Temporal changes in cardiac troponin I are associated with risk of cardiovascular events in the general population: The Nord-Trøndelag Health Study

Running head: Change in troponin I and cardiovascular risk

Magnus N Lyngbakken[1], Helge Røsjø[1], Oddgeir L Holmen[2], Håvard Dalen[3], Kristian Hveem[2], Torbjørn Omland[1]

1 Division of Medicine, Akershus University Hospital, Lørenskog, Norway and Center for Heart Failure Research, University of Oslo, Oslo, Norway

2 HUNT Research Centre, Department of Public Health and General Practice, Norwegian University of Science and Technology, Levanger, Norway

3 K.G. Jebsen Center for Exercise in Medicine, Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway

Address for correspondence:

Torbjørn Omland MD, PhD, MPH

Professor of Medicine, University of Oslo

Division of Medicine, Akershus University Hospital, Postboks 1000, 1478 Lørenskog, Norway

Tel: +47 40 10 70 50, Fax: +47 67 96 88 60, Email: torbjorn.omland@medisin.uio.no

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Abbreviations: hs-cTn, cardiac troponin measured with a high-sensitivity assay; MI, myocardial infarction; HF, heart failure; hs-cTnT, cardiac troponin T measured with a high-sensitivity assay; hs-cTnI, cardiac troponin I measured with a high-sensitivity assay; HUNT Study, Nord-Trøndelag Health Study; LoD, limit of detection; eGFR, estimated glomerular filtration rate; ICD, International Statistical Classification of Diseases; IQR, interquartile range; HDL, high-density lipoprotein; BMI, body mass index; CRP, C-reactive protein; NRI, net reclassification index; IDI, integrated discrimination improvement; HR, hazard ratio; CI, confidence interval

Abstract

Background: Cardiac troponins are associated with cardiovascular risk in the general population, but whether temporal changes in cardiac troponin I provide independent prognostic information remains uncertain. Using a large community based cohort with follow-up to the present day, we aimed to investigate the associations between temporal changes in cardiac troponin and cardiovascular events.

Methods: We measured cardiac troponin I with a high-sensitivity assay (hs-cTnI) in 4805 subjects attending both the second (HUNT 2, 1995-97) and third wave (HUNT 3, 2006-2008) of the prospective observational Nord-Trøndelag Health (HUNT) Study. We constructed statistical models with both relative and absolute changes of hs-cTnI from HUNT 2 to HUNT 3. A composite endpoint of first admission for MI or HF, or cardiovascular death was generated.

Results: Participants with relative decrease in hs-cTnI were more frequently younger and female, and had lower blood pressure and body mass index. Participants with relative increase in hs-cTnI more frequently were older and male, with higher systolic blood pressure. The adjusted hazard ratio (HR) for relative increase in hs-cTnI was 1.68 (95% CI 1.16-2.42) and the adjusted HR for relative decrease was 1.19 (95% CI 0.84-1.68). Absolute increases in hs-cTnI exhibited similar prognostic properties as relative increases in hs-cTnI. The most recent measurement of hs-cTnI outperformed the change variables in discrimination and reclassification models.

Conclusions: Both relative and absolute increases in hs-cTnI are independently associated with cardiovascular risk. For refinement of risk prediction models, the most recent measurement of hs-cTnI should be preferred in clinical practice.

Introduction

Measurement of cardiac troponin with a high-sensitivity assay (hs-cTn) is essential in the diagnosis of acute coronary syndromes, as concentrations of hs-cTn are considered sensitive and specific indicators of myocardial injury *(1)*. In recent years, hs-cTn measured in the general population has proven to be strongly associated with risk of fatal and non-fatal cardiovascular events *(2)*. This risk may be ameliorated by interventions aimed at reducing cardiovascular risk, such as statin therapy, where concomitant reductions in risk and concentrations of hs-cTn have been demonstrated *(3)*. Despite being interchangeable in the diagnosis of myocardial infarction (MI), in the chronic setting hs-cTnT and hs-cTnI are poorly correlated, and are differentially influenced by common cardiovascular risk factors *(4)*. In addition, hs-cTnT exhibits a circadian variation, whereas hs-cTnI remains stable throughout the day and night *(5)*. With regard to prognosis, there are differences between hs-cTnT and hs-cTnI, as hs-cTnT may be superior in predicting cardiovascular death and heart failure (HF) *(6)*, while the associations with incident MI appear stronger for hs-cTnI *(7)*.

