1, and 4991 (99.8%) had NT-proBNP measured.

CMR Imaging and Image Analysis

CMR imaging at examinations 1 and 5 were performed as previously described.[16] To account for the different pulse magnetic resonance imaging sequences and subsequent variances in measurements, correction equations were used to convert fast gradient echo magnetic resonance imaging pulse sequence measurements (examination 1) into steady-state free precession measurements (examination 5) for longitudinal measurement analyses.[17] Contrast enhanced CMR studies using late gadolinium enhancement (LGE) were performed during examination 5 only among those without contraindications for gadolinium. LGE images were acquired 10 to 15 minutes after intravenous administration of 0.15 mmol/kg gadolinium-diethylenetriamine pentaacetate (Magnevist, Schering) with breath-held segmented inversion-recovery sequence and acquired in the same orientations as the cine images. Inversion times were adjusted to null normal myocardium. Myocardial scar (replacement fibrosis) was defined as focal LGE in either 2 adjacent short-axis slices or 1 short-axis and a long-axis image at a corresponding location using QMass (version 7.2, Medis). Myocardial scars that involved subendocardium in a coronary artery distribution were defined as a "typical" scar. Myocardial scars predominantly affecting midwall or subepicardium without subendocardial involvement in a noncoronary artery distribution were defined as an "atypical" scar.[18]

Clinical Follow-Up and Cohort Surveillance

MESA clinical event end points considered in this analysis included HF hospitalization; acute myocardial infarction and other forms of incident coronary heart disease (CHD); and CV mortality. Events were adjudicated by the MESA group as previously described.[15,19] Incident HF and CHD events were ascertained by participant interview at semiannual study visits. Incident HF for this analysis comprised events adjudicated as probable or definite. CV death was defined as death related to atherosclerotic heart disease (fatal myocardial infarction and definite and possible fatal CHD), death after cerebrovascular disease (fatal stroke), or death from other atherosclerotic and cardiovascular diseases, as described in detail previously.[14]

Candidate Covariates

Clinical characteristics and CV risk factors were obtained as described previously.[14] The candidate covariates for this analysis include: age, sex, ethnicity, smoking status (current/former/never), hypertension medication use, systolic and diastolic blood pressure, weight, height, diabetes mellitus, lipid levels, and renal function at examination 1. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or treatment for hypertension. Individuals with diabetes mellitus were defined as either having fasting plasma glucose ≥126 mg/dL or receiving treatment for diabetes mellitus. Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine using the CKD-Epi equation.[20]

Statistical Analysis

We examined hs-cTnT as a predictor variable using 2 complementary methods: First, we predefined 5 categories of hs-cTnT concentration. The lowest category consisted of those participants with concentrations below the LOD (ie, <3 ng/L: category 1), and the remaining distribution of measurable hs-cTnT were divided into 4 categories of equal numbers of participants (categories 2–5). Second, we modeled hs-cTnT as a continuous log-linear form after taking the natural log of hs-cTnT values; values <LOD were imputed at 1.5 ng/L (ie, 50% of the lowest detectable value).

Baseline demographic, clinical, and laboratory characteristics were compared across the 5 categories of hs-cTnT using analysis of variance or Cuzik's test for trend as appropriate.[21] The relationship between hs-cTnT and NT-proBNP and aging was examined by robust locally weighted regression of each biomarker versus age and displayed graphically separately among men and women.[22] To identify factors independently associated with greater hs-cTnT, we performed multiple logistic regression with the highest category of hs-cTnT as the dependent variable and the baseline patient characteristics as independent variables.

We used multiple linear regression to examine cross-sectional relations of hs-cTnT categories with continuous measures of subclinical CVD: LV mass (LVM), LV end-diastolic volume (LVEDV), and LV ejection fraction (LVEF). Because associations with continuous measures of cardiac structure and function may fail to adequately describe relationships with subclinical cardiac disease, we additionally examined associations of hs-cTnT with abnormal LVM and LVEF with logistic regression using previously established cut points to define LVH[23] and abnormal LVEF (<50%). For all regression models, adjustment was made for demographic factors (age, gender, and race/ethnicity), traditional CVD risk factors (systolic and diastolic blood pressure, use of antihypertensive medications, diabetes mellitus, smoking), height and weight, and eGFR.

The association between baseline hs-cTnT and change in each CMR measure was examined through multiple linear regression models, with the follow-up CMR measure (LVM, LVEDV, and LVEF) as dependent variables, hs-cTnT as the primary independent variable, and adjustment variables, including the initial CMR measure, demographics, traditional CVD risk factors, and eGFR as defined previously. Robust estimates of standard errors were used to provide nonbiased estimates in the setting of heteroscedasticity. For these analyses, only those subjects with both initial and follow-up CMR measures, and without incident CHD and HF between these visits, were included; separate categorization of hs-cTnT levels as

described earlier was performed among this study sample. Each type of follow-up CMR measure was initially considered as a continuous outcome. Because continuous measures of change may fail to fully characterize the relation of hs-cTnT with changes in subclinical CVD, we also defined a priori cut points, indicating "clinically significant" longitudinal changes for each CMR measure defined as a binary outcome (progression versus no progression). Cut points defining significant progression included: (1) for LVEF, >10% relative decrease; (2) for LVM, >12% increase; and (3) for LVEDV, >8% increase. These cut points define a change more than twice the technical error of the mean (analogous to the coefficient of variation) for interobserver variability for each measure using previously reported data.[16] Change in each measure greater than these thresholds can be considered as highly unlikely to represent merely measurement error. Furthermore, we examined changes in subclinical CVD as characterized by longitudinal increases in NT-proBNP as defined previously by a >25% increase to a level ≥80 ng/L.[24] Associations between baseline hs-cTnT and these "significant" changes in CMR measures and NT-proBNP were examined using logistic regression, adjusting for baseline NT-proBNP and additional covariates as described previously.

The frequency and subtype (ischemic versus nonischemic) of the LGE pattern on follow-up MRI were compared across categories of baseline hs-cTnT with the χ-squared test. The adjusted association between hs-cTnT and LGE were examined using logistic regression, adjusting for the demographic and CVD risk factors described earlier, and in addition for LV mass and LV ejection fraction. These analyses were performed among those with complete contrast-enhanced CMR at visit 5 who remained free of HF and CVD events, with categories of hs-cTnT defined among this study sample as described earlier.

The incidence of HF, CHD, and CV mortality were compared across hs-cTnT categories using the Kaplan-Meier method and the log-rank test, with follow-up time defined as time from the baseline study visit with censoring on death (or, for the outcome of CV mortality, death from non-CV causes) or the date of the last study visit. Adjusted associations were estimated using Cox survival regression models. Adjustment covariates included the demographic and CVD risk factors described earlier. The study sample for these analyses included those with complete CMR measures and hs-cTnT measures at examination 1. Tests of Schoenfeld residuals and -ln(-ln) plots were used to verify the proportional hazards assumption. All analyses were performed with Sata SE v12.1 (Statacorp).

RESULTS

Study Population

Among 4986 participants with complete CMR and hs-cTnT at examination 1, an hs-cTnT level above the LOD was present in 3341(67%) of participants. Increasing levels of hs-cTnT were associated with older age, male sex, white race, diabetes mellitus, renal dysfunction, greater body mass index, higher NT-proBNP, lower proportion of good-excellent self-reported health, and a history of hypertension and smoking (Table 1). Factors independently associated with elevated hs-cTnT (≥8.81 ng/L, highest category) were older age, male sex, black ethnicity, diabetes mellitus and impaired fasting glucose, greater body mass index, lower eGFR, higher NT-proBNP, and use of diuretics (online-only Data Supplement Table I).

