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Complete List of Authors:	Xiao, Wenkai Ye, Ping; Chinese PLA General Hospital, Geriatric Cardiology Cao, Ruihua; Chinese PLA General Hospital, Geriatric Cardiology Liu, Yuan; Chinese PLA General Hospital, Geriatric Cardiology Bai, Yongyi; Chinese PLA General Hospital, Geriatric Cardiology Wu, Hongmei; Chinese PLA General Hospital, Geriatric Cardiology
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Cardiac Troponin T Measured by a Highly Sensitive Assay Predicts All-Cause Mortality and Cardiovascular Events in a Community-Dwelling Population

Wenkai Xiao , Ping Ye *, Ruihua Cao, Yuan Liu , Yongyi Bai , Hongmei Wu

Department of Geriatric Cardiology, Chinese PLA General Hospital, No. 28, Fuxing Road, Beijing, 100853, China

Correspondence to Ping Ye, Department of Geriatric Cardiology, Chinese PLA General Hospital, Beijing, 100853, China

Tel:+86-10-66876369; Fax:+86-10-66876349; E-mail: yeping301@sina.com

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Abstract

Objective: The prognostic value of cardiac troponins in apparently healthy population is less well established. The aim of this study is to investigate the prognostic properties of high-sensitivity cardiac troponin T (hs-cTnT) for long-term adverse outcomes.

Setting: A community-dwelling prospective survey of residents from two communities in Beijing.

Participants: From September 2007 to January 2009, 1680 participants were initially enrolled, 1,499 (870 females, mean age 61.4 years) completed and were followed up for a median of 4.8 years (interquartile range, 4.5-5.2).

Outcome measures: primary outcomes were the occurrence of all-cause mortality and major cardiovascular events.

Results: In total, 820 individuals (54.7%) had detectable hs-cTnT levels. During follow-up, 52 participants (3.5%) died, 154 (10.3%) had major cardiovascular events, and 99 (6.6%) experienced new-onset coronary events. Compared with participants with undetectable levels, those with hs-cTnT levels in the highest category(≥14 ng/L) had significantly increased risk for all-cause mortality (adjusted hazard ratio [aHR] = 2.07; 95% confidence interval [CI], 1.05 to 3.01), major cardiovascular events (aHR =3.27; 95% CI, 1.88 to 5.70), and coronary events (aHR =4.50; 95% CI, 2.26 to 9.02) but not of stroke incident (aHR =1.27; 95% CI, 0.69 to 2.62) in covariate-adjusted analyses accounting for demographics, traditional cardiovascular risk factors, renal function, and biomarkers of inflammation and cardiac wall stress. Also the significant

associations were presented when hs-cTnT levels were modeled as a continuous variable and when analyzing changes over time in the hs-cTnT levels with adverse outcomes.

Conclusions: In this cohort of individuals from community-based population, cardiac troponin T measured with a highly sensitive assay was associated with subsequent risk for all-cause mortality and major cardiovascular events, which might support selection of at risk individuals.

Strengths and limitations of this study

- Evaluating the prognostic properties of both baseline and change in hs-cTnT for long-term adverse outcomes in a large community-dwelling study.
- Reliably detecting minimal subclinical myocardial injury in apparently healthy population over a wide age range.
- Absence of echocardiographic and coronary artery imaging data and can, thus, not provide causal explanations on the associations between hs-cTnT and outcomes.

Introduction

Cardiovascular disease (CVD) is still the major disease which seriously threat to human's health and lives. There is concordant evidence that prevention is an important key to lessen the CVD burden, but the risk prediction of adverse cardiovascular events in low- to intermediate-risk individuals is an important challenge.[1] This part of population are at risk for developing CVD but not early identified by currently risk factors screening methods.[2-3] While circulating biomarkers are an important supplement, one of the most interesting biomarkers in this context is troponins. Cardiac troponin T (cTnT) is a regulatory protein expressed by cardiac myocytes and released in the setting of myocardial injury.[4-5] A sensitive and specific marker of cardiomyocytes damage, cTnT is typically used clinically in the earlier exclusion or confirmation of the diagnosis of acute myocardial infarction (AMI).

However, cTnT levels can also be elevated and clinically meaningful in the absence of myocardial ischemia. Detectable levels of cTnT can also be useful for detecting subclinical CVD and assessing CVD risk in the general population; however, cTnT is only detectable in a small percentage of the general population using standard assays,[6-7] which limit the utility for our clinical applications. Recently, a highly sensitive cTnT (Hs-cTnT) assay has been developed, which can detect 10-fold lower concentrations than the standard fourth-generation assay. The introduction of this new assay has enabled detection of very low levels of circulating cTnT, even in some asymptomatic general population.[8]

Hs-cTnT levels below the detection limit of standard assays were independently

associated with adverse cardiovascular events in patients with heart failure (HF)[9] or stable coronary heart disease (CHD).[10] But the clinical significance of detectable cTnT with the use of the new assay in the apparently healthy population is less well established. The main objective of this study was to investigate the prognostic value of minimally detectable hs-cTnT levels in predicting adverse clinical events in a population of community-based subjects.

Methods

Study population

This is a prospective observational study of people living in the Pingguoyuan area of the Shijingshan district in Beijing, China. Subjects with severe systemic diseases such as immunologic diseases, endocrinic and metabolic disease (except for diabetes mellitus [DM]), inflammation, tumorous, severe hepatic or renal diseases, and a history of ischemic heart disease or HF were excluded. Briefly, between September 2007 and January 2009, a total of 1680 participants were initially recruited for cross-sectional analysis of CVD risk factors. After the initial evaluation, recruited subjects were contacted every 2 years for follow-up, and the last follow-up visits were conducted through September 30, 2013, the median follow-up was 4.8 (interquartile range 4.5-5.2) years. In our investigation, 181 participants were lost to follow-up and were excluded from the study, complete data were acquired from 1499 participants (return rate, 89.2%). All participants provided written informed consent at time of enrollment, and the study was approved by the Ethics Committee of the Chinese People's Liberation Army (PLA) General Hospital.

Data collection

Baseline characteristics for this analysis were collected using self-reported standardized questionnaires that included demographics, life-style information, medical history, and medication use. Anthropometrical measurements were obtained by trained medical doctors, and the body mass index (BMI) was derived from height and weight measured with participants wearing light clothing and no shoes. Blood pressures were measured two times on the right arm after 5 minutes of rest in a sitting position, the mean of 2 readings were used for further analysis. Participants were followed up for clinical outcomes by interview. Outcome measures were occurrences of all-cause mortality and major adverse cardiovascular event (MACE), new events were validated by obtaining medical records and adjudicated by 2 independent and blinded reviewers.

Biomarker Assays

After at least 12 hours of overnight fasting, baseline blood samples were collected from participants between 8 AM and 10 AM at enrollment. Follow-up measurements were performed on blood samples collected 4 to 5 years later. Serum aliquots were frozen at -80°C until analysis in a central laboratory were performed. Concentrations of blood glucose (fasting and 2 hours after an oral glucose tolerance), total cholesterol (TC), triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), uric acid and serum creatinine levels were measured by routine laboratory analysis.

Hs-cTnT were measured by an electrochemiluminescence immunoassay method

using an Elecsys Troponin T highly sensitive assay (Roche Diagnostics GmbH, Mannheim, Germany) on the Modular Analytics E170 autoanalyzer (Roche Diagnostics). The lower detection limit of the novel assay was 3 ng/L and a reported 99th percentile value in apparently healthy individuals was 14 ng/L.[11] N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations were determined using an electrochemiluminescence immunoassay (Roche Diagnostics GmbH) on the Roche analyzer. Levels of high-sensitivity C-reactive protein (hs-CRP) were measured with the use of immunoturbidimetric assay (Siemens Healthcare Diagnostics, IN, USA) on a Dimension RxL Max analyzer (Siemens Healthcare Diagnostics).

Estimated glomerular filtration rate（eGFR）was calculated using the Chinese modifying Modification of Diet in Renal Disease (C-MDRD) equation, details of the computing equation have been published elsewhere.[12]

Definition of end points

For outcome, we used the incidence of mortality and CVD morbidity after the baseline screening. All-cause mortality was determined by review of death certificates. The definition of MACE comprised nonfatal MI, coronary artery insufficiency (identified by coronary artery imaging or receiving coronary revascularization), stroke (ischaemic or haemorrhagic), and CVD death. Major coronary events were defined as nonfatal MI, coronary artery insufficiency, and CHD death. Stroke was characterized as a neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause, including cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage. [13] For Cox-regression analyses, survival time was

defined as the period from the date of baseline blood sample collection to the date of the first adverse event or end of follow-up.

Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD) or median (interquartile range) and categorical variables as count and percentages. We modeled hs-cTnT as both a categorical and a continuous variable. For the analyses of hs-cTnT as a categorical variable, we divided participants into 4 categories: those with undetectable hs-cTnT were placed in the first category as the reference group; those with hs-cTnT levels greater than or equal to the previously reported 99th percentile value (14 ng/L)[11] were placed in the fourth category, and those with levels between 3 and 14 ng/L were divided into two equal-sized groups for categories 2 and 3. Demographic and clinical variables were compared across hs-cTnT categories using the one-way analysis of variance tests for continuous measures, Cuzik's nonparametric trend test for nonnormally distributed variables, and chi-squared tests were performed for categorical variables.

Cumulative incidence of MACE and all-cause mortality for each category of hs-cTnT concentration was evaluated using the Kaplan-Meier method and compared with the log-rank test for trend. Multivariable Cox proportional hazards regression models were used to analyze associations of hs-cTnT categories with outcomes with category 1 used as the referent. The models were serially adjusting for demographics, traditional cardiovascular risk factors, renal function and other biomarkers (Hs-CRP and NT-proBNP) levels. We also carried an exploratory analysis in which we regarded

hs-cTnT as a continuous variable and assessed the relationship between natural logarithm transformed hs-cTnT values and end points. In this analysis, values of hs-TnT that were below the lower limit of detection were assigned to 1.5 ng/L (i.e., one-half of the lower limit of detection).

In view of the markedly skewed distribution of hs-cTnT, changes in concentrations over time were calculated as the difference between the natural logarithm of the concentrations at follow-up and at baseline. The association between changes in hs-cTnT levels and outcomes were also evaluated in Cox proportional hazards models. The change in hs-cTnT levels was entered as a continuous variable and adjusted for baseline concentration of hs-cTnT and for the relevant variables described previously in multivariable models.

All data were analyzed using the SPSS statistical package software (version 17.0). A two-sided value of $P < 0.05$ was considered statistically significant.

Results

Participant Characteristics

For the present analyses, 1499 participants were included. The mean (±SD) age of participants was 61.4±11.4 years and 58.0% were women at enrollment. Hs-cTnT was detectable at baseline in 820 individuals (54.7%) and was equal to or higher than 14 ng/L in 172 participants (11.5%), the detectable hs-cTnT levels ranged from 3 to 176.4 ng/L. Table 1 shows baseline characteristics by hs-cTnT categories. Compared with those with lower hs-cTnT levels, individuals with higher levels were older; were more likely to be male, more frequently hypertensive, and diabetic; had lower eGFR,

HDL-C levels; and had higher uric acid, NT-proBNP levels. In cardiovascular drug use, taking of antihypertensive, antidiabetic, and aspirin use varied across levels of hs-cTnT.

Outcomes by Baseline Hs-cTnT Level

Over a median follow-up period of 4.8 years (interquartile range, 4.5-5.2), 154 participants experienced new-onset MACE (including 99 coronary events and 61 strokes, some participants had more than one event) and 52 deaths occurred from any cause. The cumulative incidence of MACE and all-cause mortality by hs-cTnT categories are shown in Figure1. Just like display in the Kaplan-Meier survival analysis, there was a graded increase in the probability of adverse clinical events across the categories. The unadjusted incidence rate for MACE ranged from 3.7% in those participants with undetectable hs-cTnT levels to 23.3% for subjects in the highest category (P<0.001, log-rank test). Similar trends were discovered for coronary events, stroke, and all-cause mortality, with a particularly high risk found for those in the highest category.

Table1. Characteristics of Study Population by Baseline high-sensitivity troponin T Levels

Characteristics	Hs-cTNT Group (ng/L)				P value
	Group 1 <3.00 (n = 679)	Group 2 3.00-6.21 (n=324)	Group 3 6.22-<14 (n= 324)	Group4 ⩾14 (n = 172)	
Demographic					
Age (years)	58.6±10.3	63.1±10.7	64.2±12.4	61.8±11.5	<0.001
Male Sex n (%)	202 (29.7）	163 (50.3)	170 (52.5)	94 (54.7)	<0.001
BMI (kg/m^2)	25.5±3.5	25.7±3.2	25.6±3.3	25.8±3.5	0.498
Medical history					
Hypertension n (%)	258 (38.0)	159 (49.1)	176 (54.3)	97 (56.4)	<0.001
Diabetes mellitus n (%)	99 (14.6)	72 (22.2)	76 (23.5)	45 (26.2)	<0.001
Current smoking n (%)	85 (12.5)	69 (21.3)	62 (19.1)	31(18.0)	0.003
Systolic BP (mm Hg)	131.5±16.5	132.7±17.3	132.8±17.2	133.2±17.1	0.041
Diastolic BP (mm Hg)	77.1±9.7	77.3±10.0	76.4±10.5	76.1±11.1	0.372
Laboratory values					
FBG (mmol/L)	5.3±1.4	5.3±1.5	5.5±1.7	5.8±1.9	0.076
PBG (mmol/L)	7.5±3.7	7.1±3.2	8.1±4.3	8.9±4.4	<0.001

Total cholesterol (mmol/L)	5.1±0.9	5.1±0.9	5.1±0.9	5.0±0.9	0.464
Triglycerides (mmol/L)	1.8±1.1	1.7±1.1	1.7±1.0	2.0±1.4	0.04
LDL cholesterol (mmol/L)	3.0±0.7	2.9±0.7	3.0±0.7	3.0±0.7	0.136
HDL cholesterol (mmol/L)	1.4±0.4	1.4±0.3	1.3±0.4	1.3±0.4	0.001
Uric acid (μmol/L)	279.0±68.2	295.9±73.3	301.2±75.4	309.5±76.2	<0.001
eGFR (mL/min/1.73m^2)	90.1±14.5	88.7±13.4	87.5±15.2	84.7±16.5	0.001
NT-proBNP (pg/mL)	37.2 (17.9, 75.3)	38.9 (17.9, 74.4)	46.6 (22.3, 90.1)	49.3 (17.1, 112)	0.003
Hs-CRP （mg/L）	2.4 (1.3, 3.4)	2.3 (1.4, 3.4)	2.2 (1.5, 3.5)	2.4 (1.6, 3.6)	0.383
Medication use					
Antihypertensives n (%)	187 (27.5)	122 (37.7)	139 (42.9)	80 (46.5)	<0.001
Antidiabetic n (%)	64 (9.4)	44 (13.6)	52 (16.0)	29 (16.9)	0.0028
Lipid lowering n (%)	109 (16.1)	61 (18.8)	58 (17.9)	34 (19.8)	0.149
Aspirin n (%)	137 (20.2)	79 (24.4)	89 (27.5)	55 (31.9)	<0.001

Values are reported as n (%), mean ± SD, or median (interquartile range). BMI=body mass index; BP=blood pressure; eGFR =estimated glomerular filtration rate; FBG=fasting blood glucose; HDL= high-density lipoprotein; Hs-CRP = high-sensitivity C-reactive protein; LDL = low-density-lipoprotein; PBG= postprandial blood glucose; NT-proBNP = N-terminal pro-type B natriuretic peptide.

Associations of Baseline hs-cTnT Levels With MACE and All-Cause Mortality

In a series of Cox proportional hazards models adjusting for age and gender (model 1) and further adjusting for traditional cardiovascular risk factors (model 2), higher hs-cTnT categories demonstrated a graded association with MACE. Only modest attenuation of the hazards was found with further adjustment for renal function (model 3). Although significant attenuation was discovered with additional adjustment for hs-CRP and NT-proBNP level (model 4), hs-cTnT in the third category (hazard ratio [HR], 2.31 [95% CI, 1.39-3.84]) and fourth category (HR, 3.27 [95% CI, 1.88-5.70]) remained independently associated with MACE in the fully adjusted models. Participants in hs-cTnT categories 3 and 4 also had a significantly higher risk of coronary events compared with participants with undetectable levels (HRs of 2.76 [95% CI, 1.44-5.31] and 4.50 [95% CI, 2.26 - 9.02], respectively, in model 4, Table2). However, associations of hs-cTnT levels with incident stroke were markedly attenuated and no longer significant after adjusting for NT-proBNP (model 4, Table2). Not only in the univariate Cox regression analysis but also in multivariate models, those participants in the highest hs-cTnT category were independently associated with the all-cause mortality risk (HR 2.07, [95% CI, 1.05-3.01]).

In an exploring research of hs-cTnT as a continuous variable after natural logarithm transformation, we disclosed a continuous association with MACE incident (per one-ln unit increment; HR, 1.67; 95% CI, 1.04–2.68; $P < 0.001$), with coronary events (HR, 1.68; 95% CI, 1.35–2.08; $P < 0.001$) and with all-cause death (HR, 1.50;

95% CI, 1.26–1.79; P=0.003) in the fully multivariate models including variables described in Table 2. The same, the relationship between hs-cTnT as a continuous variable and stroke risk were not presented in the final adjusted models (HR, 1.06; 95% CI, 0.87 – 1.32; P=0.17).