Sampling of hs-cTn at multiple time points may have the potential to refine biomarker based risk estimation, and earlier studies have documented associations between temporal increases in hs-cTnT *(8)* and hs-cTnI *(9)* and increased risk of cardiovascular events. Whether these associations hold true also in a contemporary cohort of community dwellers with follow-up close to the present day is uncertain. Accordingly, using a large cohort of subjects recruited from the general population with measurements of hs-cTnI at two time points 10 years apart, we investigated the impact of temporal changes in hs-cTnI on the risk of incident HF, MI, and cardiovascular death, using indices of relative and absolute changes in hs-cTnI.

Additionally, we identified determinants of temporal changes in hs-cTnI in a general population.

Methods

Study overview

The Nord-Trøndelag Health (HUNT) Study is the largest population-based cohort in Norway, with more than 120,000 participants from the Nord-Trøndelag county. Three waves have been conducted so far: HUNT 1 (1984-1986), HUNT 2 (1995-1997) and HUNT 3 (2006-2008) *(10)*. The HUNT Study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate Board and all participants provided informed written consent.

Participants

In the current investigation, 5338 study subjects from four selected municipalities, with serum samples available for analyses from both HUNT 2 and HUNT 3, were included. Participants with known prior cardiovascular disease were excluded, leaving a total of 4805 participants for final analyses. Individual cardiovascular risk was estimated using the Systematic COronary Risk Evaluation *(11)* and the Framingham risk score for Cardiovascular Disease *(12)*.

Blood sampling procedures and biochemical assays

Non-fasting venous blood samples were collected at HUNT 2 and 3, centrifuged at room temperature and frozen at -80°C. Serum samples from HUNT 2 underwent a thaw-freeze cycle in 2008 and were later stored at -20°C. For hs-cTnI analyses, serum samples were shipped on dry ice to Akershus University Hospital, Lørenskog, Norway. hs-cTnI was measured on the Architect i2000SR using an assay from Abbott Diagnostics, ARCHITECT STAT High Sensitive Troponin, the samples from HUNT 2 in 2014 and the samples from HUNT 3 in 2015. The same analyzer was

used at both time points, but with different reagent lots. A detailed description of the assay methods has recently been published elsewhere *(13)*. The limit of detection (LoD) for this assay is reported to be 1.2 ng/L *(14)*. Concentrations below the LoD were assigned a value of 0.6 ng/L. Concentrations of hs-cTnI were detectable in 96.1% of subjects in HUNT 2 and in 72.2% of subjects in HUNT 3. Glomerular filtration rate was estimated (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration equation *(15)*.

Outcomes

Data on cardiovascular death (International Statistical Classification of Diseases [ICD], 9th Revision or 10th Revision codes 390–459 or I00–I99) were obtained from the Cause of Death Registry of Statistics Norway. Data on incident acute MI (ICD, 9th Revision or 10th Revision codes 410 or I21-I22) and admission for HF (codes 428 or I50) were obtained from hospital records; only hospitalizations where this diagnosis was listed as the primary diagnosis were included. All events were obtained through December 31, 2016.

Statistical Methods

Baseline data are reported as absolute numbers (proportion) or median (interquartile range [IQR]) unless otherwise stated. Continuous variables were analyzed using the Mann-Whitney U test, and categorical variables with the Fisher exact test. Correlations were assessed by Spearman rank correlation. Change in hs-cTnI was modeled as relative change of < 50%, increase of ≥ 50%, or decrease of ≥ 50% from concentrations at HUNT 2 to HUNT 3, as previously suggested *(8, 16)*. We also examined change in hs-cTnI as (1) incident elevation above concentrations as

previously reported *(17)* (progression from < 4.0ng/L [♀] and < 6.0ng/L [♂] at HUNT 2 to ≥ 4.0ng/L [♀] and ≥ 6.0ng/L [♂] at HUNT 3) and (2) incident elevation above the 99th centile (progression from < 16.0ng/L [♀] and < 34.0ng/L [♂] at HUNT 2 to ≥ 16.0ng/L [♀] and ≥ 34.0ng/L [♂] at HUNT 3). Separate models were also constructed for single-time point elevation in hs-cTnI at HUNT 3 using the same thresholds. Concentrations of hs-cTnI were transformed using the natural logarithm prior to use as a single covariate in all regression models.

A multinomial regression model was utilized to assess determinants of relative changes in hs-cTnI from HUNT 2 to HUNT 3. Adjustment was made for age and sex, as well as total cholesterol and high-density lipoprotein (HDL) cholesterol, history of hypertension and diabetes mellitus, current smoking, body mass index (BMI), eGFR, C-reactive protein (CRP), and hs-cTnI measured at HUNT 2.