To better understand the influence of age on hs-cTnT, we plotted lowess estimated medians by age separately by sex and contrasted this value with NT-proBNP, the other cardiac specific biomarker measured in the cohort (Figure 1a and 1b for men and women, respectively). In men, a predominantly linear rise in hs-cTnT occurs with advancing age, with an ≈4-fold increase from the late 40s to the mid-80s, in contrast to NT-proBNP, which changes minimally until the mid-60s, with a sharp inflection and steep rise over the next 20 years of life. For women, the pattern is different. hs-cTnT levels are lower than in men and gradually increase with a rate of rise that then continues to increase over 40 years.

Last, we compared participants who did not have a CMR examination to those who did. Participants without CMR were older and had a greater prevalence of traditional risk factors, poorer self-reported healt,h and modestly higher hs-cTnT and NT-proBNP values (online-only Data Supplement Table II).

hs-cTnT and CMR Determined Left Ventricular Structure and Function

Cross-Sectional Associations of hs-cTnT With Subclinical CVD

Progressively higher hs-cTnT concentrations were associated with greater LV mass and a higher prevalence of LVH for both men and women (Table 2). These trends remained significant after adjustment for demographics, traditional CVD risk factors, and renal function, with a >5-fold greater odds of LVH among those in the highest category of hs-cTnT (odds ratio, 5.23; 95% confidence interval [CI], 3.67–7.46; online-only Data Supplement Table III). Baseline LVEDV did not differ for either sex across categories of hs-cTnT. Mean LVEF was minimally but significantly lower across higher hs-cTnT for men but not for women; however, the prevalence of an abnormal LVEF (<50%) was notably higher across progressively higher hs-cTnT categories for both sexes (Table 2). After adjustment for demographics, CV risk factors, and eGFR, those in the highest category of hs-cTnT were markedly more likely to have low LVEF compared with those with hs-cTnT below the LOD (odds ratio, 2.97; 95% CI, 1.68–5.24), with a linear relation of ln(hs-cnT) and abnormal LVEF (online-only Data Supplement Table IV).

hs-cTnT and Longitudinal Changes in CMR-Defined LV Structure and Function

There were 2831 participants with CMR exams at examinations 1 and 5, available plasma for hs-cTnT measurement, and without intervening CHD or HF events; among these individuals, 668 (23.5%) had a >12% increase in

Table 1. Characteristics of Study Population, by Concentration of hs-cTnT

	Below LOD	3.0–4.25 ng/L	4.26–5.87 ng/L	5.88–8.80 ng/L	≥8.81 ng/L	Test for Trend
N	1645	825	843	837	836	
Range (ng/L)	<3.0	3.0–4.25	4.26–5.87	5.88–8.8	8.81+	
Age	56.8 (8.5)	59.7 (9.5)	62.1 (9.6)	64.9 (9.4)	68.7 (9.4)	<0.001
Men	440 (26.8%)	367 (44.5%)	434 (51.5%)	308 (36.8%)	605 (72.4%)	<0.001
Ethnicity						
White	579 (35.2%)	324 (39.3%)	333 (39.5%)	366 (43.7%)	347 (41.5%)	<0.001
Chinese	273 (16.6%)	126 (15.3%)	108 (12.8%)	89 (10.6%)	56 (6.7%)	
Black	402 (24.4%)	185 (22.4%)	195 (23.1%)	219 (26.2%)	278 (33.3%)	
Hispanic	391 (23.8%)	190 (23.0%)	207 (24.6%)	163 (19.5%)	155 (18.5%)	
Hypertension	460 (28.0%)	306 (37.1%)	387 (45.9%)	443 (52.9%)	516 (61.7%)	<0.001
SBP (mm Hg)	119.3 (19.2)	122.6 (19.6)	126.8 (20.8)	130.4 (21.0)	133.7 (23.2)	<0.001
DBP (mm Hg)	69.9 (9.9)	71.3 (10.4)	72.8 (10.0)	73.7 (10.0)	73.3 (10.9)	<0.001
Diabetes mellitus status						
Normal	1353 (82.4%)	658 (79.9%)	654 (77.7%)	602 (72.2%)	488 (58.4%)	<0.001
IFG	180 (11.0%)	108 (13.1%)	94 (11.2%)	117 (14.0%)	146 (17.5%)	
Untreated	28 (1.7%)	13 (1.6%)	26 (3.1%)	21 (2.5%)	34 (4.1%)	
Treated	82 (5.0%)	45 (5.5%)	68 (8.1%)	94 (11.3%)	167 (20.0%)	
BMI (kg/m2)	27.4 (5.2)	27.5 (4.8)	27.7 (4.9)	28.2 (4.8)	28.3 (4.8)	<0.001
Smoking						
Never	928 (56.5%)	424 (51.5%)	435 (51.7%)	397 (47.7%)	373 (44.8%)	<0.001
Former	497 (30.3%)	288 (35.0%)	300 (35.6%)	342 (41.1%)	355 (42.7%)	
Current	217 (13.2%)	111 (13.5%)	107 (12.7%)	94 (11.3%)	104 (12.5%)	
eGFR (CKD-Epi)	84.3 (14.0)	80.1 (14.5)	77.6 (14.5)	74.0 (14.5)	69.9 (18.6)	<0.001
eGFR <60 mL/min/1.73m^2	57 (3.5%)	64 (7.8%)	96 (11.4%)	144 (17.3%)	246 (29.5%)	<0.001
LDL-C (mg/dL)	117.7 (31.0)	116.9 (31.8)	119.4 (31.1)	1117.5 (30.4)	113.6 (31.9)	.03
HDL-C (mg/dL)	53.1 (14.8)	51.7 (15.7)	51.2 (15.2)	49.6 (14.0)	48.6 (14.9)	<0.001
NT-proBNP (pg/mL)	44.5 [20.4–79.6]	43.3 [19.5–87.4]	47.9 [21.2–94.9]	55.9 [24.5– 13.4]	84.2 [39.7–202.3]	<0.001
Very good or excellent self-reported health	880 (53.5%)	427 (51.8%)	399 (47.3%)	413 (49.3%)	382 (45.7%)	.001
Medications						
Beta-blocker	108 (6.6%)	69 (8.4%)	75 (8.9%)	86 (10.3%)	115 (13.8%)	<0.001
Diuretic	108 (6.6%)	107 (13.0%)	94 (11.2%)	127 (15.2%)	173 (20.7%)	<0.001
ACEI or ARB	143 (8.7%)	96 (11.6%)	139 (16.5%)	151 (18.0%)	221 (26.4%)	<0.001

ACEI indicates, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker ; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hs-cTnT, high sensitive cardiac troponin T; IFG, impaired fasting glucose; LDL-C, low-density lipoprotein cholesterol; LOD, limit of detection; NT-proBNP, amino terminal pro B-type natriuretic peptide; and SBP, systolic blood pressure.

