Relative Prognostic Value of Cardiac Troponin I and C-Reactive Protein in the General Population (From the HUNT Study)

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Abstract

C-reactive protein and cardiac troponin I measured with high-sensitivity assays (hs-CRP and hs-TnI) have been associated with risk of fatal and nonfatal cardiovascular events in the general population. The relative prognostic merit of hs-CRP and hs-TnI, and whether these markers of inflammation and subclinical myocardial injury provide incremental information to established cardiovascular risk prediction models, remain unclear. hs-CRP and hs-TnI were measured in 9005 participants from the prospective observational HUNT study. All study subjects were free from known cardiovascular disease at baseline. During a median follow up period of 13.9 years, 733 participants reached the composite endpoint of hospitalization for acute myocardial infarction or heart failure, or cardiovascular death. In adjusted models, increased hs-TnI concentrations (>10 ng/L for women and >12 ng/L for men) were associated with the incidence of the composite endpoint (hazard ratio [HR] 3.61 [95% confidence interval (CI) 2.89-4.51]), while the risk associated with increased hs-CRP concentrations (>3 mg/L for both sexes) appeared to be weaker (HR 1.71 [1.40-2.10]). The addition of hs-TnI to established cardiovascular risk prediction models led to a net reclassification improvement (NRI) of 0.35 (95% CI 0.27-0.42), superior to that of hs-CRP (0.21 [0.13-0.28]). The prognostic accuracy of hs-TnI, assessed by C-statistics, was significantly greater than that of hs-CRP (0.753 (0.735-0.772) vs. 0.644 [0.625-0.663]). In conclusion, in subjects from the general population without a history of cardiovascular disease, hs-TnI provides prognostic information superior to that provided by hs-CRP and may therefore be a preferred marker for targeted prevention.

Key-words: CRP, cardiac troponin, cardiovascular disease

Abstract word count: 245

Introduction

Despite advances in diagnosis, treatment and risk assessment tools, cardiovascular disease (CVD) still remains the leading cause of death worldwide.[1] Various risk assessment strategies are used to predict risk of developing CVD based on data from large prospective cohorts such as the Framingham Heart Study.[2] C-reactive protein measured with high-sensitivity assays (hs-CRP) is associated with the risk of cardiovascular events (CVE) and is included in the American and European guidelines on CVD as a tool to identify individuals at high-risk.[3,4] Cardiac troponin I and T are organ-specific markers of myocardial necrosis and a standard diagnostic tools in the evaluation of acute myocardial infarction (AMI).[5] Recent studies show that cardiac troponin I measured with hs-assays (hs-TnI) are associated with increased risk of fatal and nonfatal CVE in asymptomatic individuals.[6–8] However, hs-CRP and hs-TnI reflect different pathophysiologic pathways and have the potential to complement each other for optimal CVD risk stratification. The aims of this study were to (1) assess the CVD risk associated with increased concentrations of hs-CRP and hs-TnI, (2) compare the prognostic accuracy of hs-CRP with that of hs-TnI and (3) compare the incremental prognostic information provided by hs-CRP and hs-TnI, when compared with two Framingham risk score models and their components.[2]

Methods

The Nord-Trøndelag Health (HUNT) Study is the largest ongoing prospective population-based cohort study in Norway, carried out in the county of Nord-Trøndelag.[9] The 9005 participants in the current study were selected as a subsample from the second wave of the HUNT cohort (HUNT2). HUNT2 was carried out from August 1995 to June 1997 where all 93898 residents of the county over ≥20 years of age were invited to participate and 65215 (69%) accepted the invitation. This subsample consisted of participants from four out of 24

municipalities in Nord-Trøndelag. Participants with previous known CVD were excluded. Blood samples were drawn from the participants by specially trained nurses, who also performed a physical examination with a standardized collection of clinical data, including height, weight, waist and hip circumference, and systolic and diastolic blood pressure. For all blood pressure measurements, an automated blood pressure device (Dinamap 845 XT, Criticon) was used, and the average of the second and third measurements was used in our study. Participants completed questionnaires concerning health status, medical history, and lifestyle factors. All participants provided written informed consent and the study was approved by the Regional Ethics Committee (REK 2012/859).