For prognostic analyses, a composite endpoint of time to first event of admission for MI or HF, or cardiovascular death was generated, and participants were censored at the time of the composite endpoint. Remaining participants were censored at the time of death of other causes, or for survivors, on December 31, 2016. Cox proportional hazards regression models were generated to test the relationship between changes in hs-cTnI and time to events. Cumulative incidence plots were generated and the associations between groups according to changes in hs-cTnI and the composite endpoint were compared by the log-rank test. The survival models were adjusted for sex and age, as well total cholesterol and HDL cholesterol, history of hypertension and diabetes mellitus, current smoking, BMI, eGFR and CRP. Models with relative change in hs-cTnI were additionally adjusted for hs-cTnI measured at HUNT 3. Subjects with missing covariate data were excluded from the multivariable regression analyses. The incremental value of

adding absolute and relative changes in hs-cTnI to the Systematic COronary Risk Evaluation risk score and the Framingham risk score for Cardiovascular Disease was examined by calculating the category-free net reclassification index (NRI) and integrated discrimination improvement (IDI) *(18)* by the R package “PredictABEL” *(19)*. Prognostic accuracy was assessed using *c*-statistics derived from the survival models and compared by the R package “survCOMP” *(20, 21)*. 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 25 (IBM Corporation), STATA 15 (StataCorp LP), and R 3.4.3 (R Foundation for Statistical Computing).

Results

Determinants of changes in cardiac troponin I

Baseline characteristics at HUNT 3 according to relative changes in hs-cTnI are outlined in **Table 1**. Study participants with relative decreases in hs-cTnI were more frequently younger and female, and had lower blood pressure and BMI. Participants with relative increases in hs-cTnI were more frequently older and male, with higher systolic blood pressure. Based on variables from HUNT 2, higher age, male sex, and lower total cholesterol and hs-cTnI were independent determinants of relative increase in hs-cTnI, whereas female sex, lower age, lower BMI, and higher total cholesterol and hs-cTnI were determinants of relative decrease in hs-cTnI (**Table 2**). Temporal changes in hs-cTnI were poorly correlated with temporal changes in BMI, blood pressure, blood cholesterol, renal function and CRP (online **Supplemental Table 1**). Considering the strong influence of sex and age on cardiac troponin, we assessed a possible non-linear association of age with temporal increase in hs-cTnI. For both sexes, risk of a relative increase in hs-cTnI was not present until ages were in the mid-forties, after which the risk increased steeply (**Figure 1**).

Associations of cardiac troponin I with incident cardiovascular disease

After a median follow-up time of 3503 (3248-3580) days, 249 events for the composite endpoint were registered. Concentrations of hs-cTnI at HUNT 3 were higher in participants experiencing the composite endpoint (3.9 [2.4-6.6] ng/L vs 1.7 [0.6-2.8] ng/L; P <0.001), and were associated with inferior prognosis in both crude (hazard ratio [HR] 2.06, 95% confidence interval [CI] 1.88-2.26) and adjusted analysis (HR 1.46, 95% CI 1.28-1.67).

Associations of temporal changes in cardiac troponin I with incident cardiovascular disease

The incidence rates per 1000 person years were higher in study participants exhibiting relative increases in hs-cTnI from HUNT 2 to HUNT 3 (**Table 3**). **Figure 2** demonstrates Kaplan-Meier survival curves according to changes in hs-cTnI. Participants with relative increases in hs-cTnI had higher incidence rates compared to participants with no change (*P* by log-rank test <0.001), and participants with decreasing hs-cTnI had lower incidence rates compared to participants with no change (*P* = 0.037) and participants with increasing hs-cTnI (*P* <0.001). Study participants progressing above the two predefined thresholds of hs-cTnI also had higher incidence rates compared to participants with unchanged hs-cTnI (*P* <0.001 for both).

There was a significant association between both relative increase (HR 2.65, 95% CI 1.96-3.60) and decrease (HR 0.44, 95% CI 0.32-0.60) in hs-cTnI and cardiovascular death or admission for MI or HF in crude analyses. In adjusted analyses, the protective effect associated with decreasing hs-cTnI was attenuated (HR 1.19, 95% CI 0.84-1.68). The risk associated with increasing hs-cTnI, however, remained significant in the adjusted models (HR 1.68, 95% CI 1.16-2.42). Both incident elevation (HR 1.77, 95% CI 1.16-2.70) and single-time point elevation (HR 1.71, 95% CI 1.28-2.30) of hs-cTnI ≥ 4.0ng/L for women and ≥ 6.0ng/L for men, and incident elevation (HR 3.01, 95% CI 1.59-5.71) and single-time point elevation (HR 2.32, 95% CI 1.26-4.27) of hs-cTnI ≥ 16.0ng/L for women and ≥ 34.0ng/L for men were associated with increased risk of events (**Table 3**).