LVM from baseline to follow-up CMR, 387 (13.7%) with a >8% increase in EDV, and 570 (20.1%) with a relative decline in EF >10%. The proportion with increased LVM was greater among those with higher baseline hs-cTnT (Table 3). After adjustment for baseline LVM, demographics, and traditional CVD risk factors, those in the highest hs-cTnT category were more likely to have a >12% increase in LV mass compared with participants with undetectable levels (odds ratio, 1.50, 95% CI, 1.09–2.07; Table 3). The proportion of participants with an LVEDV increase of >8% was also greater with higher categories of hs-cTnT levels after adjustment for baseline LVEDV

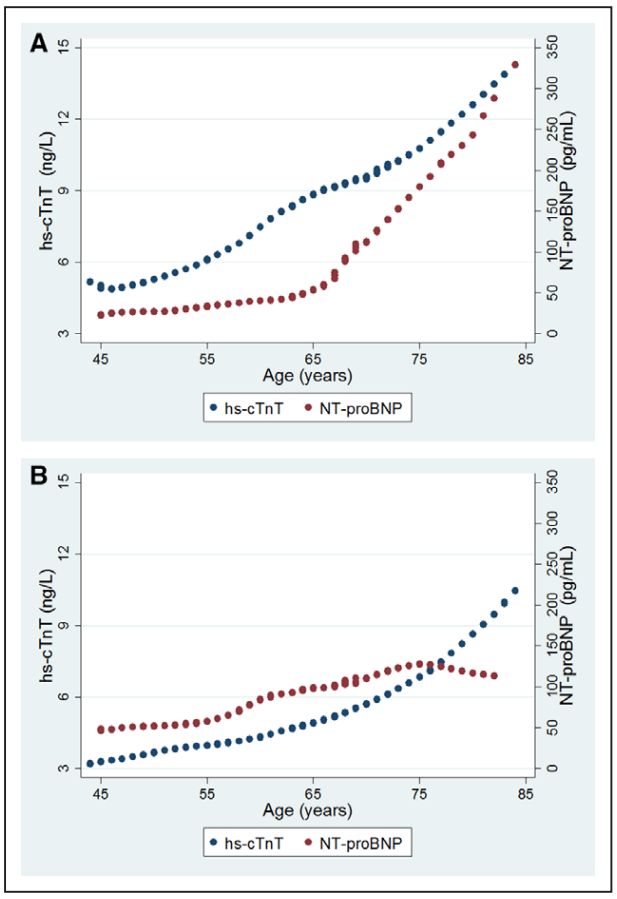

Figure 1. Biomarker levels by age and gender.
Relationship between hs-cTnT and NT-proBNP with age among (**A**) men and (**B**) women. Circles represent lowess-smoothed values of either NT-proBNP (**blue**) or hs-cTnT (**maroon**) as a function of age. The y-axis origin for hs-cTnT terminates at 3 ng/L because this is the lowest level of detection for this assay. Levels below detection were imputed at 2.99 ng/L.

and CVD risk factors (P=0.006 for trend across hs-cTnT categories; Table 3). In contrast, for a decline in LVEF >8%, no significant association was found with higher baseline hs-cTnT categories after covariate adjustment (Table 3). When examined as continuous measures of longitudinal LV changes (defined as follow-up measures adjusted for baseline), modest although significant adjusted associations of greater hs-cTnT occurred with greater follow-up LVM and LVEDV, but associations with lower LVEF were not significant after adjustment for CV risk factors (online-only Data Supplement Table V). Last, among 4290 participants with baseline and follow-up (examination 3) NT-proBNP levels and who remained free of CHD and HF, the incidence of an increase in NT-proBNP >25% to >80 pg/ml ranged from 18% for participants with hs-cTnT levels below the LOD to 37% for those with hs-cTnT levels in the 5th category (online-only Data Supplement Figure I). These associations remained significant after adjustment for baseline NT-proBNP and CV risk factors (online-only Data Supplement Table VI).

Association Between hs-cTnT and LGE

LGE was identified in 113 (6.5%) of 1723 participants with gadolinium-enhanced CMR at examination 5 who were also without an interim CVD event before the examination. LGE pattern distribution were classified as typical and likely caused by ischemia in 38 (33.6%) of these participants, whereas 75 (66.4%) participants were classified as atypical scar and likely not caused by coronary artery disease. The prevalence of participants with LGE is shown for the entire cohort in Figure 2 and by sex across progressive baseline hs-cTnT categories for men and women in online-only Data Supplement Figure IIa IIb, respectively. Overall, the proportion with LGE is as low as 1% for women with hs-cTnT below the LOD to 17% for men with hs-cTnT levels in the highest category. The majority of LGE scar types was classified as atypical in all hs-cTnT categories and did not differ across such categories. The odds of LGE scar among participants in the highest category of hs-cTnT were ≈2.5 times as great as those with undetectable hs-cTnT after adjustment for demographics, CVD risk factors, eGFR, LVH, and LVEF (odds ratio, 2.41; 95% CI, 1.15–5.06), respectively (Table 4). A significant linear relationship between hs-cTnT level and odds of LGE scar was also apparent (Table 4).

Association Between hs-cTnT and Incident HF, CHD Events, and CV Death

Participants with baseline CMR and hs-cTnT measurements were followed for a median of 12.2 years with 177 definite or probable incident HF events, 234 CHD events, and 141 CV deaths. Cumulative hazard curves are shown for incident HF, CHD, and CV death in Figure 3 and online-only Data Supplement Figures III and IV, respectively. For each event type, progressively higher levels of hs-cTnT were associated with a greater risk of each event. For incident HF, the unadjusted hazard ratio for those in the highest category of hs-cTnT versus those <LOD was 14.13 (95% CI, 8.18–24.42); risk-factor adjustment diminished these associations moderately, but they remained significant even after additional adjustment for LVM, LVEF, and NT-proBNP (Table 5). Associations were similar after excluding patients with LVH or abnormal LVEF at baseline (per 1-ln increase in hs-cTnT; adjusted hazard ratio, 2.01; 95% CI, 1.52–2.76). Similar associations were present for CHD events, although with weaker associations compared with incident HF and CV death (online-only Data Supplement Table VII).

DISCUSSION

Our results from the MESA cohort, incorporating a high-sensitivity assay for cTnT and using repeated CMR with LGE, provide several novel insights regarding the mechanisms of chronic cardiac injury in the general population. First, baseline levels of hs-cTnT are strongly associated

Table 2. Cardiac Magnetic Resonance Measures of Subclinical CVD at Baseline by hs-cTnT Category

Subclinical CVD Measure	Sex	<LOD	3.0–4.25 ng/L	4.26–5.87 ng/L	5.88–8.80 ng/L	≥8.81 ng/L	Test for Trend
LVM (g)	Men	130.5 (22.1)	132.4 (24.4)	135.9 (24.6)	138.9 (25.4)	148.3 (33.6)	<0.001
	Women	101.3 (18.3)	103.5 (18.8)	105.0 (20.2	108.2 (21.9)	115.3 (28.1)	<0.001
LVH prevalence	Men	13 (3.0%)	23 (6.3%)	30 (6.9%)	32 (6.1%)	110 (18.2%)	<0.001
	Women	85 (7.1%)	51 (11.1%)	49 (12.0%)	47 (15.3%)	64 (27.7%)	<0.001
LVEDV (mL)	Men	140.0 (26.2)	142.1 (29.0)	142.0 (29.9)	143.0 (31.0)	142.6 (35.9)	0.2
	Women	116.4 (22.3)	117.9 (23.4)	115.3 (23.3)	117.1 (24.7)	117.0 (27.8)	0.9
LVEF (%)	Men	61.0 (5.6)	61.9 (5.9)	61.5 (5.8)	61.0 (6.2)	60.4 (7.7)	0.006
	Women	63.5 (5.2)	63.9 (6.0)	63.8 (5.5)	63.9 (6.0)	63.0 (6.7)	0.2
LVEF<50%	Men	15 (3.4%)	12 (3.3%)	14 (3.2%)	24 (4.5%)	51 (8.4%)	<0.001
	Women	14 (1.2%)	6 (1.3%)	7 (1.7%)	8 (2.6%)	10 (4.3%)	<0.001

CVD indicates cardiovascular disease; LOD, limit of detection; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; and LVH, left ventricular hypertrophy. Values are mean (standard deviation) and N (%).