Table2. Cox Proportional Hazards Models Analysis for Associations Between Baseline Hs-cTnT Levels and Outcomes

	Hazard Ratio (95% Confidence Interval)			
	Group 1 <3.00 ng/L	Group 2 3.0-6.21 ng/L	Group 3 6.22-<14 ng/L	Group 4 ⩾14 ng/L
No.	679	324	324	172
MACE	n=25 (3.7%)	n=30 (9.3%)	n=59 (18.2%)	n=40 (23.3%)
Model 1	1[Reference]	1.65 (0.97-2.81)	2.65 (1.64-4.27)	4.20 (2.51-7.02)
Model 2	1[Reference]	1.52 (0.89-2.59)	2.41 (1.48-3.91)	3.82 (2.27-6.43)
Model 3	1[Reference]	1.52 (0.89-2.61)	2.38 (1.47-3.88)	3.79 (2.26-6.39)
Model 4	1[Reference]	1.68（0.97-2.92）	2.31 (1.39-3.84)	3.27 (1.88-5.70)
Coronary event	n=14 (2.1%)	n=17 (5.3%)	n=41 (12.7%)	n=27 (15.7%)
Model 1	1[Reference]	1.69（0.83-3.44）	3.39（1.82-6.29）	5.23（2.7-10.14）
Model 2	1[Reference]	1.61（0.78-3.29）	3.25（1.74-6.07）	5.5（2.84-10.64）
Model 3	1[Reference]	1.57（0.76-3.22）	3.09（1.65-5.79）	5.14（2.65-9.98）
Model 4	1[Reference]	1.42（0.71-2.89）	2.76（1.44-5.31）	4.50（2.26-9.02）
Stroke event	n=11 (1.6%)	n=13 (4.0%)	n=20 (6.2%)	n=17 (9.9%)
Model 1	1[Reference]	1.59（0.71-3.57）	1.94（0.91-4.14）	3.84（1.75-8.43）
Model 2	1[Reference]	1.47（0.65-3.29）	1.77（0.83-3.79）	3.19（1.42-7.16）
Model 3	1[Reference]	1.47（0.65-3.31）	1.70（0.79-3.66）	3.16（1.41-7.10）
Model 4	1[Reference]	1.03 (0.50-2.09)	1.13 (0.57-2.14)	1.27 (0.69-2.62)
All–cause mortality	n=8 (1.2%)	n=7 (2.2%)	n=16 (4.9%)	n=21 (12.2%)
Model 1	1[Reference]	1.13 (0.41-3.14)	1.99 (0.83-4.76)	6.14 (2.61-14.46)

Model 2	1[Reference]	1.13 (0.41-3.14)	1.78 (0.73-4.35)	4.87 (1.99-11.88)
Model 3	1[Reference]	1.14 (0.41-3.16)	1.79 (0.73-4.38)	4.87 (1.99-11.88)
Model 4	1[Reference]	1.01 (0.40-1.15)	1.09 (0.43-2.76)	2.07 (1.05-3.01)

Abbreviations: MACE, major adverse cardiovascular event.

Models are defined as follows: model 1=adjusted for age and gender; model 2=adjusted for model 1+ presence of hypertension or diabetes mellitus, smoking status (current vs not), systolic blood pressure, postprandial blood glucose, total cholesterol, high-density lipoprotein cholesterol, antihypertensive medication use, and antidiabetic medication use; model 3= adjusted for model 2+estimated glomerular filtration rate; model 4= adjusted for model 3+ high-sensitivity C-reactive protein and N-terminal pro–B-type natriuretic peptide (both ln transformed).

Changes in hs-cTnT Concentration During Follow-up and Subsequent Events

Table 3 represents the results of Cox regression analysis for subsequent events in relation to changes in hs-cTnT concentration as a continuous variable. Changes in hs-cTnT concentration were strongly associated with subsequent events except for stroke, even in multivariable analyses that additionally adjusted for baseline hs-cTnT levels. In the fully adjusted models, the HR for MACE for every unit increasing in hs-cTnT was 1.35 (95% CI: 1.08-1.68, p =0.008), as well as coronary event (HR: 1.44, 95% CI: 1.17-1.77, p =0.001). Likewise, an increase in hs-cTnT levels was not so remarkably associated with incident stroke (HR: 1.02, 95% CI: 0.64-2.19, p =0.242).

Table3. Association of Changes in hs-cTnT Concentrations With Subsequent Events

	Multivariable adjusted HR	95% CI	p Value
MACE	1.35	1.08-1.68	0.008
Coronary event	1.44	1.17-1.77	0.001

Stroke event	1.02	0.64-2.19	0.242

Abbreviations: HR, hazard ratio; CI, confidence interval; MACE, major adverse cardiovascular event. Data are presented as hazard ratio and 95% confidence intervals for a 1-unit increase of changes in hs-cTnT on a log scale. Multivariable adjusted model adjusted for the covariates listed in Table 2 Model 4 plus baseline hs-cTnT level.

Discussion

The main purpose of the current study was to evaluate the usefulness of high-sensitivity cardiac troponin T determination for prediction of major cardiovascular events and all-cause mortality in a community-based study of general population. Several valuable findings emerged from our study. First, we used the up-to-date generation of hs-cTnT assay, allowing us to reliably detect minimal subclinical myocardial injury in some of the general population over a wide age coverage, not restricted to morbid or high-risk individuals. Second, the baseline and kinetic changes of hs-cTnT were powerful and independent predictors of long term MACE and all-cause mortality. Finally, these risk prediction was persistent even after adjustment for traditional cardiovascular risk factors as well as adjustment for biomarkers of inflammation and cardiac wall strain.

Generally, cardiac troponins are the preferred biomarkers of myocardial necrosis, typically in the diagnosis of acute coronary syndromes, but the recently available hs-cTnT assay has allowed detection of much lower concentrations of circulating cTnT. More recent observations have showed that very low levels of circulating cTnT can be detectable in patients with stable coronary artery disease,[14-15] and even in the general population by this new assay.[16-17] The exact mechanisms of troponins

release in apparently healthy individuals are not well clarified, one possibility is the existence of asymptomatic cardiac ischemia with minimal myocardial injury resulting in troponins release without any symptoms.[18] Other mechanisms including cardiomyocyte apoptosis,[19] physiological cell turnover,[20] or subclinical cardiac structural or functional abnormalities.[21-22]

The independent association between circulating levels of hs-cTnT and the incidence of adverse cardiovascular outcomes were previous reported in patients with chronic HF and stable CHD, and we now extend the findings to a general population of middle-aged to elderly. One important finding is the observation that the presence of an elevated hs-cTnT level (in the highest category) was associated with adverse outcomes regarding all-cause mortality and the MACE. However, the associations of minimally detectable hs-cTnT (especially those below 6.2ng/L, in the second category) with death or MACE were not present in comparison to the undetected group. It has been proposed that such levels may be physiological, reflecting normal myocardial cell turnover and apoptosis within the senescent heart tissue.[23] Further research is required into which hs-cTnT threshold value may best be used in risk prediction.

While other biomarkers such as hs-CRP and NT-proBNP have been used to identify apparently healthy individuals who are at increased CVD risk,[24-25] our investigation indicates that hs-cTnT is also independent of these biomarkers. In this cohort, although associations with death and cardiovascular events were significantly attenuated after additional adjustment for levels of NT-proBNP, hs-cTnT remained independently predictive for end points in the final model, suggesting that the two

biomarkers convey slightly different information in cardiac structural and functional abnormalities. The HRs remained statistically significant after adjusting for traditional cardiovascular risk factors and renal function, is also in agreement with data from other studies.[8, 26] All these data indicate that very low levels of hs-cTnT may identify subclinical myocardial injury and lead to cardiovascular events risk not fully estimated by current risk assessment methods.

Our data also suggest that even minimal changes in low levels of hs-cTnT have prognostic characteristic and can help to identify individuals at long-term risk for adverse events. There seems to be a dose dependent relationship between increased hs-cTnT and increased risk. Consistently with our results, Christopher et al,[27] have reported that changes in cTnT concentrations determined with a highly sensitive assay were significantly associated with incident HF and cardiovascular death in community -based older adults. Also, in a prospective cohort of ambulatory older adults, a strong increase in the risk of sudden cardiac death [28] and incident atrial fibrillation [29] were associated with changes over time in hs-cTnT concentrations. Although these changes may reflect normal physiological variation, their relation to future adverse events regardless of baseline hs-cTnT levels indicates that they may really represent dynamic changes in risk stratification.

In contrast to the strong associations with mortality and MACE, hs-cTnT was not associated with stroke occurrence after adjustment for multiple variables. There are several potential explanations for this finding. First, cardiac troponin specially reflects myocardial necrosis or subclinical myocardial injury, some previous studies indicate

that structural heart abnormalities are more powerful determinants of myocardial injury among participants in the general population than coronary atherosclerosis. [30-31] Second, the Atherosclerosis Risk in Communities (ARIC) Study[32] showed that elevated plasma hs-cTnT levels were related with increased risk of non-lacunar ischemic strokes, and especially cardioembolic stroke, but not with hemorrhagic stroke in the general population. Epidemiological data demonstrated that there was difference in stroke subtypes between Chinese and western, intracerebral hemorrhage (ICH) accounts for only 10-15% of strokes in most western populations,[33] whereas up to 55% of strokes in the Chinese population are ICH.[34] Although analysis for likely ischemic stroke as an endpoint had also been carried out (data not shown), the number of ischemic cause was less than one half of all strokes, and it was impossible to obtain an evident difference in the results.

Our study also has several limitations. First, cardiovascular treatment has changed with time and it is possible that more prevalent use of medicines such as statins and antiplatelet drugs could lower the predictive value of hs-cTnT. Second, we lack echocardiographic and coronary artery imaging data and can, thus, not provide causal explanations on the associations between hs-cTnT, cardiac abnormalities, and outcomes. Third, the incidence rate of the adverse events is relatively low in this cohort and hs-cTnT are detected in a considerable proportion, which limits its potential for long-term predictive usefulness. So the predictive value of hs-cTnT need to be further validated in other observational studies.

Conclusion

In this prospective cohort of community-dwelling population, we found both baseline and change in cardiac troponin T which detected by a highly sensitive assay were independently associated with adverse outcomes. It is suggesed that hs-cTnT may be an important biomarker in the prediction of mortality and cardiovascular events in apparently healthy individuals. Further investigations therefore are warranted to elucidate mechanisms for hs-cTnT release in these individuals and to test whether active interventions can reduce the associated risk contributed by elevated troponin levels.

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References

1. Khot UN, Khot MB, Bajzer CT, et al. Prevalence of conventional risk factors in patients with coronary heart disease. *JAMA* 2003;290:898-904.

2. Melander O, Newton-Cheh C, Almgren P, et al. Novel and conventional biomarkers for prediction of incident cardiovascular events in the community. *JAMA* 2009;302:49-57.

3. Blankenberg S, Zeller T, Saarela O, et al. Contribution of 30 biomarkers to 10-year cardiovascular risk estimation in 2 population cohorts: the MONICA, Risk, Genetics, Archiving, and Monograph (MORGAM) biomarker project. *Circulation* 2010;121: 2388-97.

4. Thygesen K, Mair J, Katus H, et al. Recommendations for the use of cardiac troponin measurement in acute cardiac care. *Eur Heart J* 2010;31: 2197–204.

5. Bandstein N, Ljung R, Johansson M, et al. Undetectable High-Sensitivity Cardiac Troponin T Level in the Emergency Department and Risk of Myocardial Infarction. *J Am Coll Cardiol* 2014;63:2569-78.

6. Zethelius B, Berglund L, Sundstrom J, et al. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. *N Engl J Med* 2008;358: 2107–16.

7. Daniels LB, Laughlin GA, Clopton P, et al. Minimally elevated cardiac troponin T and elevated N-terminal pro-B-type natriuretic peptide predict mortality in older adults: results from the Rancho Bernardo Study. *J Am Coll Cardiol* 2008;52:450–9.

8. Eggers KM, Al-Shakarchi J, Berglund L, et al. High-sensitive cardiac troponin T and its relations to cardiovascular risk factors, morbidity, and mortality in elderly men. *Am Heart J* 2013;166:541-8.

9. Masson S, Anand I, Favero C, et al. Serial Measurement of Cardiac Troponin T Using a Highly Sensitive Assay in Patients With Chronic Heart Failure. *Circulation* 2012;125:280-8.

10. Beatty AL, Ku IA, Christenson RH, et al. High-sensitivity cardiac troponin T and secondary events in outpatients with coronary heart disease from the Heart and Soul Study. *JAMA Intern Med* 2013;173:763–9.

11. Giannitsis E, Kurz K, Hallermayer K, et al. Analytical validation of a high-sensitivity cardiac troponin T assay. *Clin Chem* 2010;56:254-261.

12. Ma YC, Zuo L, Chen JH, et al. Modified glomerular filtration rate estimating equation for chinese patients with chronic kidney disease. *J Am Soc Nephrol* 2006; 17: 2937-44.

13. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;44:2064-89.

14. Oemrawsingh RM, Cheng JM, García-García HM, et al. High-sensitivity Troponin T in relation to coronary plaque characteristics in patients with stable coronary artery disease; results of the ATHEROREMO-IVUS study. *Atherosclerosis* 2016;247:135-41.

15. Giannitsis E, Spanuth E, Horsch A, et al. High-sensitivity cardiac troponin T and

N-terminal pro-B-type natriuretic peptide predict mortality in stablecoronary artery disease: results from the Ludwigshafen Risk and Cardiovascular Health (LURIC) study. *Clin Chem Lab Med* 2013;51:2019-28.

16. Rubin J, Matsushita K, Lazo M, et al. Determinants of minimal elevation in high-sensitivity cardiac troponin T in the generalpopulation.*Clin Biochem* 2016; 49:657-62.

17. Saunders JT, Nambi V, de Lemos JA, et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. *Circulation* 2011;123:1367-76.

18. Turer AT, Addo TA, Martin JL, et al. Myocardial ischemia induced by rapid atrial pacing causes troponin T release detectable by a highly sensitive assay: insights from a coronary sinus sampling study. *J Am Coll Cardiol* 2011;57:2398-405.

19. White HD. Pathobiology of troponin elevations: do elevations occur with myocardial ischemia as well as necrosis? *J Am Coll Cardiol* 2011;57:2406-8.

20. Røsjø H, Andreassen J, Edvardsen T, et al. Prognostic usefulness of circulating high-sensitivity troponin T in aortic stenosis and relation to echocardiographic indexes of cardiac function and anatomy. *Am J Cardiol* 2011;108:88-91.

21. Kawasaki T, Sakai C, Harimoto K, et al. Usefulness of High-Sensitivity Cardiac Troponin T and Brain Natriuretic Peptide as Biomarkers of Myocardial Fibrosis in Patients With Hypertrophic Cardiomyopathy. *Am J Cardiol* 2013;112:867-72.

22. Jenab Y, Pourjafari M, Darabi F, et al. Prevalence and determinants of elevated high-sensitivity cardiac troponin T in hypertrophic cardiomyopathy. *Journal of*

Cardiology 2014;63:140-4.

23. Sze J, Mooney J, Barzi F, et al. Cardiac Troponin and its Relationship to Cardiovascular Outcomes in Community Populations – A Systematic Review and Meta-analysis. *Heart Lung Circ* 2016;25:217-28.

24. Schnell-Inderst P, Schwarzer R, Göhler A, et al. Prognostic value, clinical effectiveness, and cost-effectiveness of high - sensitivity C-reactive protein as a marker for major cardiac events in asymptomatic individuals: a health technology assessment report. *Int J Technol Assess Health Care* 2010; 26:30-9.

25. Daniels LB, Clopton P, deFilippi CR, et al. Serial measurement of N- terminal pro-B-type natriuretic peptide and cardiac troponin T for cardiovascular diseaserisk as sessment in the Multi-Ethnic Study of Atherosclerosis (MESA). *Am Heart J* 2015; 170:1170-83.

26. Scheven L, de Jong PE, Hillege HL, et al. High-sensitive troponin T and N-terminal pro –B type natriuretic peptide are associated with cardiovascular events despite the cross- sectional association with albuminuria and glomerular filtration rate. *Eur Heart J* 2012; 33:2272-81.

27. deFilippi CR, de Lemos JA, Christenson RH, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. *JAMA* 2010;304:2494-502.

28. Hussein AA, Gottdiener JS, Bartz TM, et al. Cardiomyocyte injury assessed by a highly sensitive troponin assay and sudden cardiac death in the community: the Cardiovascular Health Study. *J Am Coll Cardiol* 2013;62:2112-20.

29. Hussein AA, Bartz TM, Gottdiener JS, et al. Serial measures of cardiac troponin T levels by a highly sensitive assay and incident atrial fibrillation in a prospective cohort of ambulatory older adults. *Heart Rhythm* 2015;12:879-85.

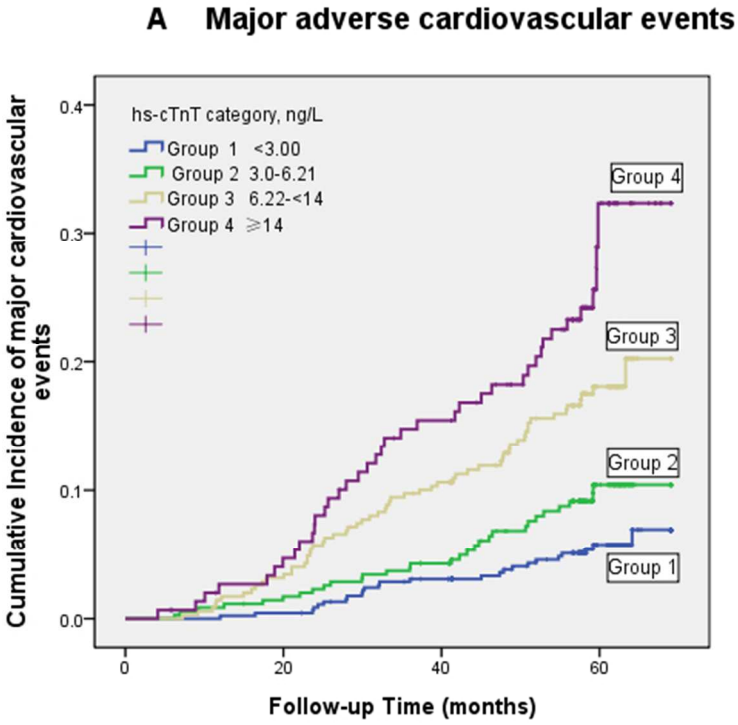
30. de Lemos JA, Drazner MH, Omland T, et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA* 2010;304:2503–12.