As previously described,[10] non-fasting venous blood samples were collected, centrifuged at room temperature and frozen at −80 °C. hs-CRP was analyzed using an assay with particle-enhanced agglutination (CRP [Latex] US, Hoffman-La Roche AG, Switzerland). The detection limit was 0.03 mg/l and measurements below the detection limit were assigned this value. According to the manufacturer, the reproducibility of the assay has been tested both within run (% coefficient of variation [CV] 0.43–1.34) and between days (% CV 2.51–5.70).[11] For the hs-TnI analysis, samples that had previously been thawed and refrozen in 2008 and subsequently stored at −20 °C were shipped on dry ice to Akershus University Hospital, Lørenskog, Norway.[12] Samples were centrifuged at 3500 relative centrifugal force (RCF) for 30 minutes before analysis. Hs-TnI was measured with the Abbott Diagnostics Architect STAT High Sensitive Troponin assay, as previously described.[10] The limit of detection for this assay has been reported to be 1.2 ng/L (range 0–50 000 ng/L), with a CV of 10% at a concentration of 3.0 ng/L.[13] Using control material from Abbott Diagnostics, a CV of 4.1% was found in the high concentration range (1500 ng/L), 4.4% in the medium concentration range (200 ng/L), and 6.3% in the low concentration range (20 ng/L) after excluding outliers. The diagnostic cutoff representing the 99th percentile in the general

population has been reported to be 15 ng/L in females and 36 ng/L in males. Measurements below the detection limit were assigned a value corresponding to 50% of the limit of detection, i.e. 0.6 ng/L. Concentrations of total cholesterol, HDL-cholesterol, and triglycerides were measured by an enzymatic colorimetric cholesterolesterase method. HDL-cholesterol was measured after precipitation with phosphortungsten and magnesium ions. Serum creatinine was measured by Jaffè method.[9] Estimated glomerular filtration rate (eGFR) was calculated using the 4-variable Modification of Diet in Renal Disease equation.[14]

The primary endpoint of this study was a composite of time to admission for AMI, heart failure (HF), or cardiovascular death. Data on admissions for AMI was obtained from hospital records and defined as a primary diagnosis of International Classification of Diseases (ICD) codes 410 (9^{th} Revision) or I21-I22 (10^{th} Revision) and for HF as primary diagnosis ICD codes 428 (9th Revision) or I50 (10th Revision). The Cause of Death Registry of Statistics in Norway provided the diagnoses stated as the primary cause of death on the death certificate. Cardiovascular death was defined as primary cause of death registered as ICD codes 390-459 (9^{th} Revision) or I00-I99 (10^{th} Revision). All survival data was obtained through December 31, 2010.

Descriptive statistics are reported as absolute numbers with percentages or medians with interquartile range (IQR) unless otherwise stated. We performed baseline comparisons across sex specific quartiles of hs-TnI. Categorical variables were analyzed with the Fisher exact test and continuous variables with the Mann-Whitney U test. We prospectively defined three categories for hs-CRP (<1, 1-3, and >3 mg/L) and hs-TnI (women: <4, 4-10, and >10 ng/L; men: <6, 6-12, and >12 ng/L). Sex specific cutoffs were used for hs-TnI, as hs-TnI concentrations and their predictive value differ by sex.[15,16] hs-CRP distributions have been shown to be comparable between the sexes.[17]

Cox proportion hazard regression models were generated to test the relationship

between the three categories of hs-TnI and hs-CRP to time of admission for AMI/HF or cardiovascular death. The survival models were adjusted for the Framingham risk scores, eGFR, and BMI.[2] Adjustment was not made for the separate factors already included in the Framingham risk scores (i.e. age, total cholesterol, HDL-cholesterol, systolic blood pressure, treatment for hypertension, smoking status, diabetes mellitus). Kaplan-Meier survival curves were generated to show the relationship between both hs-CRP and hs-TnI, and time to events. To evaluate the incremental value of hs-CRP and hs-TnI to the Framingham risk scores, we calculated the net classification index (NRI) for both variables independently and together. Prognostic accuracy of hs-TnI and hs-CRP was assessed using C-statistics derived from the survival models and compared by the R package 'survCOMP'.[18,19] Statistical significance was assumed at a p-value <0.05. The following programs were used to conduct our statistical analysis: IBM SPSS Statistics for Windows, version 22 (IBM Corp, Armonk, NY, USA), STATA 14 (StataCorp LP, College Station, TX, USA), MedCalc for Windows, version 16.2.0 (MedCalc Software, Ostend, Belgium) and R 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