with longitudinal changes in LV structure consistent with early adverse remodeling, represented by a measurable increase in LV mass and end-diastolic volume by CMR, as well as increased hemodynamic strain represented by a rise in NT-proBNP. This latter finding is also supported by the observation that cTnT is initially elevated at a younger age compared with NT-proBNP, particularly in men. Progressive remodeling of LV structure associated with higher hs-cTnT levels occurred in the absence of intervening cardiovascular events and independent of initial LV mass, LVEDV, and NT-proBNP. Second, unique to this study is the strong association of biochemical evidence of myocyte injury with subsequent imaging evidence of replacement fibrosis in the form of CMR LGE. LGE has consistently been associated with a poor outcome in multiple cardiovascular diseases as well as people with diabetes mellitus and older adult general populations.[25–27] Consistent with a probable nonischemic etiology to account for measurable hs-cTnT, no trend was discovered in the pattern of ischemic-type LGE with higher levels of hs-cTnT. Despite these consistent associations of greater baseline hs-cTnT with replacement fibrosis, measurable progression of LV mass and LVEDV by CMR, and early rise in NT-proBNP, we noted no

Table 3. Association of Baseline hs-cTnT With Odds of Significant Change in Cardiac Structure and Function*

	LV Mass		LV End-Diastolic Volume		LV Ejection Fraction	
Subclinical CVD Measure	Unadjusted	+ Risk Factors	Unadjusted	+ Risk Factors	Unadjusted	+ Risk Factors
hs-cTnT category (ng/L)†						
<LOD	Reference	Reference	Reference	Reference	Reference	Reference
3.0–4.05	1.22 (0.996, 1.49)	1.25 (0.94, 1.66)	0.69 (0.47, 1.02)	0.68 (0.44, 1.03)	1.11 (0.84, 1.48)	0.90 (0.67, 1.23)
4.06–5.42	1.06 (0.86, 1.31)	0.86 (0.63, 1.16)	1.29 (0.93, 1.79)	1.17 (0.81, 1.70)	1.04 (0.78, 1.38)	0.86 (0.63, 1.18)
5.43–7.67	1.28 (1.05, 1.55)	1.24 (0.92, 1.68)	1.69 (1.25, 2.30)	1.65 (1.14, 2.39)	1.51 (1.15, 1.97)	1.21 (0.88, 1.65)
≥7.68	1.59 (1.33, 1.90)	1.50 (1.09, 2.07)	1.89 (1.40, 2.55)	1.39 (0.93, 2.05)	1.52 (1.16, 1.98)	1.06 (0.76, 1.48)
Test for trend	*P*<0.001	*P*=0.04	*P*<0.001	*P*=0.006	*P*<0.001	*P*=0.4
ln(hs-cTnT)	1.17 (1.05, 1.32)	1.16 (1.00, 1.34)	1.38 (1.20, 1.59)	1.19 (0.99, 1.43)	1.21 (1.08, 1.37)	1.03 (0.88, 1.19)

CI indicates confidence interval; CMR, cardiac magnetic resonance; CVD, cardiovascular disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; hs-cTnT, high sensitive cardiac troponin T; LOD, limit of detection; LV, left ventricular; SBP, systolic blood pressure. Cell values represent odds ratios and respective 95% CIs. Risk factors: age, gender, race, SBP, DBP, anti-hypertensive medications, diabetes, smoking, lipids levels, height, weight, estimated GFR, and baseline CMR measure.

*Significant changes defined as >12% increase in LV mass, >8% increase in LVEDV, and >10% relative decline in LVEF.

†Categories based on distribution of hs-cTnT among subjects with both baseline and follow-up CMR.

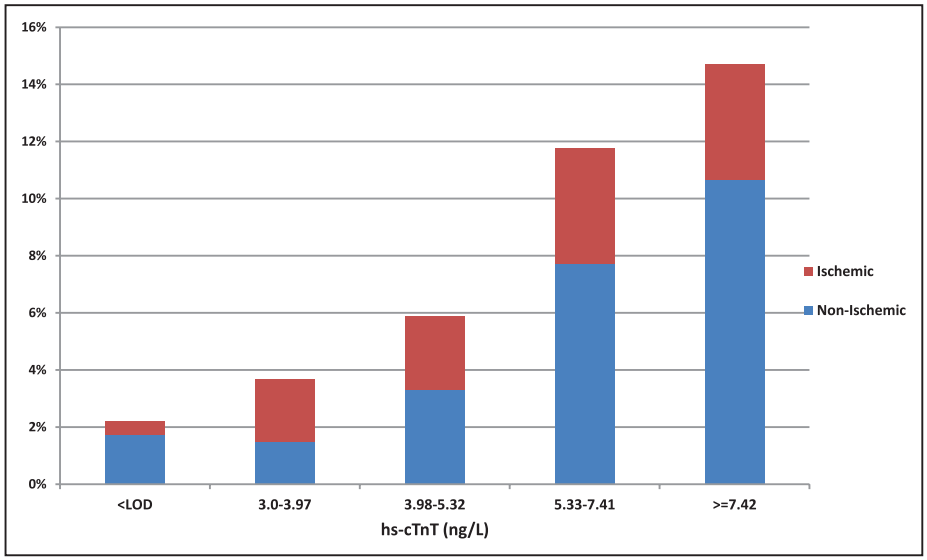

Figure 2. Frequency and subtype of left ventricular scar, by hs-cTnT category.

relationship with longitudinal decline of systolic function as reflected by LVEF. This lack of association is all the more remarkable in that a decreased LVEF is the 1 structural indication for treatment of asymptomatic patients to prevent HF, although it represents an insensitive and late manifestation in the progression of subclinical disease.[8,28] Our results support the hypothesis that, at least in the 10 years of follow-up in these MESA participants free of symptomatic cardiac disease, biochemical evidence of subclinical myocardial injury is a better marker for increasing LV mass and LV dilatation than for declining systolic function. Alternatively, those with long-term decline in LVEF may have been more likely to progress to symptomatic heart failure and thus were excluded from our analysis of subclinical changes in LV function.

Our findings also confirm cross-sectional structural abnormalities on baseline CMR, including increased LV mass and an abnormal LVEF with higher levels of hs-cTnT.[11,12] However, in light of the novel findings here that hs-cTnT levels associate with progression of structural abnormalities independent of the initial examination 1 CMR findings, cross-sectional imaging abnormalities could now be interpreted as relatively late preclinical findings in the course of cardiovascular disease. Finally, we found strong associations of even minor elevations of hs-cTnT with an independent risk for incident HF, CHD events, and cardiovascular death, for the first time demonstrating that these associations persist after accounting for CMR measurements of LV structure and function. Accounting for these measures in a multivariate model for outcomes supports the hypothesis that hs-cTnT levels provide a unique biochemical signature that is independent of even the most precise measures of cardiac structure.

LGE measured by CMR can be indicative of a previous myocardial infarction but is also present in many nonischemic heart diseases.[29] LGE has been reported in

Table 4. Association Between Baseline hs-cTnT and Myocardial Scar at Follow-Up, Among Those With Gadolinium-Enhanced CMR at Follow-Up (N=1723)

hs-cTnT Category (ng/L)*	Unadjusted	Age, Sex, Race	+ Risk Factors†, LV Mass, and LVEF
<LOD	Reference	Reference	Reference
3.0–3.97	1.68 (0.75, 3.77)	1.31 (0.57, 3.02)	1.29 (0.54, 3.09)
3.98–5.32	2.67 (1.30, 5.48)	1.86 (0.88, 3.95)	1.77 (0.80, 3.88)
5.33–7.41	5.34 (2.85, 10.02)	3.31 (1.68, 6.54)	2.49 (1.20, 5.15)
≥7.42	6.68 (3.63, 12.28)	3.26 (1.63, 6.51)	2.41 (1.15, 5.06)
Test for trend	<0.001	<0.001	0.007
ln(hs-cTnT)	2.77 (2.11, 3.63)	1.87 (1.38, 2.54)	1.57 (1.12, 2.17)

CI indicates confidence interval; CMR, cardiac magnetic resonance; DBP, diastolic blood pressure; DM, diabetes mellitus; hs-cTnT, high sensitive cardiac troponin T; LVEF, left ventricular ejection fraction; and SBP, systolic blood pressure. Cell values represent odds ratios and 95% CI.