31. de Lemos JA, deFilippi CR. Prevalence and significance of detectable troponins as measured by highly sensitive assays in the general population. *Coronary Artery Disease* 2013;24:705-9.

32. Folsom AR, Nambi V, Bell EJ, et al. Troponin T, N-Terminal Pro–B-Type Natriuretic Peptide, and Incidence of Stroke. The Atherosclerosis Risk in Communities Study. *Stroke* 2013; 44:961-7.

33. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics-2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009;119:480-6.

34. Yang QD, Niu Q, Zhou YH, et al. Incidence of cerebral hemorrhage in the Changsha community. A prospective study from 1986 to 2000. *Cerebrovasc Dis.* 2004;17:303-13.



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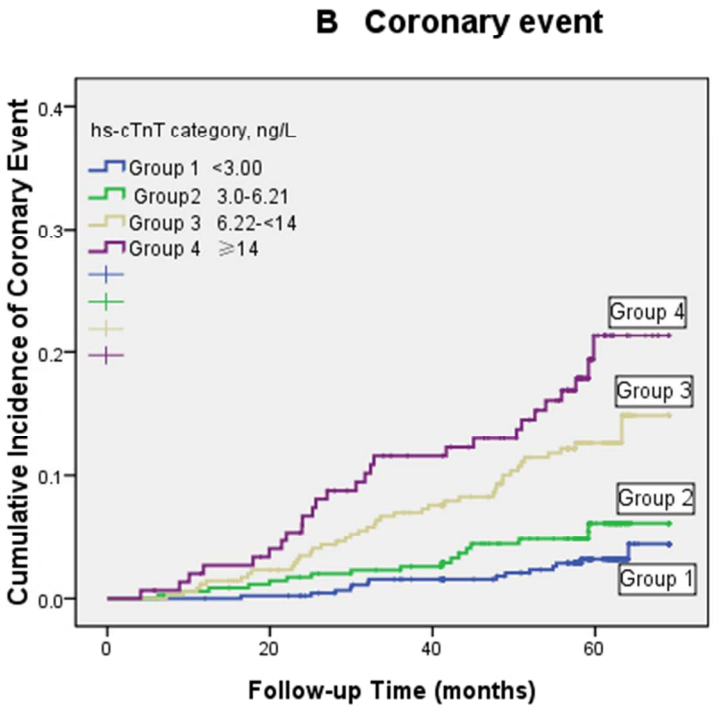

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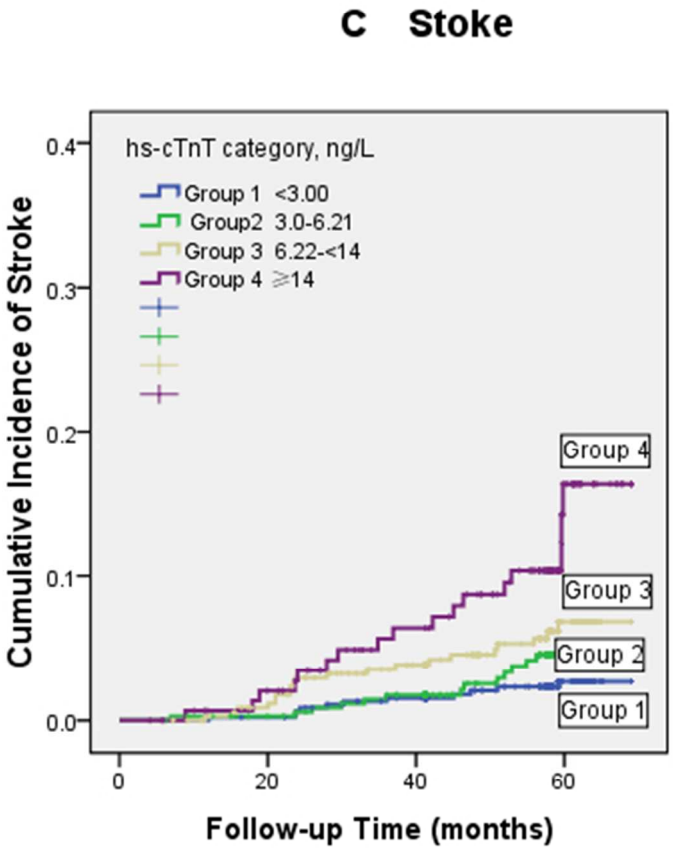

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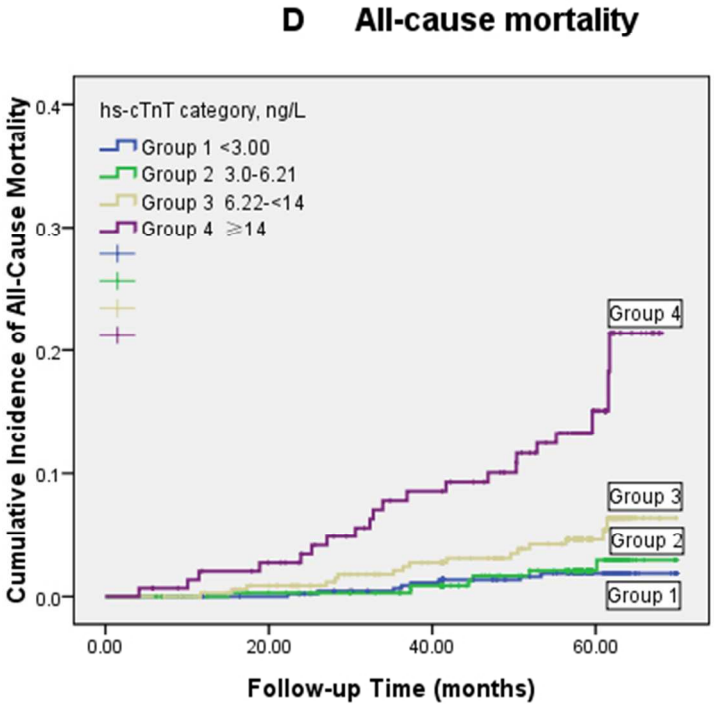

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Association of High-Sensitivity Cardiac Troponin T with Mortality and Cardiovascular Events in a Community-Based Prospective Study in Beijing

Wenkai Xiao , Ruihua Cao, Yuan Liu, Yongyi Bai, Hongmei Wu, Ping Ye *,

Department of Geriatric Cardiology, Chinese PLA General Hospital, No. 28, Fuxing Road, Beijing, 100853, China

Correspondence to Ping Ye, Department of Geriatric Cardiology, Chinese PLA General Hospital, Beijing, 100853, China

Tel:+86-10-66876369; Fax:+86-10-66876349; E-mail: yeping301@sina.com

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Abstract

Objective: The prognostic value of cardiac troponins in apparently healthy populations is not well established. The aim of this study is to investigate the prognostic properties of high-sensitivity cardiac troponin T (hs-cTnT) for long-term adverse outcomes.

Setting: A community-dwelling prospective survey of residents from two communities in Beijing.

Participants: From September 2007 to January 2009, 1680 participants were initially enrolled, of whom 1,499 (870 females, mean age 61.4 years) completed the survey and were followed up for a median of 4.8 years (interquartile range, 4.5-5.2).

Outcome measures: primary outcomes were the occurrence of all-cause mortality and major cardiovascular events.

Results: In total, 820 individuals (54.7%) had detectable hs-cTnT levels. During follow-up, 52 participants (3.5%) died, 154 (10.3%) had major cardiovascular events, and 99 (6.6%) experienced new-onset coronary events. Compared with participants with undetectable levels, those with hs-cTnT levels in the highest category(≥14 ng/L) had significantly increased risk for all-cause mortality (adjusted hazard ratio [aHR] = 2.07; 95% confidence interval [CI], 1.05 to 3.01), major cardiovascular events (aHR =3.27; 95% CI, 1.88 to 5.70), and coronary events (aHR =4.50; 95% CI, 2.26 to 9.02) but not for stroke incident (aHR =1.27; 95% CI, 0.69 to 2.62) in covariate-adjusted analyses. Also the significant associations were presented when hs-cTnT levels were modeled as a continuous variable and when analyzing changes over time in the

hs-cTnT levels with adverse outcomes. Addition of troponin T levels to clinical variables led to significant increases in risk prediction with significant improvement of the c-statistic (P=0.003 or lower).

Conclusions: In this cohort of individuals from a community-based population, cardiac troponin T measured with a highly sensitive assay was associated with subsequent risk for all-cause mortality and major cardiovascular events, which might support screening for at risk individuals.

Strengths and limitations of this study

- Evaluating the prognostic properties of both baseline and change in hs-cTnT for long-term adverse outcomes in a large community-dwelling study.
- Reliably detected minimal subclinical myocardial injury in an apparently healthy population over a wide age range.
- Absence of echocardiographic and coronary artery imaging data and thus, could not provide causal explanations on the associations between hs-cTnT and outcomes.

Introduction

Cardiovascular disease (CVD) is still the primary cause of morbidity and mortality globally. There is concordant evidence that prevention is the key to lessening the CVD burden, but risk prediction of adverse cardiovascular events in low- to intermediate-risk individuals is a big challenge.[1] This subpopulation are at risk for developing CVD but are not identified early by current risk-factor screening methods. [2-3] Circulating biomarkers can be an important supplemental screening tool, and one of the most interesting biomarkers in this context is troponins. Cardiac troponin T (cTnT) is a regulatory protein expressed by cardiac myocytes and released in the setting of myocardial injury. [4-5] A sensitive and specific marker of cardiomyocytes damage, cTnT is typically used clinically in the earlier exclusion or confirmation of the diagnosis of acute myocardial infarction (AMI).

However, cTnT levels can also be elevated and clinically meaningful in the absence of myocardial ischemia. Detectable levels of cTnT can also be useful for detecting subclinical CVD and assessing CVD risk in the general population; however, cTnT is only detectable in a small percentage of the general population using standard assays, [6-7] which limit the utility for clinical applications. Recently, a highly sensitive cTnT (Hs-cTnT) assay has been developed, which can detect 10-fold lower concentrations than the standard fourth-generation assay. The introduction of this new assay has enabled detection of very low levels of circulating cTnT, even in some asymptomatic general population. [8]

cTnT levels below the detection limit of standard assays were independently

associated with adverse cardiovascular events in patients with heart failure (HF) [9] or stable coronary heart disease (CHD). [10] But the clinical significance of detectable cTnT with the use of the new assay in the apparently healthy population is not well established. The main objective of this study was to investigate the prognostic value of minimally detectable hs-cTnT levels in predicting adverse clinical events in a population of community-based subjects.

Methods

Study population

This is a prospective observational study of people living in the Pingguoyuan area of the Shijingshan district, a metropolitan area of Beijing, China. Initially, between September 2007 and January 2009, all permanent residents of Han origin aged 45 years or older (range 45~91 years) from two communities were invited to participate in a health survey that focused on identifying CVD risk factors. 31 subjects with bedridden status, mental illness, and severe systemic diseases were excluded from the enrollment. Then 1,832 participants were included and provided questionnaires. Of those, 152 participants with overt CVD (defined as a composite of CHD [myocardial infarction, angina pectoris, or coronary insufficiency], cerebrovascular disease [stroke or transient ischemic attack], congestive HF, or peripheral vascular disease) were excluded. Thus, adequate baseline measurements and cardiac biomarkers were obtained in 1680 participants. After the initial evaluation, recruited subjects were contacted every 2 years for follow-up, and the last follow-up visits were conducted through September 30, 2013. The median follow-up was 4.8

(interquartile range 4.5-5.2) years. In our investigation, 181 participants were lost to follow-up (supplementary Table 1 shows the clinical characteristics) and were excluded from the study, complete data were acquired from 1499 participants (return rate, 89.2%). All participants provided written informed consent at time of enrollment, and the study was approved by the Ethics Committee of the Chinese People's Liberation Army (PLA) General Hospital.

Data collection

Baseline characteristics for this analysis were collected using self-reported standardized questionnaires that included demographics, life-style information, medical history, and medication use. Anthropometrical measurements were obtained by trained medical doctors, and the body mass index (BMI) was derived from height and weight measured with participants wearing light clothing and no shoes. Blood pressures were measured two times on the right arm after 5 minutes of rest in a sitting position, the mean of 2 readings were used for further analysis. Participants were followed up for clinical outcomes by interview. Outcome measures were occurrences of all-cause mortality and major adverse cardiovascular event (MACE), new events were validated by obtaining medical records and adjudicated by 2 independent and blinded reviewers. In our analyses, survival time was defined as the period from the date of baseline blood sample collection to the date of the first adverse event or end of follow-up.

Biomarker Assays

After at least 12 hours of overnight fasting, baseline blood samples were

collected from participants between 8 AM and 10 AM at enrollment. Follow-up measurements were performed on blood samples collected 4 to 5 years later. Serum aliquots were frozen at -80°C until analysis in a central laboratory were performed. Concentrations of blood glucose (fasting and 2 hours after an oral glucose tolerance), total cholesterol (TC), triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), uric acid and serum creatinine levels were measured by routine laboratory analysis.

Hs-cTnT were measured by an electrochemiluminescence immunoassay method using an Elecsys Troponin T highly sensitive assay (Roche Diagnostics GmbH, Mannheim, Germany) on the Modular Analytics E170 autoanalyzer (Roche Diagnostics). The lower detection limit of the novel assay was 3 ng/L and a reported 99th percentile value in apparently healthy individuals was 14 ng/L. [11] N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations were determined using an electrochemiluminescence immunoassay (Roche Diagnostics GmbH) on the Roche analyzer. Levels of high-sensitivity C-reactive protein (hs-CRP) were measured with the use of immunoturbidimetric assay (Siemens Healthcare Diagnostics, IN, USA) on a Dimension RxL Max analyzer (Siemens Healthcare Diagnostics).

Estimated glomerular filtration rate（eGFR）was calculated using the Chinese modifying Modification of Diet in Renal Disease (C-MDRD) equation, details of the computing equation have been published elsewhere. [12]

Definition of end points

For outcomes, we used the incidence of mortality and CVD morbidity after the

baseline screening. All-cause mortality was determined by review of death certificates. The definition of MACE comprised nonfatal MI, ischaemic heart disease (identified by coronary artery imaging or receiving coronary revascularization), stroke (ischaemic or haemorrhagic), and cardiovascular mortality. Major coronary events were defined as nonfatal MI, ischaemic heart disease, and CHD death. Stroke was characterized as a neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause, including cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage. [13] Cardiovascular mortality was defined as mortality related to atherosclerotic heart disease (fatal MI and definite fatal CHD), mortality following cerebrovascular disease, or mortality from other atherosclerotic and CVD including HF. Nonfatal MI was defined by the American Heart Association diagnostic cretiria. [14]

Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD) or median (interquartile range) and categorical variables as count and percentages. We modeled hs-cTnT as both a categorical and a continuous variable. For the analyses of hs-cTnT as a categorical variable, we divided participants into 4 categories: those with undetectable hs-cTnT were placed in the first category as the reference group; those with hs-cTnT levels greater than or equal to the previously reported 99th percentile value (14 ng/L)[11] were placed in the fourth category, and those with levels between 3 and 14 ng/L were divided into two groups for categories 2 and 3 based on the median value of hs-cTnT. Demographic and clinical variables were compared across

hs-cTnT categories using the one-way analysis of variance tests for continuous measures, Cuzik's nonparametric trend test for nonnormally distributed variables, and chi-squared tests were performed for categorical variables.

Cumulative incidence of MACE and all-cause mortality for each category of hs-cTnT concentration was evaluated using the Kaplan-Meier method and compared with the log-rank test. Multivariable Cox proportional hazards regression models were used to analyze associations of hs-cTnT categories with outcomes with category 1 used as the referent. The models were incrementally adjusting for demographics, traditional cardiovascular risk factors, renal function and other biomarkers (Hs-CRP and NT-proBNP) levels. We also carried an exploratory analysis in which we regarded cTnT as a continuous variable and assessed the relationship between natural logarithm transformed hs-cTnT values and end points. In this analysis, values of cTnT that were below the lower limit of detection were assigned to 1.5 ng/L (i.e., one-half of the lower limit of detection).

In view of the markedly skewed distribution of cTnT, changes in concentrations over time were calculated as the difference between the natural logarithm of the concentrations at follow-up and at baseline. The association between changes in hs-cTnT levels and outcomes were also evaluated in Cox proportional hazards models. The change in hs-cTnT levels was entered as a continuous variable and adjusted for baseline concentration of hs-cTnT and for the relevant variables described previously in multivariable models.

The discriminative capacity of a model with and without cTnT was estimated as

C-statistics. The area under the receiver operating characteristic curve summarized the diagnostic discrimination. All data were analyzed using the SPSS statistical package software (version 17.0). A two-sided value of $P < 0.05$ was considered statistically significant.

Results

Participant Characteristics

For the present analyses, 1499 participants were included. The mean (±SD) age of participants at enrollment was 61.4±11.4 years and 58.0% were women. cTnT was detectable at baseline in 820 individuals (54.7%) and was equal to or higher than 14 ng/L in 172 participants (11.5%), the detectable cTnT levels ranged from 3 to 176.4 ng/L. Table 1 shows baseline characteristics by hs-cTnT categories. Compared with those with lower cTnT levels, individuals with higher levels were older, were more likely to be male, more frequently hypertensive and diabetic, had lower eGFR and HDL-C levels, and had higher uric acid, NT-proBNP levels. In cardiovascular drug use, use of antihypertensive, antidiabetic, and aspirin varied across levels of hs-cTnT.