hs-CRP and hs-TnI were measured in 9005 subjects without prior known CVD, 4009 (44.5%) men and 4996 (55.5%) women, with a median age of 48.5 years. Baseline characteristics of the study population according to sex specific quartiles of hs-TnI are outlined in Table 1. Increasing age, weight, BMI, hypertension, hypercholesterolemia and diabetes, as well as hs-CRP, were associated with higher concentrations of hs-TnI (p<0.001).

After a median follow-up of 13.9 years, 733 study participants reached the composite endpoint including 267 admissions for AMI (35% in women), 135 admissions for HF (54% in women), and 331 cardiovascular deaths (52% in women). We observed an association

between high concentrations of hs-CRP and hs-TnI and the composite endpoint (Table 2). Subjects in the highest hs-TnI category (>10 ng/L for women and >12 ng/L for men) had a hazard ratio (HR) of 9.76 (95% CI 7.97-11.95) compared to the lowest category (<4 ng/L for women and <6 ng/L for men). The association appeared to be stronger for hs-TnI than for hs-CRP after adjustment for Hard Coronary Heart Disease score, BMI and eGFR (HR 3.61 [2.89-4.51] vs. 1.71 [1.40-2.10]), and CVD risk score, BMI and eGFR (HR 3.06 [CI 2.44-3.84] vs. 1.59 [1.29-1.95]).

Figure 1 and 2 shows the Kaplan-Meier survival curves of hs-TnI and hs-CRP to the composite endpoints of admission for AMI/HF or cardiovascular deaths. Both biomarkers separated subjects with more unfavorable prognosis ($p < 0.001$ by log-rank test for both biomarkers).

Adding hs-TnI to the Framingham risk score reclassified a significant proportion of subjects to their correct risk strata (Table 3). Weaker reclassification improvement was observed for hs-CRP: NRI 0.261 (0.185-0.337) for Hard Coronary Heart Disease and 0.206 (0.129-0.283) for CVD risk score. Adding both hs-TnI and hs-CRP to the CVD risk score provided additional reclassification compared to both biomarkers separately (Table 3). This was not the case for the Hard Coronary Heart Disease risk score, where hs-TnI only provided improved reclassification.

The prognostic accuracy of hs-TnI, as estimated by C-statistics, was 0.753 (95% CI 0.735-0.772). The corresponding value was 0.644 (0.625-0.663) for hs-CRP ($p<0.001$). To better elucidate the relative prognostic importance of standard and novel biomarkers, we compared the C-statistic values of hs-TnI and hs-CRP to those of the separate variables included in the Framingham risk scores. We observed that the C-statistic value of hs-TnI was greater than that of traditional biomarkers such as total cholesterol and hs-CRP, but less than

traditional risk factors such as age, history of diabetes and treatment for hypertension (Table 4).

Discussion

In a large population-based cohort, concentrations of hs-TnI were more strongly associated with admission for AMI, HF, or cardiovascular death than concentrations of hs-CRP. hs-TnI concentrations not only provided prognostic information independently of conventional risk scores and hs-CRP in multivariate models, but also provided significantly higher overall prognostic accuracy, and reclassified a greater proportion of individuals to their correct risk strata than did hs-CRP. These findings suggest that hs-TnI is a stronger candidate than hs-CRP for the use as a screening tool to discriminate between subjects at low and high cardiovascular risk.