*Categories based on distribution of hs-cTnT among those with gadolinium-enhanced-CMR at visit 5.

†SBP, DBP, anti-hypertensive medications, diabetes mellitus (normal/DM), smoking, lipids, height, weight, and estimated GFR.

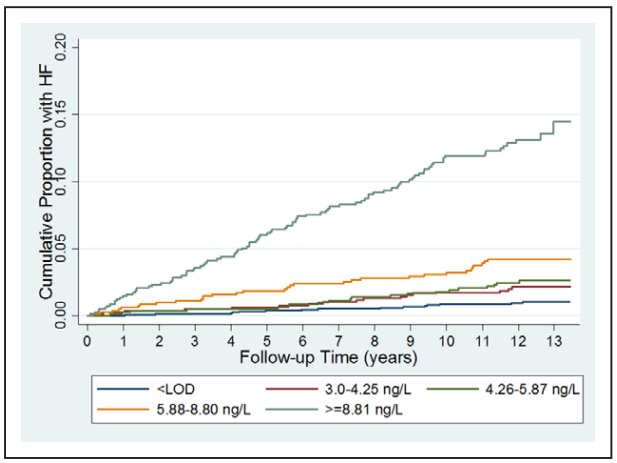

Figure 3. Cumulative incidence of heart failure by hs-cTnT category.

nearly two thirds of patients with severe aortic stenosis and half of patients with hypertension with left ventricular hypertrophy.[30] LGE is typically associated with myocyte cell loss and replacement fibrosis.[29] Its presence is also associated with a poor prognosis.[25] In older Icelandic community-dwelling adults, an LGE pattern most consistent with a myocardial infarction was found in 17% who had no previous history of a myocardial infarction and was associated with a worse prognosis compared with those without LGE.[27] More recently, in the MESA cohort, unrecognized scar was reported in 6.2% of participants of whom 62% were classified as atypical for myocardial infarction.[18] The prevalence of scar in the current study was slightly different from the previous publication as individuals with an incident HF event before examination 5 were excluded in the present analysis. The lower prevalence of LGE, and particularly typical scar compared with previous non-MESA general population studies, is likely based on the initial exclusion in MESA of known CVD, the race/ethnic heterogeneity of the cohort (with whites having the highest prevalence of LGE), and younger age of MESA participants. A previous study of older adults did not find an association between troponin and LGE, but this study focused only on subendocardial ischemic LGE patterns and did not utilize a high-sensitive troponin assay.[31] Studies measuring hs-cTn in symptomatic nonischemic heart disease populations, including nonischemic cardiomyopathy, hypertrophic cardiomyopathy, and severe aortic stenosis, all identified significant associations between the hs-cTn levels and the presence of LGE, most of which was atypical in location.[32–34] We expand these findings by showing that hs-cTnT may represent a biomarker surrogate for early myocardial fibrosis in an asymptomatic lower risk general population free of known cardiovascular disease.

By showing that hs-cTnT levels identify individuals at highest risk for adverse remodeling with changes still within the normal measurement range as well as progression to symptomatic disease and death, we identify that hs-cTnT levels represent a biochemical signature of subclinical cardiac disease that could be potentially used to target preventive interventions to at-risk individuals. Greater habitual physical activity has been associated with attenuation in the rise in hs-cTnT levels over follow-up, suggesting a potential preventive intervention.[35] Furthermore, given the strong association of hs-cTnT with imaging evidence of fibrosis and the findings by others that hs-cTnI is also strongly associated with LGE in severe aortic stenosis,[34] trials with therapies targeting remodeling and fibrosis could also be considered as an early intervention to prevent progression to symptomatic HF based on hs-cTnT levels.

Table 5. Association of hs-cTnT With Incident HF

Categories of hs-cTnT (ng/L)	Event Rate (/1000 person-years)	Unadjusted Hazard Ratios	Demographic Adjusted	+ Risk Factors*	+ LVM & LVEF	+NT-proBNP
<LOD		Reference	Reference	Reference	Reference	Reference
3.0–4.25	0.8 (0.5, 1.3)	1.72 (0.82, 3.61)	1.32 (0.62, 2.79)	1.75 (0.85, 3.62)	1.60 (0.78, 3.30)	1.60 (0.77, 3.29)
4.26–5.87	1.7 (1.0, 2.8)	2.61 (1.34, 5.10)	1.75 (0.88, 3.47)	1.74 (0.86, 3.50)	1.53 (0.76, 3.10)	1.57 (0.77, 3.17)
5.88–8.80	2.1 (1.3, 3.2)	5.38 (2.96, 9.75)	2.98 (1.60, 5.58)	2.27 (1.18, 4.44)	1.75 (0.90, 3.42)	1.70 (0.87, 3.34)
≥8.81	11.7 (9.6, 14.3)	14.13 (8.18, 24.4)	6.45 (3.54, 11.79)	5.59 (2.97, 10.68)	3.47 (1.80, 6.68)	2.93 (1.50, 5.67)
Test for trend	<0.001	<0.001	<0.001	<0.001	<0.001	0.001
ln(hs-cTnT)	N/A	3.12 (2.69, 3.63)	2.59 (2.15, 3.13)	2.35 (2.00, 2.78)	1.88 (1.50, 2.35)	1.55 (1.23, 1.95)

DM indicates diabetes mellitus; DBP, diastolic blood pressure; hs-cTnT, high sensitive cardiac troponin T; LOD, limit of detection; LVEF, left ventricular ejection fraction; LVM, left ventricular mass. Cell values represent hazard ratios (95% CI).

*Risk factors: SBP, DBP, anti-hypertensive medications, diabetes mellitus (normal/DM), smoking, lipids, height, weight, and estimated GFR.

LIMITATIONS

Several limitations of this study are to be considered. Follow-up CMR was not available in ≈40% of participants. In general, participants who did not complete CMR measures were older and less healthy than those who had a complete CMR. Although the CMR technology was contemporaneous for its time during each MESA examination period, the sequences were different as technology improved and became faster and more efficient. These differences required a correction factor to compare changes in measurements for longitudinal analyses and thereby would potentially result in small errors (addressed previously in earlier MESA CMR analyses).[17] No consensus was found on the degree of change in CMR-based measures of LV structure and function which identifies clinically important progression. We selected thresholds of change that were unlikely to represent measurement error only, but other thresholds may be more useful clinically. Only CMRs performed at examination 5 used contrast enhancement to assess fibrosis, with only 1839 (61%) receiving gadolinium. LGE sequences, although excellent at detecting small scar/fibrosis, may miss scar <1 g. In addition, because of the way LGE sequences are acquired and evaluated (scar is detected when compared with normal myocardium), it may miss diffuse myocardial fibrosis. Measures of LGE-defined replacement fibrosis were not contemporaneous with measures of cTnT. Last, nearly a third of the MESA cohort with CMR had an hs-cTnT level below the LOD. The assay system used is technically superior and provided hs-cTnT measurements that were ≈2-fold more sensitive and precise than earlier versions of the hs-cTnT analyzer. Such a technical advantage translates into less misclassification of subjects with regard to hs-cTnT, but we were still unable to classify all subjects in this study with a measurable hs-cTnT level. Nevertheless, as a group, those with hs-cTnT less than the LOD remained at low risk for HF, CVD events, or CV death.