Outcomes by Baseline Hs-cTnT Level

Over a median follow-up period of 4.8 years (interquartile range, 4.5-5.2), 154 participants experienced new-onset MACE (including 99 coronary events and 61 strokes, some participants had more than one event) and 52 deaths occurred from any cause. The cumulative incidence of MACE and all-cause mortality by hs-cTnT categories are shown in Figure1. As demonstrated by the Kaplan-Meier survival

analysis, there was a graded increase in the probability of adverse clinical events across the categories. The unadjusted incidence rate for MACE ranged from 3.7% in those participants with undetectable hs-cTnT levels to 23.3% for subjects in the highest category (P<0.001, log-rank test). Similar trends were discovered for coronary events, stroke, and all-cause mortality, with a particularly high risk was found for those in the highest category.

Table1. Characteristics of Study Population by Baseline high-sensitivity troponin T Levels

Characteristics	Hs-cTNT Group (ng/L)				P value for Trend
	Group 1 <3.00 (n = 679)	Group 2 3.00-6.21 (n=324)	Group 3 6.22-<14 (n= 324)	Group4 ⩾14 (n = 172)	
Demographic					
Age (years)	58.6±10.3	63.1±10.7	64.2±12.4	61.8±11.5	<0.001
Male Sex n (%)	202 (29.7）	163 (50.3)	170 (52.5)	94 (54.7)	<0.001
BMI (kg/m^2)	25.5±3.5	25.7±3.2	25.6±3.3	25.8±3.5	0.498
Medical history					
Hypertension n (%)	258 (38.0)	159 (49.1)	176 (54.3)	97 (56.4)	<0.001
Diabetes mellitus n (%)	99 (14.6)	72 (22.2)	76 (23.5)	45 (26.2)	<0.001
Current smoking n (%)	85 (12.5)	69 (21.3)	62 (19.1)	31(18.0)	0.003
Systolic BP (mm Hg)	131.5±16.5	132.7±17.3	132.8±17.2	133.2±17.1	0.041
Diastolic BP (mm Hg)	77.1±9.7	77.3±10.0	76.4±10.5	76.1±11.1	0.372
Laboratory values					
FBG (mmol/L)	5.3±1.4	5.3±1.5	5.5±1.7	5.8±1.9	0.076
PBG (mmol/L)	7.5±3.7	7.1±3.2	8.1±4.3	8.9±4.4	<0.001

Total cholesterol (mmol/L)	5.1±0.9	5.1±0.9	5.1±0.9	5.0±0.9	0.464
Triglycerides (mmol/L)	1.8±1.1	1.7±1.1	1.7±1.0	2.0±1.4	0.04
LDL cholesterol (mmol/L)	3.0±0.7	2.9±0.7	3.0±0.7	3.0±0.7	0.136
HDL cholesterol (mmol/L)	1.4±0.4	1.4±0.3	1.3±0.4	1.3±0.4	0.001
Uric acid (μmol/L)	279.0±68.2	295.9±73.3	301.2±75.4	309.5±76.2	<0.001
eGFR (mL/min/1.73m^2)	90.1±14.5	88.7±13.4	87.5±15.2	84.7±16.5	0.001
NT-proBNP (pg/mL)	37.2 (17.9, 75.3)	38.9 (17.9, 74.4)	46.6 (22.3, 90.1)	49.3 (17.1, 112)	0.003
Hs-CRP （mg/L）	2.4 (1.3, 3.4)	2.3 (1.4, 3.4)	2.2 (1.5, 3.5)	2.4 (1.6, 3.6)	0.383
Medication use					
Antihypertensives n (%)	187 (27.5)	122 (37.7)	139 (42.9)	80 (46.5)	<0.001
Antidiabetic n (%)	64 (9.4)	44 (13.6)	52 (16.0)	29 (16.9)	0.0028
Lipid lowering n (%)	109 (16.1)	61 (18.8)	58 (17.9)	34 (19.8)	0.149
Aspirin n (%)	137 (20.2)	79 (24.4)	89 (27.5)	55 (31.9)	<0.001

Values are reported as n (%), mean ± SD, or median (interquartile range). BMI=body mass index; BP=blood pressure; eGFR =estimated glomerular filtration rate; FBG=fasting blood glucose; HDL= high-density lipoprotein; Hs-CRP = high-sensitivity C-reactive protein; LDL = low-density-lipoprotein; PBG= postprandial blood glucose; NT-proBNP = N-terminal pro-type B natriuretic peptide.

Associations of Baseline hs-cTnT Levels With MACE and All-Cause Mortality

In a series of Cox proportional hazards models adjusting for age and gender (model 1) and further adjusting for traditional cardiovascular risk factors (model 2), higher hs-cTnT categories demonstrated a graded association with MACE. Only modest attenuation of the hazards was found with further adjustment for renal function (model 3). Although significant attenuation was discovered with additional adjustment for hs-CRP and NT-proBNP level (model 4), hs-cTnT levels in the third category (hazard ratio [HR], 2.31 [95% CI, 1.39-3.84]) and fourth category (HR, 3.27 [95% CI, 1.88-5.70]) remained independently associated with MACE in the fully adjusted models. Participants in hs-cTnT categories 3 and 4 also had a significantly higher risk of coronary events compared with participants with undetectable levels (HRs of 2.76 [95% CI, 1.44-5.31] and 4.50 [95% CI, 2.26 - 9.02], respectively, in model 4, Table2). However, associations of hs-cTnT levels with stroke incidents were markedly attenuated and no longer significant after adjusting for NT-proBNP (model 4, Table2). Not only in the univariate Cox regression analysis but also in multivariate models, membership in the highest hs-cTnT category was independently associated with the all-cause mortality risk (HR 2.07, [95% CI, 1.05-3.01]).

In an exploratory research of hs-cTnT as a continuous variable after natural logarithm transformation, we found a continuous association with MACE incident (per one-ln unit increment; HR, 1.67; 95% CI, 1.04–2.68; $P < 0.001$), with coronary events (HR, 1.68; 95% CI, 1.35–2.08; $P < 0.001$) and with all-cause mortality (HR,

1.50; 95% CI, 1.26–1.79; P=0.003) in the fully multivariate models including variables described in Table 2. The association between cTnT as a continuous variable and stroke risk was not found in the final adjusted models (HR, 1.06; 95% CI, 0.87 – 1.32; P=0.17).

Table2. Cox Proportional Hazards Models Analysis for Associations Between Baseline Hs-cTnT Levels and Outcomes

	Hazard Ratio (95% Confidence Interval)			
	Group 1 <3.00 ng/L	Group 2 3.0-6.21 ng/L	Group 3 6.22-<14 ng/L	Group 4 ⩾14 ng/L
No.	679	324	324	172
MACE	n=25 (3.7%)	n=30 (9.3%)	n=59 (18.2%)	n=40 (23.3%)
Model 1	1[Reference]	1.65 (0.97-2.81)	2.65 (1.64-4.27)	4.20 (2.51-7.02)
Model 2	1[Reference]	1.52 (0.89-2.59)	2.41 (1.48-3.91)	3.82 (2.27-6.43)
Model 3	1[Reference]	1.52 (0.89-2.61)	2.38 (1.47-3.88)	3.79 (2.26-6.39)
Model 4	1[Reference]	1.68（0.97-2.92）	2.31 (1.39-3.84)	3.27 (1.88-5.70)
Coronary event	n=14 (2.1%)	n=17 (5.3%)	n=41 (12.7%)	n=27 (15.7%)
Model 1	1[Reference]	1.69（0.83-3.44）	3.39（1.82-6.29）	5.23（2.7-10.14）
Model 2	1[Reference]	1.61（0.78-3.29）	3.25（1.74-6.07）	5.5（2.84-10.64）
Model 3	1[Reference]	1.57（0.76-3.22）	3.09（1.65-5.79）	5.14（2.65-9.98）
Model 4	1[Reference]	1.42（0.71-2.89）	2.76（1.44-5.31）	4.50（2.26-9.02）
Stroke event	n=11 (1.6%)	n=13 (4.0%)	n=20 (6.2%)	n=17 (9.9%)
Model 1	1[Reference]	1.59（0.71-3.57）	1.94（0.91-4.14）	3.84（1.75-8.43）
Model 2	1[Reference]	1.47（0.65-3.29）	1.77（0.83-3.79）	3.19（1.42-7.16）
Model 3	1[Reference]	1.47（0.65-3.31）	1.70（0.79-3.66）	3.16（1.41-7.10）
Model 4	1[Reference]	1.03 (0.50-2.09)	1.13 (0.57-2.14)	1.27 (0.69-2.62)
All–cause mortality	n=8 (1.2%)	n=7 (2.2%)	n=16 (4.9%)	n=21 (12.2%)
Model 1	1[Reference]	1.13 (0.41-3.14)	1.99 (0.83-4.76)	6.14 (2.61-14.46)

Model 2	1[Reference]	1.13 (0.41-3.14)	1.78 (0.73-4.35)	4.87 (1.99-11.88)
Model 3	1[Reference]	1.14 (0.41-3.16)	1.79 (0.73-4.38)	4.87 (1.99-11.88)
Model 4	1[Reference]	1.01 (0.40-1.15)	1.09 (0.43-2.76)	2.07 (1.05-3.01)

Abbreviations: MACE, major adverse cardiovascular event.

Models are defined as follows: model 1=adjusted for age and gender; model 2=adjusted for model 1+ presence of hypertension or diabetes mellitus, smoking status (current vs not), systolic blood pressure, postprandial blood glucose, total cholesterol, high-density lipoprotein cholesterol, antihypertensive medication use, and antidiabetic medication use; model 3= adjusted for model 2+estimated glomerular filtration rate; model 4= adjusted for model 3+ high-sensitivity C-reactive protein and N-terminal pro–B-type natriuretic peptide (both ln transformed).

Changes in hs-cTnT Concentration During Follow-up and Subsequent Events

Table 3 presents the results of Cox regression analysis for subsequent events in relation to changes in hs-cTnT concentration as a continuous variable. Changes in hs-cTnT concentration were strongly associated with subsequent events except for stroke, even in multivariable analyses that additionally adjusted for baseline hs-cTnT levels. In the fully adjusted models, the HR for MACE for every unit increasing in hs-cTnT concentration was 1.35 (95% CI: 1.08-1.68, p =0.008), as well as coronary event (HR: 1.44, 95% CI: 1.17-1.77, p =0.001). Likewise, an increase in hs-cTnT concentration was not so remarkably associated with incident stroke (HR: 1.02, 95% CI: 0.64-2.19, p =0.242).

Table3. Association of Changes in hs-cTnT Concentrations With Subsequent Events

	Multivariable adjusted HR	95% CI	p Value
MACE	1.35	1.08-1.68	0.008

Coronary event	1.44	1.17-1.77	0.001
Stroke event	1.02	0.64-2.19	0.242

Abbreviations: HR, hazard ratio; CI, confidence interval; MACE, major adverse cardiovascular event. Data are presented as hazard ratio and 95% confidence intervals for a 1-unit increase of changes in hs-cTnT on a log scale. Multivariable adjusted model adjusted for the covariates listed in Table 2 Model 4 plus baseline hs-cTnT level.

Hs-cTnT and Risk Prediction

Hs-cTnT provided incremental prognostic information regarding the three endpoints when added to a model based on established risk indicators (Table 4). The addition of hs-cTnT increased the c-statistic from 0.671 to 0.698 (P=0.003) for the prediction of all-cause mortality and improved prediction of MACE from 0.702 to 0.734 (P<0.001) .

Table4. Discrimination for adverse outcomes with the addition of hs-cTnT to clinical risk factor model.

	c-statistic (95%CI)		
Endpoint	Clinical Model	Clinical Model + hs-cTnT	p Value
All–cause mortality	0.671 (0.646-0.704)	0.698 (0.680–0.725)	P=0.003
MACE	0.702 (0.680–0.726)	0.734 (0.714–0.758)	<0.001
Coronary event	0.713 (0.701-0.735)	0.749 (0.729–0.768)	<0.001
Stroke event	0.683 (0.665–0.709)	0.697 (0.674–0.729)	P=0.09

Clinical risk factor model include age, gender, body mass index, current smoking, diabetes mellitus, systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, estimated glomerular filtration rate.

Discussion

The main purpose of the current study was to evaluate the usefulness of high-sensitivity cardiac troponin T measurement for prediction of major cardiovascular events and all-cause mortality in a community-based study of general population. Several valuable findings emerged from our study. First, we used the up-to-date generation of cTnT assay, allowing us to reliably detect minimal subclinical myocardial injury in some individuals of a general population covering a wide age range, without restricting the study to morbid or high-risk individuals. Second, the baseline and kinetic changes of hs-cTnT concentration were powerful and independent predictors of long term MACE and all-cause mortality. Finally, these risk predictions were persistent even after adjustment for traditional cardiovascular risk factors as well as adjustment for biomarkers of inflammation and cardiac wall strain.

Cardiac troponins are generally the preferred biomarkers of myocardial necrosis, typically in the diagnosis of acute coronary syndromes, but the recently available hs-cTnT assay has allowed detection of much lower concentrations of circulating cTnT. More recent observations have showed that with this new assay, very low levels of circulating cTnT can be detectable and can provide information about the coronary plaque characteristics and mortality in patients with stable CHD; [15-16] and that very low levels of circulating cTnT can even be detected in the general population. [17-18] The exact mechanisms of troponins release in apparently healthy individuals are not well clarified. One possibility is the existence of asymptomatic cardiac ischemia with minimal myocardial injury resulting in troponins release

without any symptoms. [19] Other mechanisms include cardiomyocyte apoptosis, [20] physiological cell turnover, [21] or subclinical cardiac structural or functional abnormalities. [22-23]

More recently, although the prognostic implications of hs-cTnT assays among apparently healthy individuals have been explored in three large cohort studies, [18, 24-25] all the studies are of middle-aged to elderly general populations from western countries. Now our study extends the findings to Asians and demonstrates the significance of hs-cTnT assay in risk assessment. To the best of our knowledge, this is the first study to evaluate the potential utility of hs-cTnT assay in a Chinese population. One important finding is the observation that the presence of an elevated hs-cTnT level (in the highest category) was associated with adverse outcomes regarding all-cause mortality and MACE. However, the associations of minimally detectable hs-cTnT levels (especially those below 6.2ng/L, in the second category) with death or MACE were not present in comparison to the undetected group. It has been proposed that such levels may be physiological, reflecting normal myocardial cell turnover and apoptosis within the senescent heart tissue, [26] or cortisol response to mental stress in healthy adults. [27] Further research is required into which hs-cTnT threshold value may best be used in risk prediction.

While other biomarkers such as hs-CRP and NT-proBNP have been used to identify apparently healthy individuals who are at increased CVD risk, [28-29] our investigation indicates that hs-cTnT is also independent of these biomarkers. In this cohort, although associations with death and cardiovascular events were significantly

attenuated after additional adjustment for levels of NT-proBNP, hs-cTnT remained independently predictive of end points in the final model, suggesting that the two biomarkers convey slightly different information for cardiac structural and functional abnormalities. The hazard ratios remained statistically significant after adjusting for traditional cardiovascular risk factors and renal function, consistent with results from other studies. [8, 30] All these data indicate that very low levels of cTnT may identify subclinical myocardial injury and lead to cardiovascular events risk not fully estimated by current risk assessment methods. Also, associations of hs-cTnT level with all-cause mortality and MACE were consistent in stratification analysis defined by sex.

Our data also suggest that even minimal changes in low levels of cTnT have prognostic characteristics and can help to identify individuals at long-term risk for adverse events. There seems to be a dose-dependent relationship between increased hs-cTnT and increased risk. Consistently with our results, DeFilippi et al, [24] have reported that changes in cTnT concentrations determined with a highly sensitive assay were significantly associated with incident HF and cardiovascular death in community -based older adults. Also, in a prospective cohort of ambulatory older adults, a strong increase in the risk of sudden cardiac death [31] and incident atrial fibrillation [32] was associated with changes over time in hs-cTnT concentrations. Although these changes may reflect normal physiological variation, their relation to future adverse events regardless of baseline hs-cTnT levels indicates that they may really represent dynamic changes in risk stratification.

In contrast to the strong associations with mortality and MACE, hs-cTnT concentration was not associated with stroke occurrence after adjustment for multiple variables. There are several potential explanations for this finding. First, cardiac troponin specially reflects myocardial necrosis or subclinical myocardial injury. Some previous studies indicate that structural heart abnormalities are more powerful determinants of myocardial injury among participants in the general population than coronary atherosclerosis. [33-34] Second, the Atherosclerosis Risk in Communities (ARIC) Study [35] showed that elevated plasma hs-cTnT levels were associated with increased risk of non-lacunar ischemic strokes, and especially cardioembolic stroke, but not with hemorrhagic stroke in the general population. Epidemiological data has demonstrated that there are differences in incidence rates of stroke subtypes between Chinese and western populations. Intracerebral hemorrhage (ICH) accounts for only 10-15% of strokes in most western populations, [36] whereas up to 55% of strokes in the Chinese population are ICH. [37] Although analysis for likely ischemic stroke as an end point had also been carried out (data not shown), the number of ischemic cause was less than one half of all strokes, and it was impossible to obtain an evident difference in the results.

Our study also has several limitations. First, cardiovascular treatment has changed over time and it is possible that more prevalent use of medicines such as statins and antiplatelet drugs could have lowered the predictive value of hs-cTnT. Second, we lack echocardiographic and coronary artery imaging data and thus, can not provide causal explanations for the associations between hs-cTnT level , cardiac

abnormalities, and outcomes. Third, the incidence rate of adverse events was relatively low in this cohort and hs-cTnT were detected in a considerable proportion, which limits its potential for long-term predictive usefulness. Finally, the study population was restricted to Chinese Han origin inhabitant. Therefore, extrapolation of our results to other demographic groups should be done with caution. The predictive value of hs-cTnT needs to be further validated in other observational studies.

Conclusion

In this prospective cohort of community-dwelling population, we found both baseline and changes in cardiac troponin T detected by a highly sensitive assay were independently associated with adverse outcomes. The results suggest that cTnT may be an important biomarker in the prediction of mortality and cardiovascular events in apparently healthy individuals. Further investigations therefore are warranted to elucidate mechanisms for cTnT release in these individuals and to test whether active interventions can reduce the associated risk contributed by elevated troponin levels.