hs-CRP concentrations are associated with the risk of CVD in individuals without CVD[20] and measurement of hs-CRP has been included in the American and European guidelines on CVD as a tool to identify high-risk individuals.[3,4] There are, however, several challenges associated with the use of hs-CRP in CVD prevention. The influence of external confounders and lack of specificity to CVD will often make measurements of hs-CRP difficult to interpret. hs-CRP is an acute phase protein that is secreted from the liver as a result of interleukin-6 stimulation and is therefore an indirect inflammatory marker.[21] In both a Mendelian randomization analysis and studies on hs-CRP polymorphisms there was no association between genetically raised concentrations of hs-CRP and risk of coronary heart disease.[22,23]. However, both statin treatment and anti-inflammatory therapy of individuals with levels of hs-CRP of 2 mg/L or higher reduced the incidence of major CVE.[24,25]

Cardiac troponins are widely used and recommended in clinical practice as the preferred biomarker of acute myocardial necrosis.[5] Although the pathophysiological

mechanisms for chronic low grade troponin release are not fully understood, it is believed to be related to subclinical damage to the myocardium and structural heart disease.[13,26] Higher concentrations of hs-TnI in healthy individuals are strongly associated with increased risk of CVD[7,8,10] and hs-TnI may therefore be better suited for CVD screening in an asymptomatic, general population than hs-CRP.[7,27–29]

In our study, hs-TnI provided stronger prognostic information than hs-CRP and lipid biomarkers, suggesting that hs-TnI potentially could replace other biomarkers in CVD risk scores. Although adding hs-TnI and hs-CRP to traditional risk factor models may provide no or only marginal improvement in overall prognostic performance, population screening with hs-TnI may still be cost-effective compared to traditional risk factors. Our data suggest that hs-TnI, and to a lesser degree hs-CRP, results in a significant reclassification of subjects to their correct risk stratum, which is in accordance with previous findings that hs-TnI provide additional prognostic information to traditional risk factors for CVD in asymptomatic subjects.[29]

The introduction of high-sensitivity cardiac troponin assays have clearly demonstrated that the association with risk is evident also within the normal range.[16] In contrast to hs-TnI, where higher concentrations are observed in men than in women, hs-CRP concentrations do not differ between sexes.[17] Moreover, the prognostic value of hs-TnI may differ between women than in men.[15] We therefore prospectively selected sex specific categories for hs-TnI based on cutoffs that provided good risk discrimination in other cohorts.[28]

Strengths of this study include a long follow-up of a large, prospective, population-based cohort, with a substantial number of clinical endpoint. hs-TnI was also measured using one of the most sensitive assays available.[6] Limitations include self-report of risk factors, such as smoking status. Few of the individuals who died during the follow up period were autopsied, which introduces a risk of misclassification of cause of death. This is unlikely to

have affected the differences in risk association between hs-TnI and hs-CRP concentrations. The study was conducted in an ethnically homogenous population and the results cannot directly be generalized to other ethnicities. We cannot rule out the possibility of some degree of degradation of hs-TnI during long-term storage since they were collected in 1995-1997, were thawed and frozen again in 2008 and stored at -20 °C after 2008. However, this is considered unlikely to affect the results of the study since hs-TnI concentrations have been observed to remain stable through several thaw-freezing cycles.[12] Moreover, the 99th percentile values observed in our samples were very close to the reference values provided by the manufacturer.[15]

In conclusion, data from this population-based study show that hs-TnI is associated with increased risk of AMI, HF or cardiovascular death. hs-TnI provides superior predictive information to hs-CRP. Our results suggest that hs-TnI measurement is a better screening tool than hs-CRP to identify individuals at high CVD risk and may represent the preferred biomarker for targeted prevention.

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Figure legends

Figure 1. Kaplan-Meier plot for admission for AMI/HF or cardiovascular death. Subjects stratified according to hs-CRP concentrations.

Figure 2. Kaplan-Meier plot for admission for AMI/HF or cardiovascular death. Subjects stratified according to hs-TnI concentrations.