Discrimination and reclassification models assessing the incremental prognostic value of hs-cTnI are detailed in **Table 4**. The addition of hs-cTnI at HUNT 3 to the Systematic COronary Risk Evaluation risk score resulted in significant improvement in NRI and IDI. Adding relative change in hs-cTnI (≥ 50% increase in hs-cTnI vs rest) to this model did not improve model prediction. The addition of indices of absolute increases in hs-cTnI to the Systematic COronary Risk Evaluation risk score resulted in significant improvements in NRI (0.293 [0.168-0.418]), but no improvements in IDI (0.0067 [-0.0001-0.0135]) or *c*-statistics (0.834 [0.806-0.861] vs. 0.827 [0.799-0.855]; *P*=0.05). The addition of single-time point elevation of hs-cTnI at HUNT 3 provided improvements in reclassification models superior to those of indices of absolute increases. The results from analyses using the Framingham risk score for Cardiovascular Disease as reference model were comparable to those using the Systematic COronary Risk Evaluation (online **Supplemental Table 2**).

Associations of sex and temporal changes in cardiac troponin I

For both men and women, there were strong associations between relative changes in hs-cTnI from HUNT 2 to HUNT 3 and cardiovascular risk (**Table 3**). As for the entire cohort, the associations with decreasing hs-cTnI were attenuated for both sexes in adjusted models. Additionally, for women, the association with increasing hs-cTnI was attenuated in adjusted models. We did however not observe interactions between sex and relative changes in hs-cTnI (unadjusted $P_{interaction}$=0.70, adjusted $P_{interaction}$=0.53).

In the discrimination and reclassification models, the results were fairly similar as for the entire cohort (**Table 4**). The addition of hs-cTnI from HUNT 3 to the Systematic

COronary Risk Evaluation risk score improved NRI and IDI for both sexes, but was stronger for women. The addition of relative change in hs-cTnI (≥ 50% increase in hs-cTnI vs rest) was not found to improve prediction models for either sex.

Discussion

In a large contemporary population-based cohort with measurements of biomarkers at two time points 10 years apart, both relative and absolute increases in hs-cTnI were associated with increased risk of cardiovascular death and admission for MI and HF. Absolute increases of hs-cTnI above predetermined thresholds strongly improved discrimination and reclassification models. The improvements were however inferior to the improvements provided by the most recent single-time point elevation in hs-cTnI. Sex and age, as well as blood cholesterol, were strong determinants of relative changes in hs-cTnI.

Determinants of temporal changes in cardiac troponin

Both age and sex are strongly associated with hs-cTnI *(22)* and risk of incident cardiovascular disease *(23, 24)*. In the current study, we additionally have demonstrated that male sex and higher age are associated with risk of significant *increases* in hs-cTnI over time. In contrast, younger females were at lower risk of significantly increasing concentrations of hs-cTnI, all independently of baseline concentrations of hs-cTnI. The risk of increasing concentrations of hs-cTnI was not evident until the fifth decade, consistent with midlife increases in cardiovascular risk. Changes in other cardiovascular risk factors such as BMI, blood pressure and blood cholesterol were poorly correlated with changes in hs-cTnI, and concomitant change in conventional risk factors cannot fully explain the relative changes in hs-cTnI observed in the current study.

Concentrations of total cholesterol were positively associated with risk of decreasing concentrations of hs-cTnI, and HDL cholesterol exhibited an inverse association. Total cholesterol is an independent risk factor for coronary heart

disease, whereas HDL cholesterol is assumed to have cardioprotective properties *(25)*. Statin therapy may be indicated in individuals with high total cholesterol, but the recommendation is weaker if concomitant concentrations of HDL cholesterol are high *(26)*. Since HUNT 2, the use of statins has grown exponentially in Europe, and Norway is one of the countries with the highest prevalence of statin prescription in the world *(27)*. In 2016, Ford et al. *(3)* reported a 13% reduction in hs-cTnI measured with a high-sensitivity assay following treatment with statins compared with placebo. Even though we lack data on lipid modifying therapy in our cohort, it is not unreasonable to speculate that study participants with high concentrations of total cholesterol at baseline more frequently were prescribed a statin and consequently would experience reductions in hs-cTnI on follow-up due to this very phenomenon.