Contributorship statement: The manuscript has been read and approved by all of the authors. All authors contributed to the intellectual development of this paper. Conceived and designed the experiments: Ping Ye. Performed the experiments: Wenkai Xiao, Yuan Liu. Analyzed the data: Wenkai Xiao and Yongyi Bai. Wrote the manuscript: Wenkai Xiao. Supervised data collection: Rui Cao, Hongmei Wu.

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Data sharing statement: The additional unpublished data from the study are available. We can share the original data for this research article.

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References

1. Khot UN, Khot MB, Bajzer CT, et al. Prevalence of conventional risk factors in patients with coronary heart disease. *JAMA* 2003;290:898-904.

2. Melander O, Newton-Cheh C, Almgren P, et al. Novel and conventional biomarkers for prediction of incident cardiovascular events in the community. *JAMA* 2009;302:49-57.

3. Blankenberg S, Zeller T, Saarela O, et al. Contribution of 30 biomarkers to 10-year cardiovascular risk estimation in 2 population cohorts: the MONICA, Risk, Genetics, Archiving, and Monograph (MORGAM) biomarker project. *Circulation* 2010;121: 2388-97.

4. Thygesen K, Mair J, Katus H, et al. Recommendations for the use of cardiac troponin measurement in acute cardiac care. *Eur Heart J* 2010;31: 2197–204.

5. Bandstein N, Ljung R, Johansson M, et al. Undetectable High-Sensitivity Cardiac

Troponin T Level in the Emergency Department and Risk of Myocardial Infarction. *J Am Coll Cardiol* 2014;63:2569-78.

6. Zethelius B, Berglund L, Sundstrom J, et al. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. *N Engl J Med* 2008;358: 2107–16.

7. Daniels LB, Laughlin GA, Clopton P, et al. Minimally elevated cardiac troponin T and elevated N-terminal pro-B-type natriuretic peptide predict mortality in older adults: results from the Rancho Bernardo Study. *J Am Coll Cardiol* 2008;52:450–9.

8. Eggers KM, Al-Shakarchi J, Berglund L, et al. High-sensitive cardiac troponin T and its relations to cardiovascular risk factors, morbidity, and mortality in elderly men. *Am Heart J* 2013;166:541-8.

9. Masson S, Anand I, Favero C, et al. Serial Measurement of Cardiac Troponin T Using a Highly Sensitive Assay in Patients With Chronic Heart Failure. *Circulation* 2012;125:280-8.

10. Beatty AL, Ku IA, Christenson RH, et al. High-sensitivity cardiac troponin T and secondary events in outpatients with coronary heart disease from the Heart and Soul Study. *JAMA Intern Med* 2013;173:763–9.

11. Giannitsis E, Kurz K, Hallermayer K, et al. Analytical validation of a high-sensitivity cardiac troponin T assay. *Clin Chem* 2010;56:254-261.

12. Ma YC, Zuo L, Chen JH, et al. Modified glomerular filtration rate estimating equation for chinese patients with chronic kidney disease. *J Am Soc Nephrol* 2006; 17: 2937-44.

13. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for

the 21st century: statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;44:2064-89.

14. Luepker RV, Apple FS, Christenson RH, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies. *Circulation* 2003;108: 2543-9.

15. Oemrawsingh RM, Cheng JM, García-García HM, et al. High-sensitivity Troponin T in relation to coronary plaque characteristics in patients with stable coronary artery disease; results of the ATHEROREMO-IVUS study. *Atherosclerosis* 2016;247:135-41.

16. Giannitsis E, Spanuth E, Horsch A, et al. High-sensitivity cardiac troponin T and N-terminal pro-B-type natriuretic peptide predict mortality in stable coronary artery disease: results from the Ludwigshafen Risk and Cardiovascular Health (LURIC) study. *Clin Chem Lab Med* 2013;51:2019-28.

17. Rubin J, Matsushita K, Lazo M, et al. Determinants of minimal elevation in high-sensitivity cardiac troponin T in the generalpopulation.*Clin Biochem* 2016; 49:657-62.

18. Saunders JT, Nambi V, de Lemos JA, et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. *Circulation* 2011;123:1367-76.

19. Turer AT, Addo TA, Martin JL, et al. Myocardial ischemia induced by rapid atrial pacing causes troponin T release detectable by a highly sensitive assay: insights from a coronary sinus sampling study. *J Am Coll Cardiol* 2011;57:2398-405.

20. White HD. Pathobiology of troponin elevations: do elevations occur with myocardial ischemia as well as necrosis? *J Am Coll Cardiol* 2011;57:2406-8.

21. Røsjø H, Andreassen J, Edvardsen T, et al. Prognostic usefulness of circulating high-sensitivity troponin T in aortic stenosis and relation to echocardiographic indexes of cardiac function and anatomy. *Am J Cardiol* 2011;108:88-91.

22. Kawasaki T, Sakai C, Harimoto K, et al. Usefulness of High-Sensitivity Cardiac Troponin T and Brain Natriuretic Peptide as Biomarkers of Myocardial Fibrosis in Patients With Hypertrophic Cardiomyopathy. *Am J Cardiol* 2013;112:867-72.

23. Ravassa S, Kuznetsova T, Varo N, et al. Biomarkers of cardiomyocyte injury and stress identify left atrial and left ventricular remodelling and dysfunction: A population-based study. *Int J Cardiol* 2015;185:177-85.

24. deFilippi CR, de Lemos JA, Christenson RH, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. *JAMA* 2010;304:2494-502.

25. de Lemos JA, Drazner MH, Omland T, et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA* 2010;304:2503-12.

26. Sze J, Mooney J, Barzi F, et al. Cardiac Troponin and its Relationship to Cardiovascular Outcomes in Community Populations – A Systematic Review and Meta-analysis. *Heart Lung Circ* 2016;25:217-28.

27. Lazzarino AI, Hamer M, Gaze D, et al. The association between cortisol response to mental stress and high-sensitivity cardiac troponin T plasma concentration in

healthy adults. *J Am Coll Cardiol* 2013; 62:1694-701.

28. Schnell-Inderst P, Schwarzer R, Göhler A, et al. Prognostic value, clinical effectiveness, and cost-effectiveness of high - sensitivity C-reactive protein as a marker for major cardiac events in asymptomatic individuals: a health technology assessment report. *Int J Technol Assess Health Care* 2010; 26:30-9.

29. Daniels LB, Clopton P, deFilippi CR, et al. Serial measurement of N- terminal pro-B-type natriuretic peptide and cardiac troponin T for cardiovascular diseaserisk as sessment in the Multi-Ethnic Study of Atherosclerosis (MESA). *Am Heart J* 2015; 170:1170-83.

30. Scheven L, de Jong PE, Hillege HL, et al. High-sensitive troponin T and N-terminal pro –B type natriuretic peptide are associated with cardiovascular events despite the cross- sectional association with albuminuria and glomerular filtration rate. *Eur Heart J* 2012; 33:2272-81.

31. Hussein AA, Gottdiener JS, Bartz TM, et al. Cardiomyocyte injury assessed by a highly sensitive troponin assay and sudden cardiac death in the community: the Cardiovascular Health Study. *J Am Coll Cardiol* 2013;62:2112-20.

32. Hussein AA, Bartz TM, Gottdiener JS, et al. Serial measures of cardiac troponin T levels by a highly sensitive assay and incident atrial fibrillation in a prospective cohort of ambulatory older adults. *Heart Rhythm* 2015;12:879-85.

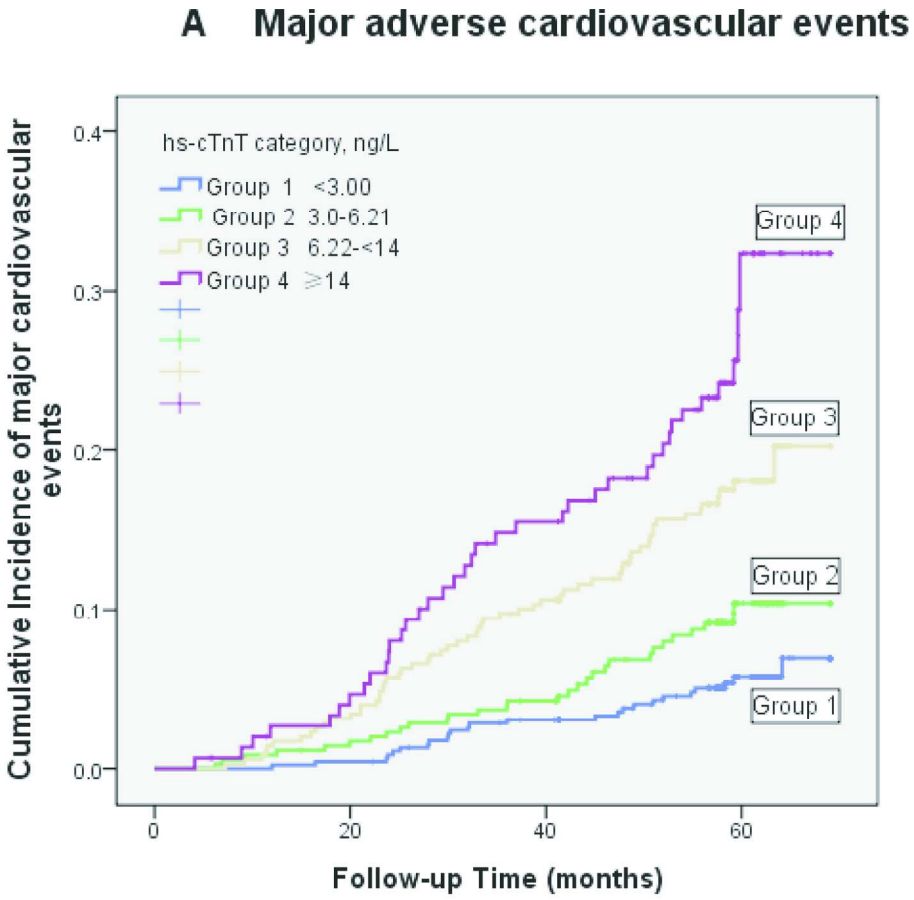
33. Masson S, Latini R, Mureddu GF, et al. High-sensitivity cardiac troponin T for detection of subtle abnormalities of cardiac phenotype in a general population of elderly individuals. *J Intern Med* 2013;273:306-17.

34. de Lemos JA, deFilippi CR. Prevalence and significance of detectable troponins as measured by highly sensitive assays in the general population. *Coronary Artery Disease* 2013;24:705-9.

35. Folsom AR, Nambi V, Bell EJ, et al. Troponin T, N-Terminal Pro–B-Type Natriuretic Peptide, and Incidence of Stroke. The Atherosclerosis Risk in Communities Study. *Stroke* 2013; 44:961-7.

36. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics-2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009;119:480-6.

37. Yang QD, Niu Q, Zhou YH, et al. Incidence of cerebral hemorrhage in the Changsha community. A prospective study from 1986 to 2000. *Cerebrovasc Dis.* 2004;17:303-13.



No. at risk

Group 1	679	676	649	344
Group 2	324	318	307	103
Group 3	324	311	285	105
Group 4	172	161	140	45

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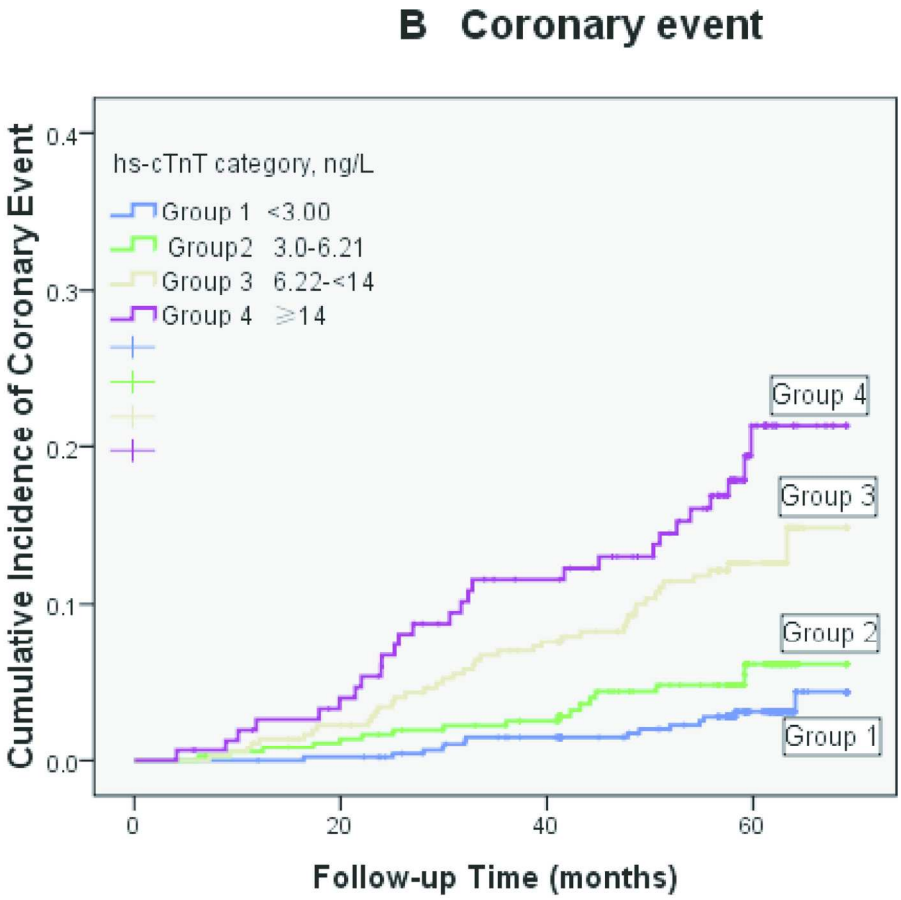

No. at risk

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Group 2	324	318	307	103
Group 3	324	311	285	105
Group 4	172	161	140	45

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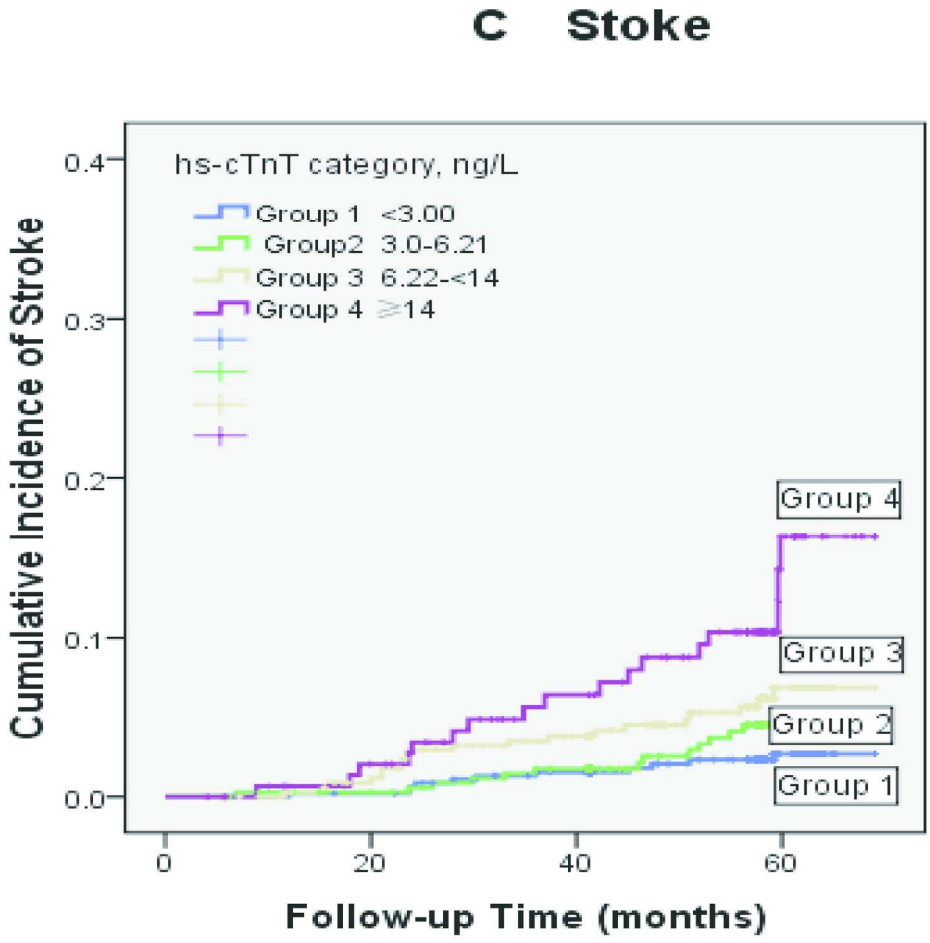

No. at risk

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Group 2	324	318	307	103
Group 3	324	311	285	105
Group 4	172	161	140	45

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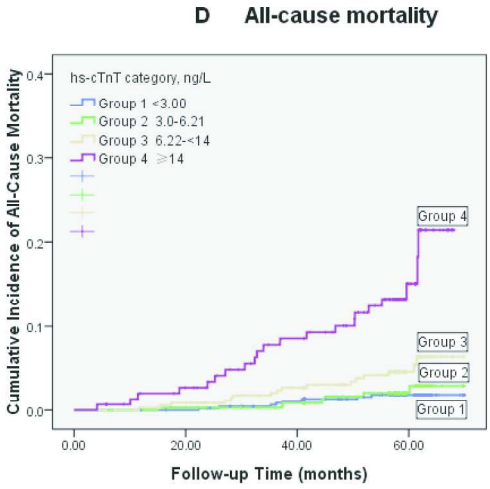

No. at risk

Group 1	679	674	649	344
Group 2	324	318	307	103
Group 3	324	311	285	105
Group 4	172	161	140	45

Figure1. Risk for Cardiovascular Events and All-Cause Mortality by Baseline hs-cTnT Level

Kaplan-Meier survival curves indicating cumulative incidence of MACE (A), Coronary event (B), Stroke (C) and All–cause mortality (D) across baseline hs-cTnT categories. Groups are indicated by colors, P<0.001 for all between-group comparisons by the log-rank test.