CONCLUSIONS

Among adults without clinically overt CVD, higher hs-cTnT levels associate with myocardial pathology identified by CMR and pathological cardiac remodeling. Moreover, hs-cTnT identifies individuals with imaging evidence of nonischemic replacement fibrosis. The association of measurable hs-cTnT with subsequent LV remodeling and progression to symptomatic HF and cardiovascular death suggests that hs-cTnT levels could biochemically define early subclinical cardiac disease. Moving forward, clinical studies of lifestyle changes or pharmacological therapy may consider using hs-cTnT levels in middle-age and older adults to identify those most likely to benefit from specific therapy to prevent remodeling and fibrosis.

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DISCLOSURES

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FOOTNOTES

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High-Sensitive Cardiac Troponin T as an Early Biochemical Signature for Clinical and Subclinical Heart Failure: MESA (Multi-Ethnic Study of Atherosclerosis)

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SUPPLEMENTAL MATERIAL

Supplemental Table 1: Characteristics at baseline associated with increased hs-cTnT (≥8.81 ng/L)

	Adjusted Odds Ratio (95%CI)
Age (per year)	1.06 (1.05, 1.08)
Male	6.94 (5.46, 8.83)
Ethnicity	
Caucasian	Reference
Chinese	0.44 (0.30, 0.64)
African-Am	1.54 (1.22, 1.95)
Hispanic	0.74 (0.57, 0.97)
Anti-hypertensive medication	0.99 (0.76, 1.29)
SBP (mm Hg)	1.00 (0.99, 1.01)
DBP (mm Hg)	1.00 (0.99, 1.02)
Diabetes Status	
Normal	Reference
IFG	1.45 (1.12, 1.86)
Untreated DM	2.56 (1.58, 4.15)
Treated DM	3.56 (2.66, 4.76)
BMI (kg/m^2)	1.05 (1.03, 1.08)
Smoking	
Never	Reference
Former	0.91 (0.75, 1.10)
Current	1.26 (0.94, 1.69)
eGFR (1-ml/min/1.73m^2increment)	0.98 (0.97, 0.98)
LDL-C (mg/dL)	1.00 (0.99, 1.00)
HDL-C (mg/dL)	1.00 (0.99, 1.01)
ln(NT-proBNP)	1.67 (1.51, 1.85)
ACEI or ARB	1.11 (0.85, 1.46)
Beta-blocker	0.79 (0.58, 1.07)
Diuretic	1.39 (1.06, 1.83)
Good or Excellent Self-reported health	0.96 (0.79, 1.18)

Cell values represent adjusted odds ratios for elevated hs-cTnT at baseline from logistic regression analysis.

Supplemental Table 2: Characteristics of participants with complete vs. missing CMR measurements

	No Cardiac MRI	Cardiac MRI complete	p-value
Age	63.9 (10.4)	61.5 10.1)	<.001
Male	45.9 %	47.6%	0.2
Hypertension	51.8%	42.4%	<.001
BMI (kg/m2)	30.0 (6.5)	27.7 (4.9)	<.001
Diabetes Status			
Normal	68.2%	75.4%	<.001
IFG	16.3%	12.9%	
Untreated DM	3.2%	2.4%	
Treated DM	12.3%	9.2%	
Good-Excellent general health	45.8%	50.2%	.001
hs-TnT (pg/mL)	4.91 [<3.00, 8.85]	4.28 [<2.99, 6.12]	<.001
Detectable hs-TnT	70.8%	55.8%	.001
NT-proBNP (pg/mL)	57.4 [27.6, 120.6]	51.4 [23.0, 103.2]	<.001

Cell values represent N(%), mean (standard deviation) or median[inter-quartile range]

Supplemental Table 3: Association of hs-cTnT with LV Mass and LVH prevalence

hs-cTnT Categories	LV Mass (grams)*		LVH prevalence†	
	Unadjusted	**Adjusted‡**	**Unadjusted**	**Adjusted‡**
<LOD	Reference	Reference	Reference	Reference
3.0-4.25 ng/L	7.2 (5.1, 9.3)	2.1 (0.7, 3.5)	1.56 (1.14, 2.12)	1.88 (1.34, 2.63)
4.26-5.87 ng/L	11.8 (9.6, 13.9)	3.9 (2.5, 5.3)	1.63 (1.20, 2.22)	1.80 (1.27, 2.53)
5.88-8.80 ng/L	18.5 (16.2, 20.7)	5.7 (4.1, 7.4)	1.65 (1.21, 2.24)	1.97 (1.37, 2.82)
≥8.81 ng/L	30.0 (27.4, 32.7)	13.9 (11.7, 16.1)	4.15 (3.19, 5.40)	5.23 (3.67, 7.46)
Test for trend	<.001	<.001	<.001	<.001
ln(hs-cTnT)	13.2 (12.1, 14.2)	6.1 (5.2, 7.0)	1.89 (1.69, 2.11)	2.16 (1.86, 2.52)

* Cell values are β regression coefficients and 95% CIs and represent the difference in LV mass between those with each category of hscTnT compared to those with hs-cTnT <LOD.

†Cell values are odds ratios and 95% CIs and represent the prevalence of LVH among those with a given category of hs-cTnT relative to those with hs-cTnT below limit of detection.

‡Adjusted for age, gender, race, SBP, DBP, anti-hypertensive medications, diabetes, smoking, lipids, height, weight, and eGFR.

Supplemental Table 4: Odds of abnormal LVEF (<50%), by hs-cTnT

hs-cTnT Categories	Unadjusted Odds Ratio	Demographic adjusted	+ risk factors* + eGFR
<LOD	Reference	Reference	Reference
3.0-4.25 ng/L	1.24 (0.69, 2.25)	1.08 (0.59, 1.98)	1.03 (0.55, 1.92)
4.26-5.87 ng/L	1.42 (0.81, 2.51)	1.17 (0.65, 2.09)	1.16 (0.64, 2.12)
5.88-8.80 ng/L	2.22 (1.33, 3.69)	1.66 (0.96, 2.87)	1.62 (0.91, 2.88)
≥8.81 ng/L	4.39 (2.80, 6.88)	2.96 (1.74, 5.05)	2.97 (1.68, 5.24)
Test for trend	<.001	<.001	<.001
ln(hs-cTnT)	1.98 (1.65, 2.37)	1.68 (1.36, 2.08)	1.69 (1.34, 2.14)

* SBP, DBP, anti-hypertensive medications, diabetes (normal/IFG/DM), smoking, lipids, height, weight, and eGFR.

Cell values represent Odds Ratios and 95% CI.

Supplemental Table 5: Association of hs-cTnT with follow-up CMR measures of subclinical CVD

Subclinical CVD Measure	Adjustment	<LOD	3.0-4.05 ng/L	4.06-5.42 ng/L	5.43-7.67 ng/L	≥7.68 ng/L	p-value for trend
LVM (g)	Adjusted for baseline LMV	Reference	1.96 (0.04, 3.86)	1.98 (0.06, 3.91)	2.73 (0.51, 4.96)	2.74 (0.38, 5.10)	<.001
	+ Risk factors	Reference	1.55 (-0.15, 3.25)	1.42 (-0.42, 3.26)	2.07 (-.06, 4.20)	2.11 (0.35, 4.59)	.04
LVEDV (ml)	Adjusted for baseline LVEDV	Reference	-0.28 (-2.28, 1.73)	1.00 (-1.33, 3.32)	3.88 (1.53, 6.22)	2.78 (0.14, 5.43)	.001
	+ Risk factors	Reference	0.03 (-1.93, 1.99)	1.15 (-1.11, 3.41)	3.98 (1.58, 6.38)	1.65 (-1.21, 4.51)	0.02
LVEF (%)	Adjusted for baseline LVEF	Reference	-0.54 (-1.28, 0.21)	-0.95 (-1.70, -0.21)	-0.57 (-1.31, 0.17)	-1.42 (-2.16, -0.68)	<.001
	+ Risk factors	Reference	0.45 (-0.29, 1.18)	0.03 (-0.71, 0.78)	0.32 (-0.44, 1.08)	-0.26 (-1.06, 0.54)	0.7

Regression coefficients represent baseline-adjusted differences in follow-up LVM, LVEDV, or LVEF between participants in each hs-cTnT category compared to those with hs-cTnT below the limit of detection.