Temporal changes in cardiac troponins and cardiovascular risk

Concentrations of cardiac troponin are strongly associated with an adverse prognosis, both in subjects with established cardiovascular disease *(6, 28)* and in previously healthy subjects recruited from the general population *(2)*. Two previous studies investigating the temporal changes of cardiac troponin in presumably healthy individuals merit discussion in relation to the current study. Using data from the ARIC Study, McEvoy et al. *(8)* examined the impact of six-year change in hs-cTnT on the risk of incident coronary heart disease, HF and cardiovascular death. Temporal changes in hs-cTnT were associated with clinical end points, and they found significant improvements in *c*-statistics and NRI for HF and cardiovascular death when implementing concentrations of hs-cTnT measured at two time points. More recently, Hughes et al. *(9)* examined the association of change in hs-cTnI with incident cardiovascular disease in 3875 Danish community dwellers. They found

significant associations between changes in hs-cTnI and risk of fatal and nonfatal cardiovascular disease, but change in hs-cTnI did not improve risk prediction models compared to the most recent single measurement of hs-cTnI. The results of the current study are principally in line with the aforementioned, but three important differences warrant mention.

First, evidence is currently amassing for both analytical and biological differences of hs-cTnT and hs-cTnI. Especially concerning for analyses of cardiac troponin concentrations close to the limit of detection is the circadian variation evident for hs-cTnT *(5)*. Analyses focusing on relative changes in very low concentrations could easily be affected by such bias, in general making measurement of hs-cTnI preferable to hs-cTnT measurement in this setting.

Second, for both previous studies, follow-up of study participants started in the mid-nineties through 2009-2010. Our cohort was followed from 2006-2008 through 2016, and given the changes in population risk profile and spectrum of cardiovascular disease in the last twenty years *(29)*, differences in study populations should be expected. The absolute number of events were lower in our study, more accurately reflecting contemporary incidence of cardiovascular morbidity and death in the general population.

Third, we firmly believe that a category-based approach is the most appropriate in the evaluation of change in cardiac troponin, despite assertions that more sensitive statistical models may be derived by using a continuous approach. For hs-cTnI and even more so for hs-cTnT *(30)*, the biological and analytical variation is high and the use of a continuous approach leaves the question of whether actual change in biomarker concentrations has occurred.

Discrimination and reclassification

The incremental value of relative increases in hs-cTnI to established risk models and single-time point measurements of hs-cTnI was limited. Absolute increases in hs-cTnI surpassing thresholds within the reference interval (≥ 4.0ng/L for women and ≥ 6.0ng/L for men), on the other hand, provided strong improvements in NRI, as well as weaker improvements in IDI. The improvements provided by single-time point elevations in hs-cTnI were superior to those provided by delta values obtained from serial measurements. Using the most recent measurement of hs-cTnI in such a dichotomized manner, accordingly, may be preferred when predicting risk of incident cardiovascular disease. Nevertheless, considering the pronounced cardiovascular risk associated with cardiac troponin, we believe that an increase in cardiac troponin on serial sampling should merit increased vigilance with regard to investigation and possible preventive measures. Our data do not enable us to estimate the optimal interval for serial testing.

The impact of sex

Sex is one of the strongest determinants of cardiovascular risk and men generally develop cardiovascular disease a decade before their female counterparts. After menopause and in the later decades, the cardiovascular risk differences attributable to sex seem to diminish *(31, 32)*. Cardiac troponins are also affected by sex, and women exhibit lower concentrations than men for both hs-cTnT and hs-cTnI. The relative risk associated with cardiac troponins, however, appears stronger in women, especially for prediction of incident MI *(33)* and cardiovascular death *(13)* in presumably healthy subjects recruited from the general population.

Both absolute and relative increases in hs-cTnI were associated with unfavorable outcomes in the current study. For absolute changes, we used sex specific cut-offs as previously established. In the models constructed on relative changes in hs-cTnI, the association with risk was attenuated for women. These models were also adjusted for baseline hs-cTnI. As the prognostic impact of single-time point measurements of hs-cTnI is significantly stronger in women *(13, 33)*, it is not entirely surprising that this adjustment would attenuate the association with relative changes in hs-cTnI. Considering the weaker association with single-time point measurements of hs-cTnI in men, it is possible that men may benefit to a greater extent from serial measurements with calculation of delta values of cardiac troponins compared to women. However, given that the prognostic value of the most recent measurement tended to be stronger in women, the recommended frequency of measurement should probably be the same for both sexes.