113x89mm (600 x 600 DPI)

Supplementary Table1. Characteristics of Study Population between the follow up and lost groups

Characteristics	Baseline population		P value
	Follow up group （n=1499）	lost to follow up group （n=181）	
Demographic			
Age (years)	61.4±11.4	57.6±10.5	<0.01
Male Sex n (%)	629 (42.0)	83(45.9)	0.316
BMI (kg/m^2)	25.6±3.3	25.8±3.4	0.273
Medical history			
Hypertension n (%)	690(46.0)	72(39.8)	0.111
Diabetes mellitus n (%)	292(19.5)	30(16.6)	0.348
Current smoking n (%)	247(16.5)	35(19.3)	0.331
Systolic BP (mm Hg)	132.7±17.0	130.6±16.7	0.136
Diastolic BP (mm Hg)	76.6±10.3	77.8±10.7	0.077
Laboratory values			
FBG (mmol/L)	5.4±1.6	5.3±1.5	0.474
PBG (mmol/L)	8.0±4.2	7.5±3.7	<0.05
Total cholesterol (mmol/L)	5.1±0.9	5.0±0.9	0.321
Triglycerides (mmol/L)	1.8±1.2	1.9±1.1	0.054
LDL cholesterol (mmol/L)	3.0±0.7	2.9±0.6	0.21
HDL cholesterol (mmol/L)	1.4±0.3	1.4±0.3	0.386
Uric acid (μmol/L)	291.4±73.3	276.9±70.8	<0.01
eGFR (mL/min/1.73m^2)	88.9±15.5	92.1±16.0	0.009
NT-proBNP (pg/mL)	41.7(19.8,81.9)	37.4(17.3,73.9)	<0.01
Hs-CRP （mg/L）	2.3 (1.4, 3.5)	2.2 (1.3, 3.4)	0.189
Medication use			
Antihypertensives n (%)	528（35.2）	55 (30.4)	0.197
Antidiabetic n (%)	189（12.6）	19（10.5）	0.415

Lipid lowering	n (%)	262（17.5）	29(16.0)	0.625
Aspirin	n (%)	360（24.0）	37（20.4）	0.285

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	
Objectives	3	State specific objectives, including any prespecified hypotheses	5	
Methods				
Study design	4	Present key elements of study design early in the paper	5	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-6	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-7*	
Bias	9	Describe any efforts to address potential sources of bias		
Study size	10	Explain how the study size was arrived at		

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8-9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12-13
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*10*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14-16
		(*b*) Report category boundaries when continuous variables were categorized	15
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	17
Discussion			
Key results	18	Summarise key results with reference to study objectives	18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	22
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association of High-Sensitivity Cardiac Troponin T with Mortality and Cardiovascular Events in a Community-Based Prospective Study in Beijing

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Association of High-Sensitivity Cardiac Troponin T with Mortality and Cardiovascular Events in a Community-Based Prospective Study in Beijing

Wenkai Xiao, Ruihua Cao, Yuan Liu, Fan Wang, Yongyi Bai, Hongmei Wu, Ping Ye*

Department of Geriatric Cardiology, Chinese PLA General Hospital, No. 28, Fuxing Road, Beijing, 100853, China

Correspondence to Ping Ye, Department of Geriatric Cardiology, Chinese PLA General Hospital, Beijing, 100853, China

Tel:+86-10-66876369; Fax:+86-10-66876349; E-mail: yeping301@sina.com

Keywords: Biomarkers; High-sensitivity cardiac troponin T; Cardiovascular diseases; Prognosis; Risk assessment.

Word count: 5860

Abstract

Objective: The prognostic value of cardiac troponins in apparently healthy populations is not well established. The aim of this study was to investigate the prognostic properties of high-sensitivity cardiac troponin T (hs-cTnT) for long-term adverse outcomes.

Setting: A community-dwelling prospective survey of residents from two communities in Beijing.

Participants: From September 2007 to January 2009, 1680 participants were initially enrolled. Of these, 1499 (870 females, mean age: 61.4 years) participants completed the survey and were followed up for a median of 4.8 years (interquartile range: 4.5–5.2).

Outcome measures: The primary outcome was the occurrence of all-cause mortality and major cardiovascular events.

Results: Overall, 820 individuals (54.7%) had detectable hs-cTnT levels. During the follow-up, 52 participants (3.5%) died, 154 (10.3%) had major cardiovascular events, and 99 (6.6%) experienced new-onset coronary events. Compared with those with undetectable hs-cTnT levels, participants with hs-cTnT levels in the highest category(≥14 ng/L) had a significantly increased risk for all-cause mortality (adjusted hazard ratio [aHR] : 2.07, 95% confidence interval [CI]: 1.05–3.01), major cardiovascular events (aHR: 3.27, 95% CI: 1.88–5.70), and coronary events (aHR: 4.50, 95% CI: 2.26–9.02) in covariate-adjusted analyses. No differences in stroke incidence were found (aHR: 1.27; 95% CI: 0.69–2.62). Also, significant associations

were presented when hs-cTnT levels were modelled as a continuous variable and when analysing changes in hs-cTnT levels over time with adverse outcomes. The addition of troponin T levels to clinical variables led to significant increases in risk prediction with a marked improvement in the c-statistic (P=0.003 or lower).

Conclusions: In this cohort of individuals from a community-based population, cardiac troponin T levels measured with a highly sensitive assay were associated with increases in the subsequent risk for all-cause mortality and major cardiovascular events. These results might support screening for at-risk individuals.

Strengths and limitations of this study

- Evaluating the prognostic properties of both baseline hs-cTnT and change in hs-cTnT for long-term adverse outcomes in a large community-dwelling study.
- Reliably detecting minimal subclinical myocardial injury in an apparently healthy population over a wide age range.
- Due to the lack of echocardiographic and coronary artery imaging data, no causal explanations on the associations between hs-cTnT and outcomes could be provided.

Introduction

Cardiovascular disease (CVD) is still the primary cause of morbidity and mortality worldwide. There is concordant evidence that prevention is the key to lessening the CVD burden, but predicting the risk of adverse cardiovascular events in low- to intermediate-risk individuals is a considerable challenge.[1] This subpopulation is at risk for developing CVD but is not identified during the early stages by current risk screening methods. [2-3] Circulating biomarkers can be an important supplemental screening tool, and troponins are one of the most interesting biomarkers in this context. Cardiac troponin T (cTnT) is a regulatory protein that is expressed by cardiac myocytes and is released in the setting of myocardial injury. [4-5] As a sensitive and specific marker of cardiomyocyte damage, cTnT is typically used to exclude or confirm the diagnosis of acute myocardial infarction in the clinical setting.

However, cTnT levels can also be elevated and clinically meaningful in the absence of myocardial ischaemia. Detectable levels of cTnT can also be useful for detecting subclinical CVD and assessing CVD risk in the general population. However, the use of cTnT for clinical applications is limited, as it is only detectable in a small percentage of the general population using standard assays. [6-7] Recently, a highly sensitive cTnT (Hs-cTnT) assay has been developed, which can detect concentrations that are 10-fold lower than those detectable with the standard fourth-generation assay. The introduction of this new assay has enabled the detection of very low levels of circulating cTnT, even in an asymptomatic general population. [8]

Levels of cTnT, below the detection limit of standard assays, have been shown to

be independently associated with adverse cardiovascular events in patients with heart failure (HF) [9] or stable coronary heart disease (CHD). [10] However, the clinical significance of detectable cTnT with the use of the new assay in the apparently healthy population has not been well established. The main objective of this study was to investigate the prognostic value of minimally detectable hs-cTnT levels in predicting adverse clinical events in a population of community-based subjects.

Methods

Study population

This was a prospective observational study of people living in the Pingguoyuan area of the Shijingshan district, which is a metropolitan area of Beijing, China. Between September 2007 and January 2009, all permanent residents of the Han origin, aged 45 years or older (range 45–91 years) , from two communities, were invited to participate in a health survey that focused on identifying CVD risk factors. Thirty-one subjects with bedridden status, mental illness, and severe systemic diseases were excluded from enrolment. Then, 1832 participants were included and asked to complete questionnaires. Of these, 152 participants with overt CVD (defined as a composite of CHD [myocardial infarction, angina pectoris, or coronary insufficiency], cerebrovascular disease [stroke or transient ischaemic attack], congestive HF, or peripheral vascular disease) were excluded. Adequate baseline measurements and cardiac biomarkers were obtained in 1680 participants. After the initial evaluation, the recruited subjects were contacted every 2 years for follow-up, and the last follow-up visits were conducted through September 30, 2013. The median follow-up was 4.8

(interquartile range: 4.5–5.2) years. In our investigation, 181 participants were lost to follow-up (Supplementary Table 1) and were excluded from the study. Complete data were acquired from 1499 participants (return rate: 89.2%). All participants provided written informed consent at the time of enrolment, and the study was approved by the Ethics Committee of the Chinese People's Liberation Army General Hospital.

Data collection

Baseline characteristics were collected using self-reported standardized questionnaires that included demographics, life-style information, medical history, and medication use. Anthropometrical measurements were obtained by trained medical doctors, and the body mass index (BMI) was derived from heights and weights that were measured in participants wearing light clothing and no shoes. Blood pressures were measured twice on the right arm after 5 minutes of rest in a sitting position, and the mean of two readings was used for further analysis. Participants were followed up for clinical outcomes by interview. Outcome measures were the occurrences of all-cause mortality and major adverse cardiovascular events (MACE). New events were validated by obtaining medical records and adjudicated by two independent and blinded reviewers. In the analyses, survival time was defined as the period from the date of baseline blood sample collection to the date of the first adverse event or end of follow-up.

Biomarker assays

At the time of enrolment, baseline blood samples were collected from participants between 8 AM and 10 AM after at least 12 hours of overnight fasting.

Follow-up measurements were performed on blood samples, which were collected 4 to 5 years later. Serum aliquots were frozen at -80°C until further analyses in a central laboratory. Concentrations of blood glucose (fasting and 2 hours after an oral glucose tolerance), total cholesterol (TC), triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), uric acid, and serum creatinine were measured by routine laboratory analysis.

Hs-cTnT levels were measured by an electrochemiluminescence immunoassay method using an Elecsys Troponin T highly sensitive assay (Roche Diagnostics GmbH, Mannheim, Germany) on the Modular Analytics E170 autoanalyser (Roche Diagnostics). The lower detection limit of the novel assay was 3 ng/L, and the 99th percentile value in apparently healthy individuals has been reported to be 14 ng/L. [11] N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations were determined using an electrochemiluminescence immunoassay (Roche Diagnostics GmbH) on the Roche analyser. Levels of high-sensitivity C-reactive protein (hs-CRP) were measured with the use of an immunoturbidimetric assay (Siemens Healthcare Diagnostics, IN, USA) on a Dimension RxL Max analyser (Siemens Healthcare Diagnostics).

Estimated glomerular filtration rate (eGFR) was calculated using the Chinese Modification of Diet in Renal Disease equation. Details of the computing equation have been published elsewhere. [12]

Definition of end points

For outcomes, we used the incidence of mortality and CVD morbidity after the

baseline screening. All-cause mortality was determined by review of death certificates. The definition of MACE comprised nonfatal myocardial infarction, newly diagnosed CHD (identified by coronary artery imaging or receiving coronary revascularization), stroke (ischaemic or haemorrhagic), and cardiovascular mortality. Major coronary events were defined as nonfatal myocardial infarction, newly diagnosed CHD, and CHD death. Stroke was characterized as a neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause, including cerebral infarction, intracerebral haemorrhage, and subarachnoid hemorrhage. [13] Cardiovascular mortality was defined as mortality related to atherosclerotic heart disease (fatal myocardial infarction and definite fatal CHD), mortality following cerebrovascular disease, or mortality from HF and other CVD. Nonfatal myocardial infarction was defined by the American Heart Association diagnostic criteria. [14]

Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD) or median (interquartile range), and categorical variables are presented as counts and percentages. Hs-cTnT was modelled as both a categorical and continuous variable. For the analyses of hs-cTnT as a categorical variable, participants were divided into four categories. Participants with undetectable hs-cTnT were placed in the first category as the reference group. Those with hs-cTnT levels greater than or equal to the previously reported 99th percentile value (14 ng/L) [11] were placed in the fourth category, and those with levels between 3 and 14 ng/L were divided into two groups for categories 2 and 3, respectively, based on the median value of hs-cTnT.

Demographic and clinical variables were compared across hs-cTnT categories using the one-way analysis of variance tests for continuous measures, Cuzik's nonparametric trend test for nonnormally distributed variables, and chi-squared tests for categorical variables.

The cumulative incidence of MACE and all-cause mortality for each category of hs-cTnT concentration were evaluated using the Kaplan-Meier method and compared with the log-rank test. Multivariable Cox proportional hazards regression models were used to analyse associations of hs-cTnT categories with outcomes, and category 1 was used as the reference. The models were incrementally adjusted for demographics, traditional cardiovascular risk factors, renal function, and other biomarkers (Hs-CRP and NT-proBNP). We also carried out an exploratory analysis, in which cTnT was regarded as a continuous variable, and the relationship between natural logarithm-transformed hs-cTnT values and end points was assessed. In this analysis, values of cTnT that were below the lower limit of detection were assigned to 1.5 ng/L (i.e., one-half of the lower limit of detection).

In view of the markedly skewed distribution of cTnT, changes in concentrations over time were calculated as the difference between the natural logarithm of the concentrations at follow-up and baseline. The association between changes in hs-cTnT levels and outcomes were also evaluated in Cox proportional hazards models. The change in hs-cTnT levels was entered as a continuous variable and was adjusted for the baseline concentration of hs-cTnT and other relevant variables.

The discriminative capacity of a model with and without cTnT was estimated as

C-statistics. The area under the receiver operating characteristic curve summarised the diagnostic discrimination. All data were analysed using the SPSS statistical package software (version 17.0). A two-sided value of $P < 0.05$ was considered statistically significant.

Results

Participant characteristics

For the present analyses, 1499 participants were included. The mean (±SD) age of participants at enrolment was 61.4±11.4 years and 58.0% were women. Detectable baseline cTnT levels were found in 820 individuals (54.7%; ranged from 3 to 176.4 ng/L) and were equal to or higher than 14 ng/L in 172 participants (11.5%). Table 1 shows baseline characteristics by hs-cTnT categories. Compared with those with lower cTnT levels, individuals with higher levels were older, more likely to be male, more frequently hypertensive and diabetic, had lower eGFR and HDL-C levels, and had higher uric acid and NT-proBNP levels. The use of antihypertensive drugs, antidiabetic drugs, and aspirin varied across levels of hs-cTnT.

Outcomes by baseline hs-cTnT

Over a median follow-up period of 4.8 years (interquartile range: 4.5–5.2), 154 participants experienced new-onset MACE (including 99 coronary events and 61 strokes, and some participants had more than one event). Fifty-two deaths occurred from any cause. The cumulative incidences of MACE and all-cause mortality by hs-cTnT categories are shown in Figure 1. As demonstrated by the Kaplan-Meier survival analysis, there was a graded increase in the probability of adverse clinical

events across categories. The unadjusted incidence rate for MACE ranged from 3.7% in participants with undetectable hs-cTnT levels to 23.3% in participants in the highest category (P<0.001, log-rank test). Similar trends were discovered for coronary events, stroke, and all-cause mortality, and a particularly high risk was found for participants in the highest category.

Table 1. Characteristics of the study population by baseline high-sensitivity troponin T levels

Characteristics	Hs-cTNT Group (ng/L)				P value for Trend
	Group 1 <3.00 (n = 679)	Group 2 3.00-6.21 (n=324)	Group 3 6.22-<14 (n= 324)	Group4 ⩾14 (n = 172)	
Demographics					
Age (years)	58.6±10.3	63.1±10.7	64.2±12.4	61.8±11.5	<0.001
Male Sex; n (%)	202 (29.7）	163 (50.3)	170 (52.5)	94 (54.7)	<0.001
BMI (kg/m^2)	25.5±3.5	25.7±3.2	25.6±3.3	25.8±3.5	0.498
Medical history					
Hypertension; n (%)	258 (38.0)	159 (49.1)	176 (54.3)	97 (56.4)	<0.001
Diabetes mellitus; n (%)	99 (14.6)	72 (22.2)	76 (23.5)	45 (26.2)	<0.001
Current smoking; n (%)	85 (12.5)	69 (21.3)	62 (19.1)	31(18.0)	0.003
Systolic BP (mm Hg)	131.5±16.5	132.7±17.3	132.8±17.2	133.2±17.1	0.041
Diastolic BP (mm Hg)	77.1±9.7	77.3±10.0	76.4±10.5	76.1±11.1	0.372
Laboratory values					
FBG (mmol/L)	5.3±1.4	5.3±1.5	5.5±1.7	5.8±1.9	0.076
PBG (mmol/L)	7.5±3.7	7.1±3.2	8.1±4.3	8.9±4.4	<0.001

Total cholesterol (mmol/L)	5.1±0.9	5.1±0.9	5.1±0.9	5.0±0.9	0.464
Triglycerides (mmol/L)	1.8±1.1	1.7±1.1	1.7±1.0	2.0±1.4	0.04
LDL cholesterol (mmol/L)	3.0±0.7	2.9±0.7	3.0±0.7	3.0±0.7	0.136
HDL cholesterol (mmol/L)	1.4±0.4	1.4±0.3	1.3±0.4	1.3±0.4	0.001
Uric acid (μmol/L)	279.0±68.2	295.9±73.3	301.2±75.4	309.5±76.2	<0.001
eGFR (mL/min/1.73m^2)	90.1±14.5	88.7±13.4	87.5±15.2	84.7±16.5	0.001
NT-proBNP (pg/mL)	37.2 (17.9, 75.3)	38.9 (17.9, 74.4)	46.6 (22.3, 90.1)	49.3 (17.1, 112)	0.003
Hs-CRP（mg/L）	2.4 (1.3, 3.4)	2.3 (1.4, 3.4)	2.2 (1.5, 3.5)	2.4 (1.6, 3.6)	0.383
Medication use					
Antihypertensives; n (%)	187 (27.5)	122 (37.7)	139 (42.9)	80 (46.5)	<0.001
Antidiabetics; n (%)	64 (9.4)	44 (13.6)	52 (16.0)	29 (16.9)	0.0028
Lipid lowering drugs; n (%)	109 (16.1)	61 (18.8)	58 (17.9)	34 (19.8)	0.149
Aspirin; n (%)	137 (20.2)	79 (24.4)	89 (27.5)	55 (31.9)	<0.001

Values are reported as n (%), mean ± SD, or median (interquartile range). BMI=body mass index; BP=blood pressure; eGFR =estimated glomerular filtration rate; FBG=fasting blood glucose; HDL= high-density lipoprotein; Hs-CRP = high-sensitivity C-reactive protein; LDL = low- density lipoprotein; PBG= postprandial blood glucose; NT-proBNP = N-terminal pro-type B natriuretic peptide.

