

Impact of Sex on the Prognostic Value of High-Sensitivity Cardiac Troponin I in the General Population: The HUNT Study

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BACKGROUND: A new, high-sensitivity assay for cardiac troponin I (hs-cTnI) permits evaluation of the prognostic value of cardiac troponins within the reference interval. Men have higher hs-cTnI concentrations than women, but the underlying pathophysiological mechanisms and prognostic implications are unclear. The aim of this study was to assess the potential impact of sex on the association between hs-cTnI and cardiovascular death.

METHODS: By use of the Architect STAT High-Sensitive Troponin assay, we measured hs-cTnI in 4431 men and 5281 women aged ≥ 20 years participating in the prospective observational Nord-Trøndelag Health Study (HUNT).

RESULTS: hs-cTnI was detectable in 98.5% of men and 94.7% of women. During a mean follow-up period of 13.9 years, 708 cardiovascular deaths were registered. hs-cTnI was associated with the incidence of cardiovascular death [adjusted hazard ratio (HR) per 1 SD in log hs-cTnI 1.23 (95% CI 1.15–1.31)], with higher relative risk in women than men [HR 1.44 (1.31–1.58) vs 1.10 (1.00–1.20); $P_{\text{interaction}} < 0.001$]. This finding was mediated by both lower risk associated with low hs-cTnI concentrations in women than in men and higher risk associated with high concentrations of hs-cTnI in women than in men. Male sex was associated with a higher risk of cardiovascular death [HR 1.28 (1.11–1.49)], but after adjustment for hs-cTnI, this association disappeared [HR 0.87 (0.75–1.02)].

CONCLUSIONS: The prognostic value of hs-cTnI concentrations in the general population is stronger in women

than in men. Subtle impairment of cardiovascular status may contribute to higher hs-cTnI concentrations in men, reflecting sex-dependent differences in cardiovascular risk.

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Important differences exist between men and women with respect to the prevalence of risk factors for and the incidence of cardiovascular events. For instance, for a given age, blood pressure is higher in men than in women (1); after puberty, left ventricular mass is greater in men than in women (2); and women generally develop cardiovascular disease at an older age than men (3).

The recent introduction of assays with enhanced analytical sensitivity allows accurate determination of very low concentrations of circulating cardiac troponins (4, 5). The use of these high-sensitivity assays has permitted enhanced characterization of the distribution and cross-sectional correlates of cardiac troponin concentrations. One consistent and potentially important observation made in these studies is that circulating concentrations of cardiac troponins are markedly higher in men than in women (6–12). For instance, for a new, highly sensitive assay for cardiac troponin I (hs-cTnI),¹¹ the 99th percentile values in a healthy reference population have been reported to be 15 ng/L in women and 36 ng/L in men (13). However, the underlying pathophysiological mechanisms and potential prognostic implications of the sex differences in cardiac troponin concentrations are unknown. The objectives of the current study, which uses a novel assay with high analytic sensitivity, were therefore (a) to assess the distribution of

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¹¹ Nonstandard abbreviations: hs-cTnI, high-sensitivity cardiac troponin I; HUNT, Nord-Trøndelag Health Study; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; ICD, *International Classification of Diseases*; AMI, acute myocardial infarction; HR, hazard ratio.

hs-cTnI concentrations across sexes in a large population-based epidemiological study in Norway, (b) to investigate whether the association of hs-cTnI and risk of cardiovascular death differs between women and men, and (c) to assess whether sex-dependent differences in cardiovascular risk are modified by hs-cTnI concentrations.