Strengths and limitations

The current study has its strengths and limitations. The analyses are based on a substantial sample from a contemporary prospective cohort with a relatively large number of clinical end points assessed up to the current date. Concentrations of hs-cTnI were additionally measured with one of the most sensitive assays currently available. Observational bias cannot be excluded, as clinical end points were based on diagnosis codes from hospital records and not from a study end point adjudication committee. The lack of data on medication is an obvious limitation, especially considering the impact of lipid lowering agents on concentrations of cardiac troponins. Cardiac imaging data examining longitudinal changes in cardiac structure and function could have provided additional mechanistic insights to temporal

changes in hs-cTnI, as left ventricular mass strongly influences concentrations of cardiac troponin *(34)*. Although the assay used was one of the most sensitive on the market, the analytical precision was not as good in the low as it was in the medium to high portions of the reference interval. This is also reflected in the different proportions of subjects with detectable concentrations of hs-cTnI in HUNT 2 and HUNT 3. Variability between reagent lots for hs-cTnI is most likely the cause of this discrepancy *(35)*. Detection of an increase in concentrations is accordingly likely to be more robust and less influenced by noise, than detection of a reduction. This may have contributed to the attenuation of the association between reductions in hs-cTnI concentrations and outcome. Finally, given the observational nature of the study, we cannot rule out residual confounding influencing our results.

Conclusions

In a large contemporary cohort recruited from the general population, temporal increases in hs-cTnI were associated with increased risk of cardiovascular death and admission for MI and HF. For refinement of clinical risk prediction models, the most recent measurement of hs-cTnI was found to outperform serial measurements. Therefore, single-time point measurement should be preferred in clinical practice.

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Text tables

Table 1. Baseline characteristics at HUNT 3 according to relative change in cardiac troponin I from HUNT 2 to HUNT 3

	Change in cardiac troponin I					
	≥50% decrease		<50% change		≥50% increase	
	n	Value	n	Value	n	Value
Female sex, n (%)	1991	1241 (62.3)[c]	2396	1293 (54.0)	418	189 (45.2)[b]
Age, years	1991	51.6 (43.9-60.4)[c]	2396	59.5 (49.9-68.5)	418	61.5 (50.7-74.2)[b]
Current smoker, n (%)	1955	370 (18.9)[b]	2340	368 (15.7)	404	49 (12.1)[a]
Alcohol consumption, units/2 weeks	1206	3 (0-6)	1377	3 (0-7)	248	3 (0-8)
Body weight, kg	1989	77.4 (67.0-88.1)[c]	2387	78.8 (69.5-89.0)	411	80.1 (69.2-87.9)
BMI, kg/m^2	1989	26.4 (23.9-29.4)[c]	2386	27.0 (24.6-29.8)	411	26.6 (24.6-29.4)
Systolic blood pressure, mmHg	1990	126 (117-137)[c]	2392	136 (124-149)	417	139 (124-155)[a]
Diastolic blood pressure, mmHg	1990	73 (66-80)[c]	2392	76 (69-83)	417	75 (68-84)
Hypertension, n (%)	1990	622 (31.3)[c]	2392	1251 (52.3)	417	234 (56.1)
Diabetes mellitus, n (%)	1991	66 (3.3)	2396	100 (4.2)	418	27 (6.5)[a]
Glucose nonfasting, mg/dL[d]	1973	97 (88-106)[c]	2379	97 (90-110)	413	99 (90-112)
Triglycerides nonfasting, mg/dL[d]	1991	124 (89-186)[b]	2395	133 (89-186)	418	124 (89-177)[b]
Total cholesterol, mg/dL[d]	1973	220 (193-244)[c]	2379	224 (197-255)	412	217 (190-244)[c]
HDL cholesterol, mg/dL[d]	1973	50 (43-62)[b]	2379	50 (43-62)	412	54 (43-62)
eGFR, ml/min/1.73m^2	1991	83.8 (74.1-94.7)[c]	2395	77.7 (66.8-89.5)	418	75.7 (64.7-88.1)[a]
CRP, mg/L	1991	1.1 (0.5-2.5)[c]	2395	1.4 (0.7-2.7)	418	1.6 (0.8-3.0)[a]
Cardiac troponin I (HUNT 2), ng/L	1991	2.9 (2.1-4.0)[b]	2396	3.0 (2.2-4.2)	418	3.0 (1.8-4.6)
Cardiac troponin I (HUNT 3), ng/L	1991	0.6 (0.6-1.5)[c]	2396	2.3 (1.7-3.5)	418	6.5 (3.7-11.4)[c]

[a]*P*<0.05, [b]*P*<0.01, [c]*P*<0.001 versus <50% change, [d]To convert glucose concentrations from mg/dL to mmol/L, multiply by 0.05556. To convert triglyceride concentrations from mg/dL to mmol/L, multiply by 0.01129. To convert cholesterol concentrations from mg/dL to mmol/L, multiply by 0.02586.