Associations of baseline hs-cTnT levels with MACE and all-cause mortality

In a series of Cox proportional hazards models adjusting for age and gender (model 1), and further adjusting for traditional cardiovascular risk factors (model 2), higher hs-cTnT categories demonstrated a graded association with MACE. Only a modest attenuation of the hazards was found with further adjustment for renal function (model 3). Although a significant attenuation was discovered with additional adjustments for hs-CRP and NT-proBNP levels (model 4), hs-cTnT levels in the third category (hazard ratio [HR]: 2.31, 95% CI: 1.39–3.84) and fourth category (HR: 3.27, 95% CI: 1.88–5.70) remained independently associated with MACE in the fully adjusted models. Participants in hs-cTnT categories 3 and 4 also had a significantly higher risk of coronary events compared with participants with undetectable levels (HRs of 2.76 [95% CI: 1.44–5.31] and 4.50 [95% CI: 2.26–9.02], respectively, in model 4; Table 2). However, associations of hs-cTnT levels with stroke events were markedly attenuated and no longer significant after adjusting for NT-proBNP (model 4; Table 2). Membership in the highest hs-cTnT category was independently associated with all-cause mortality (HR: 2.07, 95% CI: 1.05–3.01) in both univariate and multivariate analyses.

In an exploratory research of hs-cTnT as a continuous variable after natural logarithmic transformation, we found a continuous association with MACE incidence (per one- logarithmic unit increment; HR: 1.67; 95% CI, 1.04–2.68; P<0.001), coronary events (HR: 1.68; 95% CI, 1.35–2.08; P <0.001) or all-cause mortality (HR:

1.50; 95% CI, 1.26–1.79; P=0.003) in fully multivariate models encompassing the variables described in Table 2. No association between stroke risk and cTnT as a continuous variable was found in the final adjusted models (HR: 1.06; 95% CI, 0.87–1.32; P=0.17).

Table 2. Cox proportional hazards models analysis for associations between baseline hs-cTnT levels and outcomes

	Hazard Ratio (95% Confidence Interval)			
	Group 1 <3.00 ng/L	Group 2 3.0–6.21 ng/L	Group 3 6.22–<14 ng/L	Group 4 ⩾14 ng/L
No.	679	324	324	172
MACE	n=25 (3.7%)	n=30 (9.3%)	n=59 (18.2%)	n=40 (23.3%)
Model 1	1[Reference]	1.65 (0.97–2.81)	2.65 (1.64–4.27)	4.20 (2.51–7.02)
Model 2	1[Reference]	1.52 (0.89–2.59)	2.41 (1.48–3.91)	3.82 (2.27–6.43)
Model 3	1[Reference]	1.52 (0.89–2.61)	2.38 (1.47–3.88)	3.79 (2.26–6.39)
Model 4	1[Reference]	1.68（0.97–2.92）	2.31 (1.39–3.84)	3.27 (1.88–5.70)
Coronary event	n=14 (2.1%)	n=17 (5.3%)	n=41 (12.7%)	n=27 (15.7%)
Model 1	1[Reference]	1.69（0.83–3.44）	3.39（1.82–6.29）	5.23（2.7–10.14）
Model 2	1[Reference]	1.61（0.78–3.29）	3.25（1.74–6.07）	5.5（2.84–10.64）
Model 3	1[Reference]	1.57（0.76–3.22）	3.09（1.65–5.79）	5.14（2.65–9.98）
Model 4	1[Reference]	1.42（0.71–2.89）	2.76（1.44–5.31）	4.50（2.26–9.02）
Stroke event	n=11 (1.6%)	n=13 (4.0%)	n=20 (6.2%)	n=17 (9.9%)
Model 1	1[Reference]	1.59（0.71–3.57）	1.94（0.91–4.14）	3.84（1.75–8.43）
Model 2	1[Reference]	1.47（0.65–3.29）	1.77（0.83–3.79）	3.19（1.42–7.16）
Model 3	1[Reference]	1.47（0.65–3.31）	1.70（0.79–3.66）	3.16（1.41–7.10）
Model 4	1[Reference]	1.03 (0.50–2.09)	1.13 (0.57–2.14)	1.27 (0.69–2.62)
All–cause mortality	n=8 (1.2%)	n=7 (2.2%)	n=16 (4.9%)	n=21 (12.2%)
Model 1	1[Reference]	1.13 (0.41–3.14)	1.99 (0.83–4.76)	6.14 (2.61–14.46)

Model 2	1[Reference]	1.13 (0.41–3.14)	1.78 (0.73–4.35)	4.87 (1.99–11.88)
Model 3	1[Reference]	1.14 (0.41–3.16)	1.79 (0.73–4.38)	4.87 (1.99–11.88)
Model 4	1[Reference]	1.01 (0.40–1.15)	1.09 (0.43–2.76)	2.07 (1.05–3.01)

Abbreviations: MACE, major adverse cardiovascular event.

Models are defined as follows: model 1=adjusted for age and gender; model 2=adjusted for model 1 + presence of hypertension or diabetes mellitus, current smoking status, systolic blood pressure, postprandial blood glucose, total cholesterol, high-density lipoprotein cholesterol, antihypertensive medication use, and antidiabetic medication use; model 3= adjusted for model 2 + estimated glomerular filtration rate; model 4= adjusted for model 3 + high-sensitivity C-reactive protein and N-terminal pro–B-type natriuretic peptide (both after logarithmic transformation).

Changes in hs-cTnT concentration during follow-ups and subsequent events

Table 3 presents the results of Cox regression analysis for subsequent events in relation to changes in hs-cTnT concentration as a continuous variable. Changes in hs-cTnT concentration were strongly associated with subsequent events except for stroke, even in multivariable analyses that additionally adjusted for baseline hs-cTnT levels. In the fully adjusted models, the HRs for MACE, and coronary events for every unit increasing in hs-cTnT concentration, were 1.35 (95% CI: 1.08–1.68, P=0.008) and 1.44 (95% CI: 1.17–1.77, P=0.001), respectively. However, an increase in hs-cTnT concentration was not significantly associated with stroke events (HR: 1.02, 95% CI: 0.64–2.19, P=0.242).

Table 3. Association of changes in hs-cTnT concentrations with subsequent events

	Multivariable-adjusted HR	95% CI	P Value

MACE	1.35	1.08–1.68	0.008
Coronary event	1.44	1.17–1.77	0.001
Stroke event	1.02	0.64–2.19	0.242

Abbreviations: HR, hazard ratio; CI, confidence interval; MACE, major adverse cardiovascular event. Data are presented as hazard ratios and 95% confidence intervals for a 1-unit increase in the change in hs-cTnT on a log scale. Multivariable model was adjusted for the covariates listed for Model 4 in Table 2, plus the baseline hs-cTnT level.

Hs-cTnT and risk prediction

Hs-cTnT provided incremental prognostic information regarding the three endpoints when added to a model based on established risk indicators (Table 4). The addition of hs-cTnT increased the c-statistic from 0.671 to 0.698 (P=0.003) for the prediction of all-cause mortality. The prediction of MACE also improved from 0.702 to 0.734 (P<0.001).

Table 4. Discrimination of adverse outcomes with the addition of hs-cTnT to the clinical risk factor model

	c-statistic (95%CI)		
Endpoint	Clinical Model	Clinical Model + hs-cTnT	P Value
All-cause mortality	0.671 (0.646–0.704)	0.698 (0.680–0.725)	0.003
MACE	0.702 (0.680–0.726)	0.734 (0.714–0.758)	<0.001
Coronary event	0.713 (0.701–0.735)	0.749 (0.729–0.768)	<0.001
Stroke event	0.683 (0.665–0.709)	0.697 (0.674–0.729)	0.09

Abbreviations: CI, confidence interval; MACE, major adverse cardiovascular event.

The clinical risk factor model included age, gender, body mass index, current smoking status, diabetes mellitus, systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, and estimated glomerular filtration rate.

Discussion

The main purpose of the current study was to evaluate the usefulness of measuring hs-cTnT for predicting major cardiovascular events and all-cause mortality in a community-dwelling study of general population. There were several valuable findings. First, the up-to-date generation of cTnT assay allowed for minimal subclinical myocardial injury to be reliably detected in some individuals of a general population covering a wide age range. There was no need to restrict the study to morbid or high-risk individuals. Second, baseline and kinetic changes in hs-cTnT concentration were powerful and independent predictors of long-term MACE and all-cause mortality. Finally, these risk predictions were persistent, even after adjusting for traditional cardiovascular risk factors and biomarkers of inflammation and cardiac wall strain.

Cardiac troponins are generally the preferred biomarkers of myocardial necrosis and are typically used in the diagnosis of acute coronary syndromes. But the recently available hs-cTnT assay has allowed for the detection of much lower concentrations of circulating cTnT. More recent observations using this new assay have shown that very low levels of circulating cTnT can be detectable, these levels of circulating cTnT can provide information about coronary plaque characteristics and mortality in patients with stable CHD, [15-16] and very low levels of circulating cTnT

can even be detected in the general population. [17-18] The exact mechanisms of troponin release in apparently healthy individuals are not well clarified. One possibility is the existence of asymptomatic cardiac ischaemia with minimal myocardial injury, which results in the asymptomatic release of troponins. [19] Other mechanisms include cardiomyocyte apoptosis, [20] physiological cell turnover, [21] or subclinical cardiac structural or functional abnormalities. [22-23]

The prognostic implications of hs-cTnT assays among apparently healthy individuals have recently been explored in three large cohort studies. [18, 24-25] However, these studies focused on middle-aged and elderly subjects from western countries. Our study extends the findings to the Asian population and demonstrates the significance of the hs-cTnT assay in risk assessment. To the best of our knowledge, this is the first study to evaluate the potential utility of the hs-cTnT assay in a Chinese population. One important finding is the observation that the presence of an elevated hs-cTnT level (in the highest category) was associated with adverse outcomes regarding all-cause mortality and MACE. However, there were no associations between minimally detectable hs-cTnT levels, especially those below 6.2 ng/L, and death or MACE. It has been proposed that such levels may be physiological, reflecting normal myocardial cell turnover and apoptosis within the senescent heart tissue. [26] The levels may also be a result of the cortisol response to mental stress in healthy adults. [27] Further research is required to determine which hs-cTnT threshold value may best be used in risk prediction.

Although other biomarkers, such as hs-CRP and NT-proBNP, have been used to

identify apparently healthy individuals who are at increased CVD risk, [28-29] our investigation indicates that hs-cTnT was also independent of these biomarkers. In this cohort, although associations with death and cardiovascular events were significantly attenuated after additional adjustments for levels of NT-proBNP, hs-cTnT remained independently predictive of end points in the final model, suggesting that the two biomarkers convey slightly different information for cardiac structural and functional abnormalities. The HRs remained statistically significant after adjusting for traditional cardiovascular risk factors and renal function, and were consistent with results from other studies. [8, 30] These data indicate that very low levels of cTnT may be used to identify subclinical myocardial injury and estimate the risk of cardiovascular events, which are currently not fully estimated by established methods. Also, associations of hs-cTnT concentration with all-cause mortality and MACE were consistent in the stratification analysis defined by sex.

Our data also suggest that even minimal changes in low levels of cTnT have prognostic characteristics and can help to identify individuals at long-term risk for adverse events. There seemed to be a dose-dependent relationship between increased hs-cTnT and increased risk. Similarly, DeFilippi et al. [24] have reported that changes in cTnT concentrations , which were determined with a highly sensitive assay, are significantly associated with incident HF events and cardiovascular death in community-based older adults. Furthermore, in a prospective cohort of ambulatory older adults, a strong increase in the risk of sudden cardiac death [31] and incident atrial fibrillation [32] was associated with changes in hs-cTnT concentrations over time.

Although these changes may reflect normal physiological variation, their relation to future adverse events, regardless of baseline hs-cTnT levels, indicates that they may really represent dynamic changes in risk stratification.

In contrast to the strong associations with mortality and MACE, hs-cTnT concentration was not associated with stroke occurrence after adjusting for multiple variables. There are several potential explanations for this finding. First, cardiac troponin specifically reflects myocardial necrosis or subclinical myocardial injury. Some studies have indicated that in comparison to coronary atherosclerosis, structural heart abnormalities are more powerful determinations of myocardial injury in the general population. [33-34] Second, the Atherosclerosis Risk in Communities Study [35] showed that elevated plasma hs-cTnT levels are associated with an increased risk of non-lacunar ischaemic strokes, and especially cardioembolic stroke, but not with hemorrhagic stroke in the general population. Epidemiological data have demonstrated that there are differences in incidence rates of stroke subtypes between Chinese and western populations. Intracerebral haemorrhage (ICH) accounts for only 10–15% of strokes in most western populations, [36] whereas up to 55% of strokes in the Chinese population are due to ICH. [37] Although an analysis for ischaemic stroke as an endpoint was conducted (data not shown), less than half of all strokes were due to ischaemia, and it was impossible to achieve statistical significance.

Our study has several limitations. First, cardiovascular treatment has changed over time, and it is possible that a higher frequency of the use of medications, such as statins and antiplatelet drugs, could have lowered the predictive value of hs-cTnT.

Second, no echocardiographic and coronary artery imaging data were obtained. Thus, no causal explanations for the associations among hs-cTnT levels, cardiac abnormalities, and outcomes could be provided. Third, the incidence rate of adverse events was relatively low in this cohort, and hs-cTnT levels were detected in a considerable proportion. This could limit its potential for predicting long-term events. Finally, the study population was restricted to Chinese residents of Han origin. Extrapolation of the results to other demographic groups should be done with caution. The predictive value of hs-cTnT needs to be further validated in other observational studies.

Conclusion

In this prospective cohort of a community-dwelling population, we found that both baseline cTnT and changes in cTnT, as detected by a highly sensitive assay, were independently associated with adverse outcomes. The results suggest that cTnT may be an important biomarker in the prediction of mortality and cardiovascular events in apparently healthy individuals. Further investigations are warranted to elucidate the mechanisms for cTnT release in these individuals and to test whether active interventions can reduce the associated risk contributed by elevated troponin levels.

Contributorship statement: The manuscript has been read and approved by all of the authors. All authors contributed to the intellectual development of this paper. Conceived and designed the experiments: Ping Ye. Performed the experiments: Wenkai Xiao, Yuan Liu. Analyzed the data: Wenkai Xiao and Yongyi Bai. Wrote the

manuscript: Wenkai Xiao. Supervised data collection: Rui Cao, Fan Wang, Hongmei Wu.

Competing Interests: The authors have declared that no competing interests exist.

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Data sharing statement: The additional unpublished data from the study are available. We can share the original data for this research article.

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References

1. Khot UN, Khot MB, Bajzer CT, et al. Prevalence of conventional risk factors in patients with coronary heart disease. *JAMA* 2003;290:898-904.

2. Melander O, Newton-Cheh C, Almgren P, et al. Novel and conventional biomarkers for prediction of incident cardiovascular events in the community. *JAMA* 2009;302:49-57.

3. Blankenberg S, Zeller T, Saarela O, et al. Contribution of 30 biomarkers to 10-year cardiovascular risk estimation in 2 population cohorts: the MONICA, Risk, Genetics, Archiving, and Monograph (MORGAM) biomarker project. *Circulation* 2010;121:

2388-97.

4. Thygesen K, Mair J, Katus H, et al. Recommendations for the use of cardiac troponin measurement in acute cardiac care. *Eur Heart J* 2010;31: 2197–204.

5. Bandstein N, Ljung R, Johansson M, et al. Undetectable High-Sensitivity Cardiac Troponin T Level in the Emergency Department and Risk of Myocardial Infarction. *J Am Coll Cardiol* 2014;63:2569-78.

6. Zethelius B, Berglund L, Sundstrom J, et al. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. *N Engl J Med* 2008;358: 2107–16.

7. Daniels LB, Laughlin GA, Clopton P, et al. Minimally elevated cardiac troponin T and elevated N-terminal pro-B-type natriuretic peptide predict mortality in older adults: results from the Rancho Bernardo Study. *J Am Coll Cardiol* 2008;52:450–9.

8. Eggers KM, Al-Shakarchi J, Berglund L, et al. High-sensitive cardiac troponin T and its relations to cardiovascular risk factors, morbidity, and mortality in elderly men. *Am Heart J* 2013;166:541-8.

9. Masson S, Anand I, Favero C, et al. Serial Measurement of Cardiac Troponin T Using a Highly Sensitive Assay in Patients With Chronic Heart Failure. *Circulation* 2012;125:280-8.

10. Beatty AL, Ku IA, Christenson RH, et al. High-sensitivity cardiac troponin T and secondary events in outpatients with coronary heart disease from the Heart and Soul Study. *JAMA Intern Med* 2013;173:763–9.

11. Giannitsis E, Kurz K, Hallermayer K, et al. Analytical validation of a high-sensitivity cardiac troponin T assay. *Clin Chem* 2010;56:254-261.