Supplemental Table 6: Association of hs-cTnT with subsequent increase in NTproBNP*

hs-cTnT category (ng/L)	Adjusted for baseline NT-proBNP	+ Demographics	+ Risk factors†
<LOD	Reference	Reference	Reference
3.0-4.25	1.05 (0.83, 132)	0.95 (0.75, 1.21)	0.94 (0.72, 1.19)
4.26-5.87	1.44 (1.16, 1.79)	1.22 (0.97, 1.55)	1.19 (0.94, 1.51)
5.88-8.80	1.77 (1.43, 2.18)	1.42 (1.11, 1.81)	1.36 (1.06, 1.75)
≥8.81	1.77 (1.43, 2.19)	1.93 (1.48, 2.50)	1.87 (1.42, 2.45)
Test for trend	<.001	<.001	<.001
ln(hs-cTnT)	1.46 (1.33, 1.60)	1.31 (1.17, 1.47)	1.29 (1.15, 1.45)

* NT-proBNP increase >25% from baseline to >80 pg/mL at follow-up

† Adjusted for age, gender, race, SBP, DBP, anti-hypertensive medications, diabetes (normal/IFG/DM), smoking, lipids, height and weight, and eGFR

Cell Values represent Odds Ratios and 95% CIs

Supplemental Table 7: Association of hs-cTnT with incident CHD and CV-related death

CHD					
hs-cTnT (ng/L)	**Event Rate (/1000 p-yrs)**	**Unadjusted Hazard Ratios**	**Demographic adjusted**	**+ risk factors***	**+NT-proBNP**
<LOD	1.8 (1.3, 2.5)	Reference	Reference	Reference	Reference
3.0-4.25	3.1 (2.1, 4.4)	1.76 (1.07, 2.89)	1.37 (0.83, 2.27)	1.33 (0.80, 2.21)	1.31 (0.78, 2.18)
4.26-5.87	4.3 (3.2, 5.9)	2.48 (1.57, 3.91)	1.65 (1.03, 2.65)	1.44 (0.89, 2.34)	1.42 (0.87, 2.31)
5.88-8.80	4.9 (3.6, 6.5)	2.78(1.78, 4.36)	1.56 (0.96, 2.52)	1.39 (0.85, 2.27)	1.30 (0.79, 2.13)
≥8.81	10.4 (8.4, 12.8)	6.00(4.01, 8.97)	2.72 (1.71, 4.733)	2.05 (1.26, 3.35)	1.75 (1.06, 2.89)
Test for trend	<.001	<.001	<.001	.005	.050
ln(hs-cTnT)	N/A	2.27 (1.96, 2.62)	1.75 (1.46, 2.10)	1.59 (1.31, 1.94)	1.41(1.16, 1.73)
CV-related death					
hs-cTnT (ng/L)	**Event Rate (/1000 p-yrs)**	**Unadjusted Hazard Ratios**	**Demographic adjusted**	**+ risk factors***	**+NT-proBNP**
<LOD	0.5 (0.3, 0.9)	Reference	Reference	Reference	Reference
3.0-4.25	2.0 (1.3, 3.1)	3.97 (1.85, 8.49)	2.86 (1.33, 6.16)	2.75 (1.28, 5.93)	2.59 (1.20, 5.60)
4.26-5.87	2.0 (1.3, 3.1)	3.91 (1.83, 8.35)	2.26 (1.04, 2.33 (1.08, 5.01)	1.91 (0.87, 4.21)	1.85 (0.84, 4.08)
5.88-8.80	2.5 (1.7, 3.8)	5.05 (2.42, 10.52)	2.33 (1.08, 5.01)	1.94 (0.89 4.20)	1.72 (0.79, 3.74)
≥8.81	7.4 (5.8, 9.5)	15.32 (7.88, 29.80)	5.11 (2.45, 10.64)	3.65 (1.73, 7.75)	2.70 (1.26, 5.82)
Test for trend	<.001	<.001	<.001	.003	.065
ln(hs-cTnT)	N/A	2.83 (2.37, 3.39)	2.05 (1.63, 2.58)	1.79 (1.39, 2.30)	1.44 (1.11, 1.88)

* Adjusted for age, gender, race, SBP, DBP, anti-hypertensive medications, diabetes (normal/IFG/DM), smoking, lipids, height, weight, and eGFR.

Cell values represent hazard ratios and 95% CI.

SUPPLEMENTAL FIGURE LEGEND

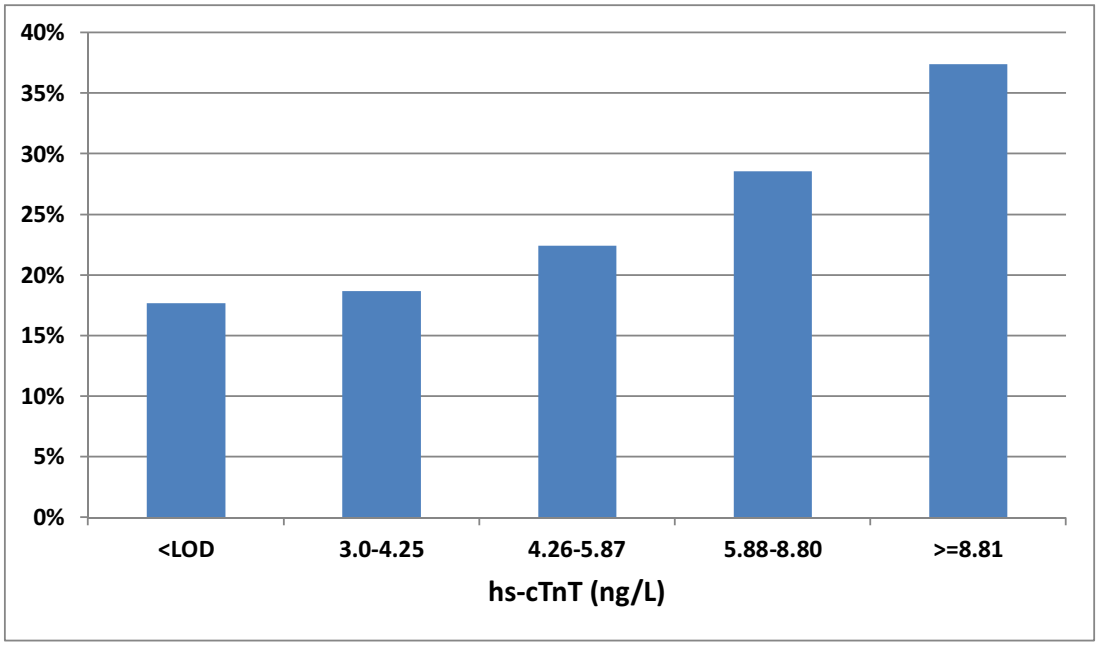
Supplemental Figure 1: Baseline hs-cTnT and subsequent increase in NT-proBNP

Supplemental Figure 2: Frequency and subtype of LV scar, by hs-cTnT category among (a) Males and (b) Females

Supplemental Figure 3: Cumulative Incidence of coronary heart disease events, by hs-cTnT category