Table 2. Determinants of relative change in cardiac troponin I from HUNT 2 to HUNT 3

	Odds ratio (95% CI)			
	Univariable		Multivariable	
	≥ 50% decrease	≥ 50% increase	≥ 50% decrease	≥ 50% increase
Female sex	1.41 (1.25-1.59)	0.70 (0.57-0.87)	2.12 (1.82-2.48)	0.56 (0.44-0.73)
Age	0.96 (0.95-0.96)	1.01 (1.01-1.02)	0.95 (0.94-0.96)	1.03 (1.02-1.04)
Current smoking	1.24 (1.08-1.42)	0.88 (0.69-1.14)	1.07 (0.93-1.25)	0.92 (0.71-1.20)
BMI	0.96 (0.94-0.97)	0.98 (0.96-1.01)	0.97 (0.95-0.99)	0.99 (0.96-1.02)
Hypertension	0.43 (0.38-0.49)	1.18 (0.96-1.46)	0.61 (0.52-0.71)	1.15 (0.91-1.46)
Diabetes mellitus	0.53 (0.29-0.96)	2.27 (1.21-4.25)	0.85 (0.45-1.61)	1.68 (0.86-3.26)
Total cholesterol	0.91 (0.86-0.95)	0.88 (0.81-0.97)	1.14 (1.07-1.22)	0.83 (0.75-0.93)
HDL cholesterol	0.81 (0.69-0.94)	1.05 (0.81-1.36)	0.66 (0.55-0.80)	1.19 (0.88-1.59)
eGFR	1.02 (1.02-1.03)	1.00 (0.99-1.01)	1.01 (1.00-1.01)	1.00 (0.99-1.01)
CRP	1.00 (0.98-1.01)	1.01 (0.99-1.03)	0.99 (0.98-1.01)	1.01 (0.99-1.03)
Cardiac troponin I	1.05 (0.95-1.15)	0.85 (0.72-1.00)	1.84 (1.62-2.08)	0.63 (0.51-0.78)

Odds ratio compared to participants with < 50% change. All independent determinants assessed at HUNT 2.

Table 3. Associations of changes in cardiac troponin I from HUNT 2 to HUNT 3 with incident myocardial infarction, heart failure, or cardiovascular death.

		≥50% decrease (1241 women, 750 men)	<50% change (1293 women, 1103 men)	≥50% increase (189 women, 229 men)
Number of events	Women	23	58	23
	Men	29	80	36
	Both sexes	52	138	59
Incidence rate (per 1000 patient years)	Women	2.1[b]	5.0	13.7[b]
	Men	4.2[a]	8.1	19.1[b]
	Both sexes	2.8[b]	6.4	16.9[b]
HR (unadjusted)	Women (n = 2723)	0.40 (0.25-0.65)	Reference	2.89 (1.78-4.68)
	Men (n = 2082)	0.52 (0.34-0.79)		2.37 (1.60-3.52)
	Both sexes (n = 4805)	0.44 (0.32-0.60)		2.65 (1.96-3.60)
HR (adjusted)	Women (n = 2614)	1.24 (0.72-2.14)	Reference	1.65 (0.90-3.01)
	Men (n = 2022)	1.11 (0.70-1.75)		1.65 (1.04-2.62)
	Both sexes (n = 4636)	1.19 (0.84-1.68)		1.68 (1.16-2.42)

	hs-cTnI < 4.0ng/L (♀), < 6.0ng/L (♂) (HUNT 2); hs-cTnI ≥ 4.0ng/L (♀), ≥ 6.0ng/L (♂) (HUNT 3)		hs-cTnI < 16.0ng/L (♀), < 34.0ng/L (♂) (HUNT 2); hs-cTnI ≥ 16.0ng/L (♀), ≥ 34.0ng/L (♂) (HUNT 3)	
	No (n = 3747)	Yes (n = 235)	No (n = 4721)	Yes (n = 49)
Number of events	128	33	235	10
Incidence rate (per 1000 patient years)	3.7	16.8[b]	5.5	25.1[b]