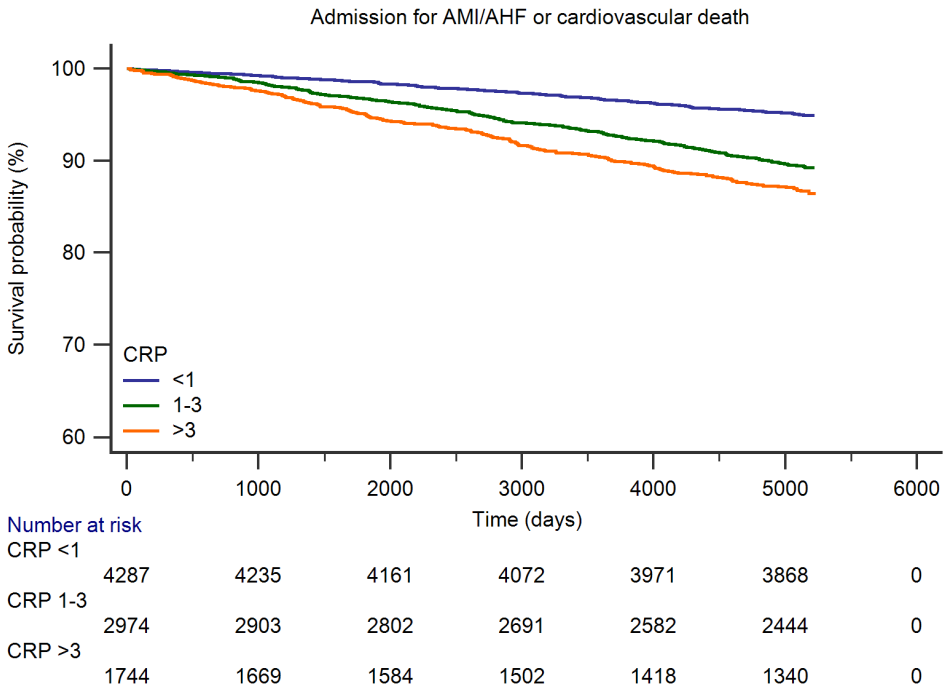
Admission for AMI/AHF or cardiovascular death
Survival probability (%)
100
90
80
70
60
CRP
<1
1-3
>3
0
1000
2000
3000
4000
5000
6000
Time (days)
Number at risk
CRP <1
4287 4235 4161 4072 3971 3868 0
CRP 1-3
2974 2903 2802 2691 2582 2444 0
CRP >3
1744 1669 1584 1502 1418 1340 0

Figure 1

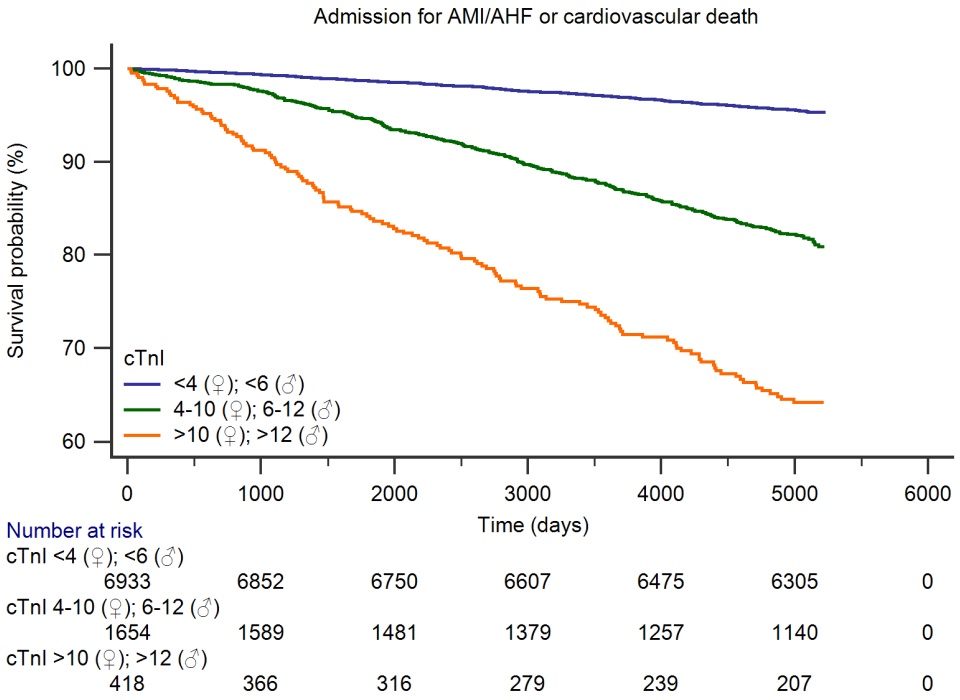
Admission for AMI/AHF or cardiovascular death
Survival probability (%)
100
90
80
70
60
cTnI
<4 (♀); <6 (♂)
4-10 (♀); 6-12 (♂)
>10 (♀); >12 (♂)
0
1000
2000
3000
4000
5000
6000
Time (days)
Number at risk
cTnI <4 (♀); <6 (♂)
6933 6852 6750 6607 6475 6305 0
cTnI 4-10 (♀); 6-12 (♂)
1654 1589 1481 1379 1257 1140 0
cTnI >10 (♀); >12 (♂)
418 366 316 279 239 207 0