12. Ma YC, Zuo L, Chen JH, et al. Modified glomerular filtration rate estimating equation for chinese patients with chronic kidney disease. *J Am Soc Nephrol* 2006; 17: 2937-44.

13. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;44:2064-89.

14. Luepker RV, Apple FS, Christenson RH, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies. *Circulation* 2003;108: 2543-9.

15. Oemrawsingh RM, Cheng JM, García-García HM, et al. High-sensitivity Troponin T in relation to coronary plaque characteristics in patients with stable coronary artery disease; results of the ATHEROREMO-IVUS study. *Atherosclerosis* 2016;247:135-41.

16. Giannitsis E, Spanuth E, Horsch A, et al. High-sensitivity cardiac troponin T and N-terminal pro-B-type natriuretic peptide predict mortality in stable coronary artery disease: results from the Ludwigshafen Risk and Cardiovascular Health (LURIC) study. *Clin Chem Lab Med* 2013;51:2019-28.

17. Rubin J, Matsushita K, Lazo M, et al. Determinants of minimal elevation in high-sensitivity cardiac troponin T in the generalpopulation.*Clin Biochem* 2016; 49:657-62.

18. Saunders JT, Nambi V, de Lemos JA, et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in

the Atherosclerosis Risk in Communities Study. *Circulation* 2011;123:1367-76.

19. Turer AT, Addo TA, Martin JL, et al. Myocardial ischemia induced by rapid atrial pacing causes troponin T release detectable by a highly sensitive assay: insights from a coronary sinus sampling study. *J Am Coll Cardiol* 2011;57:2398-405.

20. White HD. Pathobiology of troponin elevations: do elevations occur with myocardial ischemia as well as necrosis? *J Am Coll Cardiol* 2011;57:2406-8.

21. Røsjø H, Andreassen J, Edvardsen T, et al. Prognostic usefulness of circulating high-sensitivity troponin T in aortic stenosis and relation to echocardiographic indexes of cardiac function and anatomy. *Am J Cardiol* 2011;108:88-91.

22. Kawasaki T, Sakai C, Harimoto K, et al. Usefulness of High-Sensitivity Cardiac Troponin T and Brain Natriuretic Peptide as Biomarkers of Myocardial Fibrosis in Patients With Hypertrophic Cardiomyopathy. *Am J Cardiol* 2013;112:867-72.

23. Ravassa S, Kuznetsova T, Varo N, et al. Biomarkers of cardiomyocyte injury and stress identify left atrial and left ventricular remodelling and dysfunction: A population-based study. *Int J Cardiol* 2015;185:177-85.

24. deFilippi CR, de Lemos JA, Christenson RH, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. *JAMA* 2010;304:2494-502.

25. de Lemos JA, Drazner MH, Omland T, et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA* 2010;304:2503-12.

26. Sze J, Mooney J, Barzi F, et al. Cardiac Troponin and its Relationship to

Cardiovascular Outcomes in Community Populations – A Systematic Review and Meta-analysis. *Heart Lung Circ* 2016;25:217-28.

27. Lazzarino AI, Hamer M, Gaze D, et al. The association between cortisol response to mental stress and high-sensitivity cardiac troponin T plasma concentration in healthy adults. *J Am Coll Cardiol* 2013; 62:1694-701.

28. Schnell-Inderst P, Schwarzer R, Göhler A, et al. Prognostic value, clinical effectiveness, and cost-effectiveness of high - sensitivity C-reactive protein as a marker for major cardiac events in asymptomatic individuals: a health technology assessment report. *Int J Technol Assess Health Care* 2010; 26:30-9.

29. Daniels LB, Clopton P, deFilippi CR, et al. Serial measurement of N- terminal pro-B-type natriuretic peptide and cardiac troponin T for cardiovascular diseaserisk as sessment in the Multi-Ethnic Study of Atherosclerosis (MESA). *Am Heart J* 2015; 170:1170-83.

30. Scheven L, de Jong PE, Hillege HL, et al. High-sensitive troponin T and N-terminal pro –B type natriuretic peptide are associated with cardiovascular events despite the cross- sectional association with albuminuria and glomerular filtration rate. *Eur Heart J* 2012; 33:2272-81.

31. Hussein AA, Gottdiener JS, Bartz TM, et al. Cardiomyocyte injury assessed by a highly sensitive troponin assay and sudden cardiac death in the community: the Cardiovascular Health Study. *J Am Coll Cardiol* 2013;62:2112-20.

32. Hussein AA, Bartz TM, Gottdiener JS, et al. Serial measures of cardiac troponin T levels by a highly sensitive assay and incident atrial fibrillation in a prospective

cohort of ambulatory older adults. *Heart Rhythm* 2015;12:879-85.

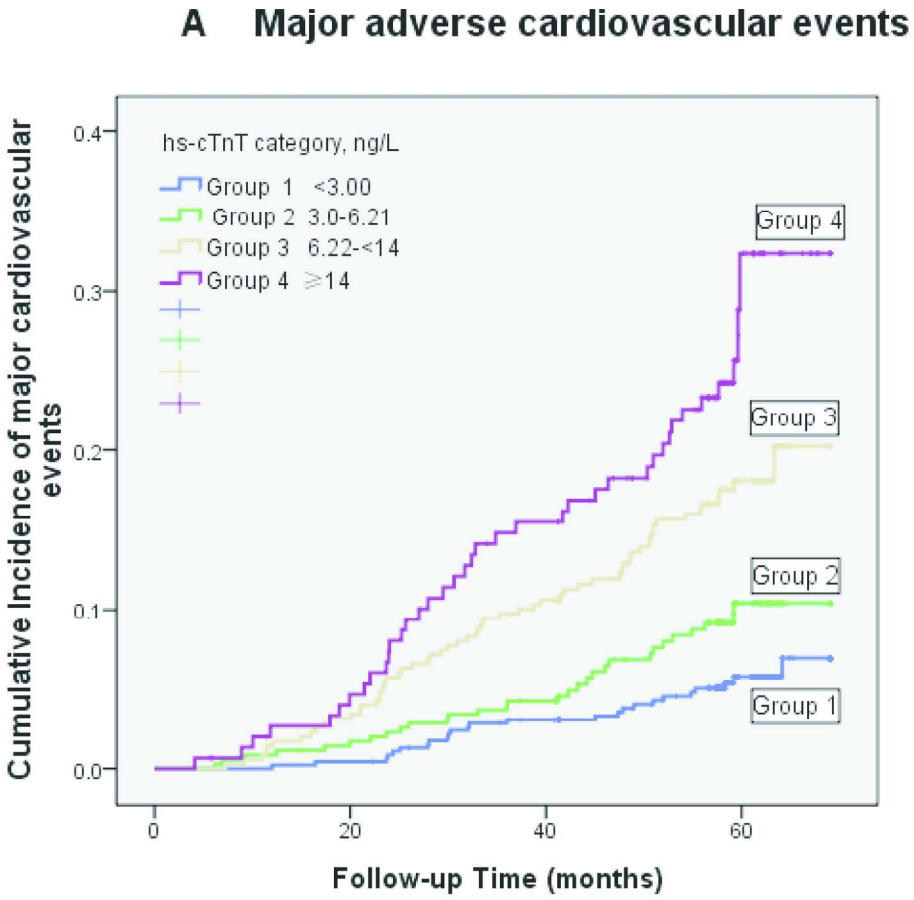
33. Masson S, Latini R, Mureddu GF, et al. High-sensitivity cardiac troponin T for detection of subtle abnormalities of cardiac phenotype in a general population of elderly individuals. *J Intern Med* 2013;273:306-17.

34. de Lemos JA, deFilippi CR. Prevalence and significance of detectable troponins as measured by highly sensitive assays in the general population. *Coronary Artery Disease* 2013;24:705-9.

35. Folsom AR, Nambi V, Bell EJ, et al. Troponin T, N-Terminal Pro–B-Type Natriuretic Peptide, and Incidence of Stroke. The Atherosclerosis Risk in Communities Study. *Stroke* 2013; 44:961-7.

36. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics-2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009;119:480-6.

37. Yang QD, Niu Q, Zhou YH, et al. Incidence of cerebral hemorrhage in the Changsha community. A prospective study from 1986 to 2000. *Cerebrovasc Dis.* 2004;17:303-13.



No. at risk

Group 1	679	676	649	344
Group 2	324	318	307	103
Group 3	324	311	285	105
Group 4	172	161	140	45

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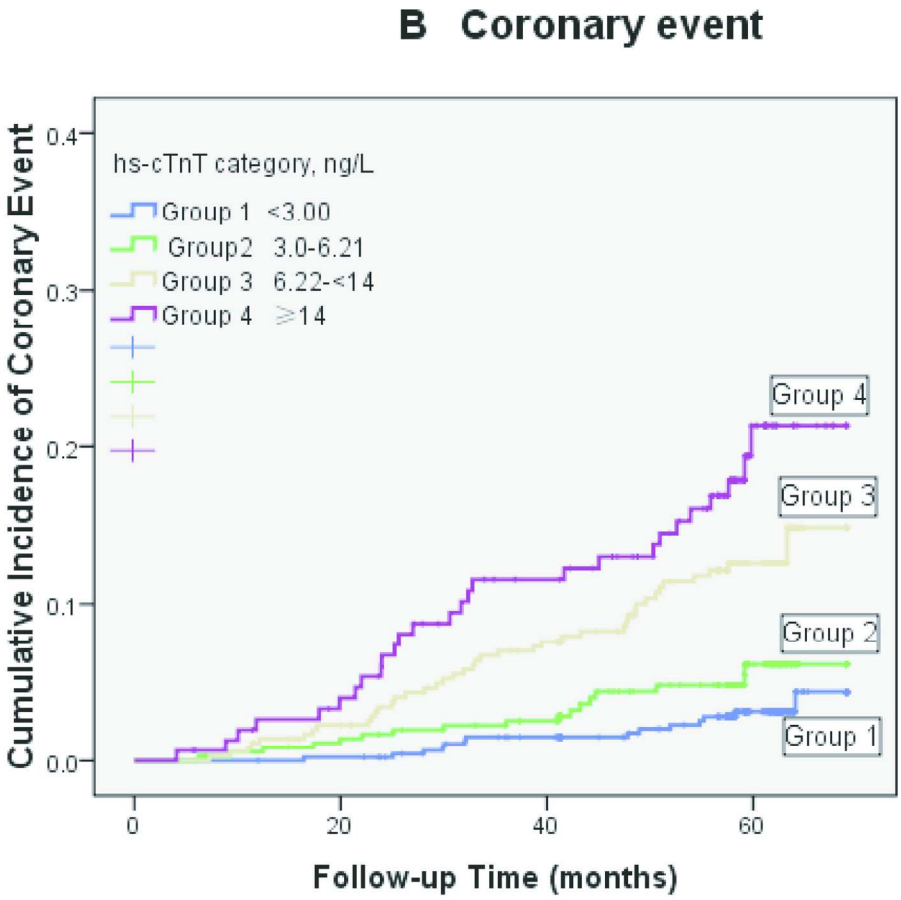

No. at risk

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Group 2	324	318	307	103
Group 3	324	311	285	105
Group 4	172	161	140	45

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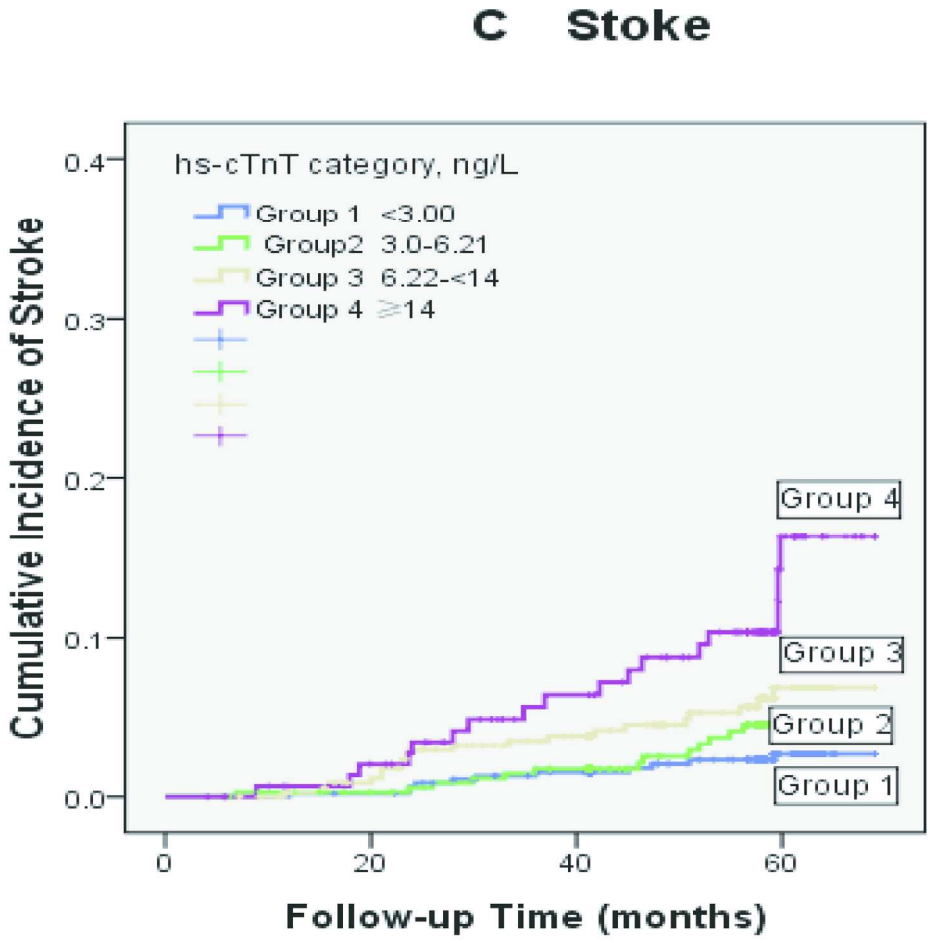

No. at risk

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Group 2	324	318	307	103
Group 3	324	311	285	105
Group 4	172	161	140	45

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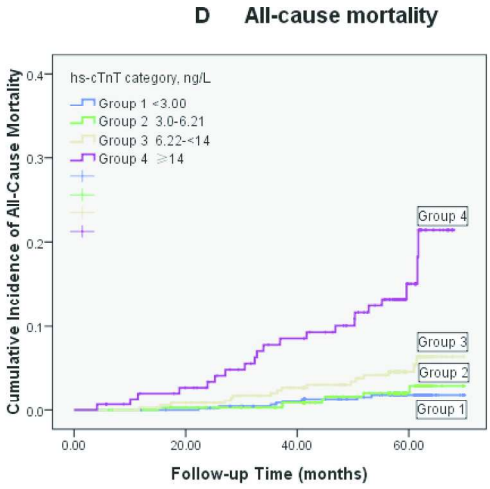

No. at risk

Group 1	679	674	649	344
Group 2	324	318	307	103
Group 3	324	311	285	105
Group 4	172	161	140	45

Figure1. Risk for Cardiovascular Events and All-Cause Mortality by Baseline hs-cTnT Level

Kaplan-Meier survival curves indicating cumulative incidence of MACE (A), Coronary event (B), Stroke (C) and All–cause mortality (D) across baseline hs-cTnT categories. Groups are indicated by colors, P<0.001 for all between-group comparisons by the log-rank test.

113x89mm (600 x 600 DPI)

Supplementary Table1. Characteristics of Study Population between the follow up and lost groups

Characteristics	Baseline population		P value
	Follow up group （n=1499）	lost to follow up group （n=181）	
Demographic			
Age (years)	61.4±11.4	57.6±10.5	<0.01
Male Sex n (%)	629 (42.0)	83(45.9)	0.316
BMI (kg/m^2)	25.6±3.3	25.8±3.4	0.273
Medical history			
Hypertension n (%)	690(46.0)	72(39.8)	0.111
Diabetes mellitus n (%)	292(19.5)	30(16.6)	0.348
Current smoking n (%)	247(16.5)	35(19.3)	0.331
Systolic BP (mm Hg)	132.7±17.0	130.6±16.7	0.136
Diastolic BP (mm Hg)	76.6±10.3	77.8±10.7	0.077
Laboratory values			
FBG (mmol/L)	5.4±1.6	5.3±1.5	0.474
PBG (mmol/L)	8.0±4.2	7.5±3.7	<0.05
Total cholesterol (mmol/L)	5.1±0.9	5.0±0.9	0.321
Triglycerides (mmol/L)	1.8±1.2	1.9±1.1	0.054
LDL cholesterol (mmol/L)	3.0±0.7	2.9±0.6	0.21
HDL cholesterol (mmol/L)	1.4±0.3	1.4±0.3	0.386
Uric acid (μmol/L)	291.4±73.3	276.9±70.8	<0.01
eGFR (mL/min/1.73m^2)	88.9±15.5	92.1±16.0	0.009
NT-proBNP (pg/mL)	41.7(19.8,81.9)	37.4(17.3,73.9)	<0.01
Hs-CRP （mg/L）	2.3 (1.4, 3.5)	2.2 (1.3, 3.4)	0.189
Medication use			
Antihypertensives n (%)	528（35.2）	55 (30.4)	0.197
Antidiabetic n (%)	189（12.6）	19（10.5）	0.415

Lipid lowering	n (%)	262（17.5）	29(16.0)	0.625
Aspirin	n (%)	360（24.0）	37（20.4）	0.285

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	
Objectives	3	State specific objectives, including any prespecified hypotheses	5	
Methods				
Study design	4	Present key elements of study design early in the paper	5	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-6	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-7*	
Bias	9	Describe any efforts to address potential sources of bias		
Study size	10	Explain how the study size was arrived at		

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8-9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12-13
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*10*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14-16
		(*b*) Report category boundaries when continuous variables were categorized	15
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	17
Discussion			
Key results	18	Summarise key results with reference to study objectives	18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	22
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.