Supplemental Figure 4: Cumulative Incidence of cardiovascular related death, by hs-cTnT category

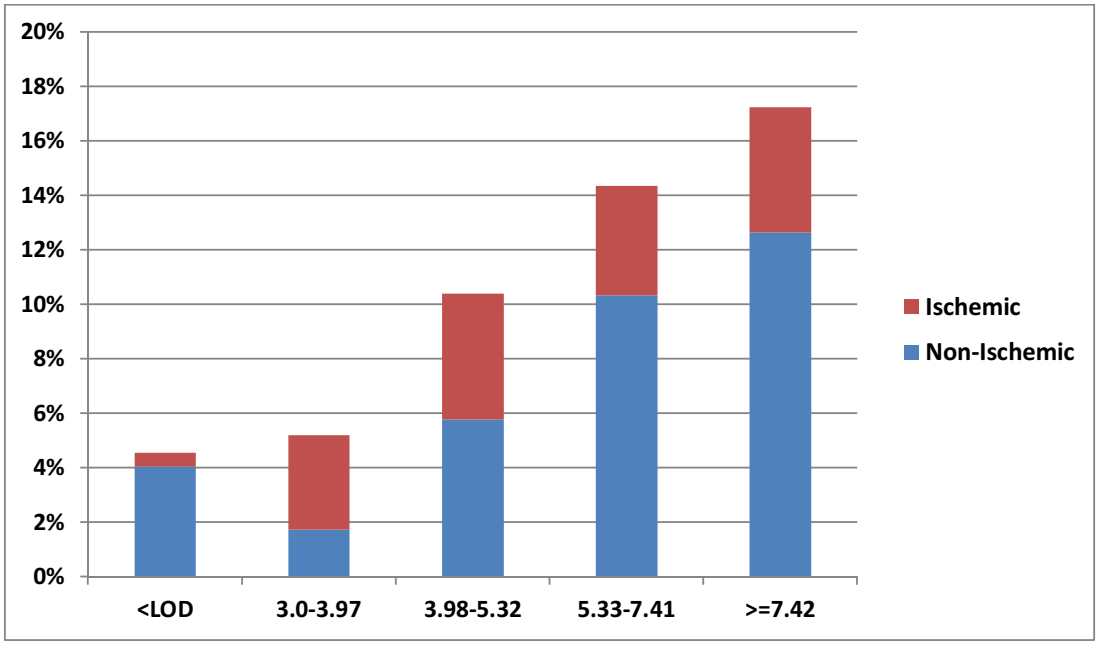
Supplemental Figure 1: Baseline hs-cTnT and subsequent significant* increase in NT-proBNP



* "Significant Increase" defined as >25% increase from baseline to ≥80 ng/L at follow-up

Supplemental Figure 2: Frequency and subtype of LV scar, by hs-cTnT category among (A) Males and (B) Females

A)



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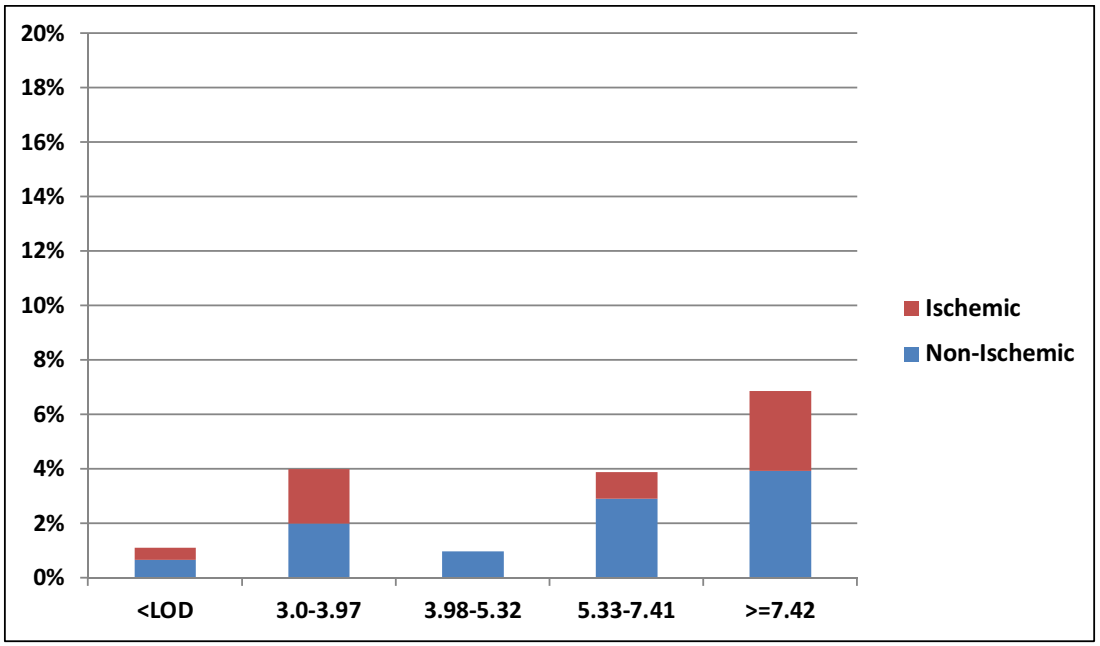
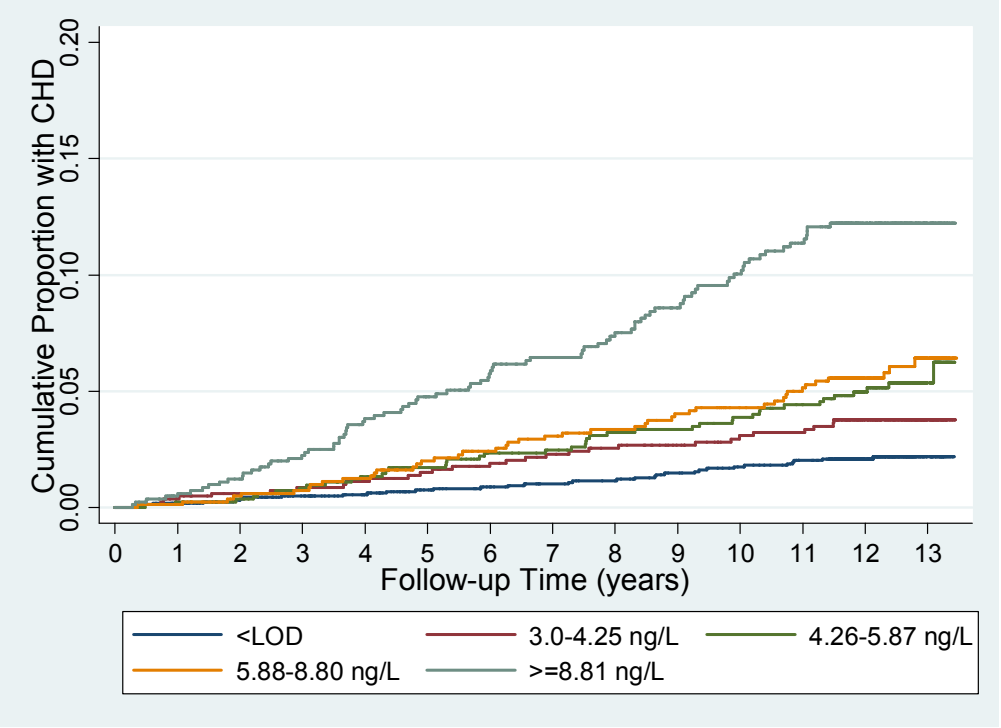


Supplemental Figure 3: Cumulative Incidence of CHD, by hs-cTnT category



Supplemental Figure 4: Cumulative Incidence of CV-related death, by hs-cTnT category