Figure 2

Table 1. Baseline characteristics according to sex specific quartiles of cardiac troponin I measured with high-sensitivity assay.

Variable	Quartile 1		Quartile 2		Quartile 3		Quartile 4	
	N	Value	n	Value	n	Value	n	Value
Women	2318	1264 (54.5%)	2283	1239 (54.3%)	2373	1341 (56.5%)	2031	1152 (56.7%)
Age (years)	2318	37.4 (29.6-46.1)	2283	43.1 (33.9-53.2)*	2373	51.0 (40.4-61.5)*	2031	64.0 (50.5-73.6)*
Weight (kg)	2314	72.5 (64.0-81.5)	2282	75.5 (66.5-85.5)*	2368	76.5 (67.6-86.5)*	2007	77.0 (67.0-87.0)*
Body mass index (kg/m^2)	2314	24.5 (22.4-26.6)	2282	25.6 (23.4-28.1)*	2368	26.3 (24.1-28.9)*	2007	27.0 (24.5-29.8)*
Waist hip ratio	2295	0.82 (0.76-0.87)	2260	0.83 (0.78-0.89)*	2342	0.84 (0.79-0.90)*	2008	0.85 (0.80-0.91)*
Current smoker	2304	790 (34.1%)	2263	670 (29.3%)†	2347	708 (29.8%)†	1999	412 (20.3%)*
History of hypertension	2309	446 (19.2%)	2269	723 (31.7%)*	2362	1079 (45.5%)*	2025	1383 (68.1%)*
History of diabetes mellitus	2318	21 (0.9%)	2282	25 (1.1%)	2369	51 (2.1%)†	2029	105 (5.2%)*
Systolic blood pressure (mmHg)	2311	125 (115-134)	2273	129 (118-141)*	2365	135 (123-149)*	2021	148 (131-166)*
Diastolic blood pressure (mmHg)	2311	75 (68-82)	2273	78 (71-85)*	2365	81 (74-89)*	2021	84 (76-94)*
Glucose nonfasting (mmol/L) (mg/dL)	2318	5.0 (4.7-5.5) 90 (85-99)	2283	5.1 (4.7-5.6)* 92 (85-101)*	2373	5.2 (4.8-5.8)* 94 (86-104)*	2031	5.4 (5.0-6.0)* 97 (90-108)*
Triglycerides nonfasting (mmol/L) (mg/dL)	2318	1.12 (0.80-1.70) 99 (71-150)	2283	1.38 (0.99-1.94)* 122 (88-172)*	2373	1.56 (1.11-2.24)* 138 (98-198)*	2031	1.62 (1.16-2.28)* 143 (103-202)*
Total cholesterol (mmol/L) (mg/dL)	2318	5.0 (4.4-5.7) 193 (170-220)	2283	5.6 (4.9-6.3)* 216 (189-243)*	2373	6.1 (5.4-6.9)* 236 (209-266)*	2031	6.4 (5.5-7.3)* 247 (212-282)*
HDL cholesterol (mmol/L) (mg/dL)	2318	1.4 (1.2-1.7) 54 (46-66)	2283	1.4 (1.1-1.6)* 54 (43-62)*	2373	1.3 (1.1-1.6)* 50 (43-62)*	2031	1.3 (1.1-1.6)* 50 (43-62)*
eGFR (mL/min/1,73m^2)	2318	76.6 (69.2-85.0)	2283	73.7 (66.3-81.5)*	2373	70.4 (62.9-78.7)*	2031	65.8 (56.8-74.2)*
CRP (mg/L)	2318	0.7 (0.3-2.0)	2283	1.0 (0.3-2.2)*	2373	1.1 (0.5-2.4)*	2031	1.4 (0.6-3.0)*