HR (unadjusted)	Reference	4.61 (3.14-6.76)	Reference	4.65 (2.47-8.75)
HR (adjusted)	Reference	1.77 (1.16-2.70)	Reference	3.01 (1.59-5.71)

	hs-cTnI ≥ 4.0ng/L (♀), ≥ 6.0ng/L (♂) (HUNT 3)		hs-cTnI ≥ 16.0ng/L (♀), ≥ 34.0ng/L (♂) (HUNT 3)	
	No (n = 4221)	Yes (n = 584)	No (n = 4741)	Yes (n = 64)
Number of events	162	87	237	12
Incidence rate (per 1000 patient years)	2.3	33.7[b]	5.5	23.2[b]
HR (unadjusted)	Reference	4.38 (3.38-5.69)	Reference	4.26 (2.39-7.62)
HR (adjusted)	Reference	1.71 (1.28-2.30)	Reference	2.32 (1.26-4.27)

[a]*P* < 0.01, [b]*P* < 0.001 compared to reference (<50% change or no elevation in concentrations of hs-cTnI). Adjusted model includes age, sex, total cholesterol and HDL cholesterol, history of hypertension and diabetes mellitus, current smoking, BMI, eGFR, CRP. Models with relative changes in hs-cTnI additionally adjusted for hs-cTnI measured at HUNT 3.

Table 4. Incremental prognostic value of cardiac troponin I to established risk prediction algorithms

		Net reclassification index	Integrated discrimination improvement	*c* statistics
Women	SCORE (reference)			0.854 (0.822-0.887)
	SCORE + hs-cTnI	0.674 (0.482-0.866)[c]	0.0263 (0.0092-0.0435)[b]	0.835 (0.795-0.874)
	SCORE + hs-cTnI+ Δ hs-cTnI	-0.203 (-0.397- -0.009)[a]	0.0007 (-0.0005-0.0018)	0.834 (0.794-0.874)
Men	SCORE (reference)			0.789 (0.755-0.823)
	SCORE + hs-cTnI	0.475 (0.307-0.643)[c]	0.0192 (0.0078-0.0306)[c]	0.763 (0.722-0.803)[a]
	SCORE + hs-cTnI+ Δ hs-cTnI	-0.092 (-0.255-0.070)	0.0008 (-0.0007-0.0022)	0.762 (0.722-0.802)[a]
Both sexes	SCORE (reference)			0.826 (0.803-0.849)
	SCORE + hs-cTnI	0.624 (0.498-0.750)[c]	0.0250 (0.0145-0.0356)[c]	0.804 (0.777-0.832)[a]
	SCORE + hs-cTnI+ Δ hs-cTnI	-0.159 (-0.282- -0.035)[a]	0.0008 (-0.0004-0.0017)	0.804 (0.776-0.803)[a]
Both sexes	SCORE (reference)			0.834 (0.806-0.861)
	SCORE + incident elevation hs-cTnI ≥ 4.0ng/L (♀) and ≥ 6.0ng/L (♂)	0.293 (0.168-0.418)[c]	0.0067 (-0.0001-0.0135)	0.827 (0.799-0.855)
	SCORE (reference)			0.830 (0.808-0.852)
	SCORE + incident elevation hs-cTnI ≥ 16.0ng/L (♀) and ≥ 34.0ng/L (♂)	0.068 (0.016-0.199)[a]	0.0053 (-0.0002-0.0107)	0.827 (0.805-0.849)[a]
	SCORE (reference)			0.826 (0.803-0.849)
	SCORE + single-time point elevation hs-cTnI ≥ 4.0ng/L (♀) and ≥ 6.0ng/L (♂)	0.466 (0.345-0.587)[c]	0.0093 (0.0029-0.0158)[b]	0.819 (0.797-0.841)
	SCORE (reference)			0.826 (0.803-0.849)

	SCORE + single-time point elevation hs-cTnI ≥ 16.0ng/L (♀) and ≥ 34.0ng/L (♂)	0.077 (0.022-0.132)[b]	0.0044 (-0.0004-0.0092)	0.826 (0.804-0.848)

Δ hs-cTnI, ≥50% increase in hs-cTnI vs rest. [a]*P*<0.05, [b]*P*<0.01, [c]*P*<0.001 compared to reference model.

Figure legends

Figure 1. Association of baseline age at HUNT 2 with risk of increasing concentrations hs-cTnI. Adjusted restricted cubic spline models centered at the median, 45.9 years (♀) and 45.2 years (♂). OR, odds ratio for trend above and below median.

Figure 2. Kaplan-Meier plots for the composite endpoint of cardiovascular death or admission for MI or HF. Subjects stratified according to **(A)** relative change in hs-cTnI from HUNT 2 to HUNT 3, **(B)** incident elevation ≥ 4.0 ng/L (♀), ≥ 6.0ng/L (♂) from HUNT 2 to HUNT 3 and **(C)** incident elevation ≥ 16.0ng/L (♀), ≥ 34.0ng/L (♂) from HUNT 2 to HUNT 3.