p-values compared to quartile 1: * p<0.001. † p<0.01. ‡ p<0.05.
Quartile 1, <1.9 ng/L (women); <2.6 ng/L (men). Quartile 2, 1.9-2.6 ng/L (women); 2.6-3.6 ng/L (men). Quartile 3, 2.7-3.9 ng/L (women); 3.7-5.2 ng/L (men). Quartile 4, >3.9 ng/L (women); >5.2 ng/L (men). CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein.

Table 2. Associations between hs-TnI and hs-CRP concentrations and cardiovascular death or admission for AMI or HF.

	Category	Hazard ratio (95% confidence interval)				
		Model 1 (events=733)	Model 2 (events=705)	Model 3 (events=705)	Model 4 (events=696)	Model 5 (events=696)
hs-TnI	<4 (♀); <6 (♂)	REF	REF	REF	REF	REF
	4-10 (♀); 6-12 (♂)	4.33 (3.69-5.08)*	2.47 (2.08-2.92)*	1.95 (1.64-2.33)*	2.12 (1.78-2.52)*	1.82 (1.52-2.18)*
	>10 (♀); >12 (♂)	9.76 (7.97-11.95)*	4.25 (3.43-5.28)*	3.23 (2.58-4.05)*	3.61 (2.89-4.51)*	3.06 (2.44-3.84)*
hs-CRP	<1	REF	REF	REF	REF	REF
	1-3	2.20 (1.84-2.62)*	1.45 (1.21-1.74)*	1.39 (1.16-1.67)*	1.42 (1.18-1.71)*	1.40 (1.16-1.68)*
	>3	2.81 (2.32-3.39)*	1.79 (1.47-2.18)*	1.61 (1.32-1.96)*	1.71 (1.40-2.10)*	1.59 (1.29-1.95)*

* p<0.001. Model 1, unadjusted; model 2, adjusted for Hard Coronary Heart Disease; model 3, adjusted for Cardiovascular Disease; model 4, adjusted for Hard Coronary Heart Disease, BMI and eGFR; model 5, adjusted for Cardiovascular Disease, BMI and eGFR.

Table 3. Net reclassification improvement of hs-TnI and hs-CRP when added to the Framingham risk scores.

	Hard Coronary Heart Disease	Cardiovascular Disease
hs-TnI	0.4672 (0.3912-0.5431)*	0.3456 (0.2690-0.4222)*
hs-CRP	0.2607 (0.1845-0.3369)*	0.2059 (0.1293-0.2825)*
hs-TnI + hs-CRP	0.4301 (0.3541-0.5061)*	0.3608 (0.2844-0.4372)*

* $p<0.001$.

Table 4. Prognostic accuracy of individuals varibles included in Framingham cardiovascular risk scores, hs-TnI, and hs-CRP, on cardiovascular death or admission for AMI or HF

Variable	C-index (95% CI)	p compared to cTnI	p compared to CRP
Age	0.862 (0.850-0.874)	<0.001	<0.001
History of diabetes mellitus	0.823 (0.781-0.864)	<0.001	<0.001
Treatment for hypertension	0.813 (0.788-0.838)	<0.001	<0.001
Systolic blood pressure	0.765 (0.747-0.782)	0.13	<0.001
hs-TnI	0.753 (0.735-0.772)		<0.001
Total cholesterol	0.652 (0.632-0.671)	<0.001	0.28
hs-CRP	0.644 (0.625-0.663)	<0.001	
HDL cholesterol	0.536 (0.512-0.561)	<0.001	<0.001
Current smoking	0.506 (0.465-0.547)	<0.001	<0.001