Materials and Methods

STUDY PARTICIPANTS

The Nord-Trøndelag Health Study (HUNT) is a large-scale, prospective, population-based cohort study conducted in the county of Nord-Trøndelag in Norway (14). We used data and serum samples from the second wave (HUNT 2) collected from August 1995 to June 1997. All 93 898 residents in the county aged ≥ 20 years were invited to participate in the study, and 65 215 (69%) accepted the invitation. The population is ethnically homogeneous (97% white) and shows modest migratory activity, i.e., annual net emigration is 0.3%. We selected a subsample of 9712 participants from 4 of 24 municipalities in the county for this hs-cTnI substudy. The main study and this substudy were both approved by the Regional Ethics Committee, and all participants provided written informed consent.

BASELINE DATA

Baseline investigations included health status questionnaires completed by the participants and physical examination and blood sampling by specially trained nurses. Clinical data collected in a standardized fashion included height, weight, and waist and hip circumference. Systolic and diastolic blood pressure was measured with an automated device (Dinamap 845 XT, Criticon) on the basis of oscillometry, and the average of the second and third measurements was used. Information concerning health status, medical history, and lifestyle factors was by self-report.

BLOOD SAMPLING PROCEDURES AND BIOCHEMICAL ASSAYS

Nonfasting samples of venous blood were centrifuged at room temperature, and serum was aspirated and frozen at -80°C . For hs-cTnI analysis, samples that had been thawed and refrozen once in 2008 and subsequently stored at -20°C were shipped on dry ice to Akershus University Hospital, Lørenskog, Norway. Prior studies have suggested that hs-cTnI concentrations are not affected by long-term storage or repeated freeze-thaw cycles (15, 16). Before analysis, thawed samples were centrifuged at 3000 relative centrifugal force for 30 min. We measured hs-cTnI with the Abbott Diagnostics Architect STAT High Sensitive Troponin assay, as described previously (17, 18). The limit of detection for this assay has been reported to be 1.2 ng/L (range 0–50 000 ng/L), with CV 10% at a concentration of 3.0 ng/L (19). Using control material from Abbott Diagnostics, we found a CV of 4.1% 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 (13). Concentrations 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, triglycerides, and creatinine in serum were measured by routine laboratory methods (14). Estimated glomerular filtration rate (eGFR) was calculated with the 4-variable Modification of Diet in Renal Disease equation (20). The concentration of C-reactive protein (CRP) was measured with a high-sensitivity assay, as described previously (21).

OUTCOMES

We obtained mortality status through December 31, 2011, by linking the HUNT database to the Cause of Death Registry of Statistics Norway, which provides the diagnosis stated as the primary cause of death on the death certificate. The primary outcome measure of the current study was time to cardiovascular death. Deaths were defined as cardiovascular if *International Classification of Diseases* (ICD) codes 390–459 (Ninth Revision) or I00–I99 (10th Revision) were recorded. A secondary outcome measure was time to mortality from all causes.

STATISTICAL ANALYSIS

We performed comparisons across sex-specific quartiles of hs-cTnI by ANOVA for continuous variables and the Cochran–Armitage test for categorical variables. We compared baseline characteristics and outcomes across sexes by ANOVA and χ^2 tests, as appropriate. We used Cox proportional hazards regression models to test the relationship between hs-cTnI and the time to events. For the primary outcome of cardiovascular death, participants were censored at the time of noncardiovascular death or, for survivors, on January 1, 2012. Likewise, for the end point death from all causes, survivors were censored on January 1, 2012. Cox multivariate models were adjusted for components of the Framingham Heart Study general cardiovascular risk profile, i.e., age, total and HDL cholesterol, systolic blood pressure, treatment of hypertension, smoking status, and diabetes status, as well as eGFR, history of acute myocardial infarction (AMI), and CRP. A potential interaction with sex was evaluated by creating interaction terms between hs-cTnI and sex and by testing for statistical significance in unadjusted and adjusted Cox proportional hazards models. We calculated estimates of the *c*-index with and without the addition of hs-cTnI according to the method of Pencina and d'Agostino (22). ROC curves for the ability to predict cardiovascular death were generated for men and women, and the optimal cutoffs were determined according to the Youden index. Cumula-

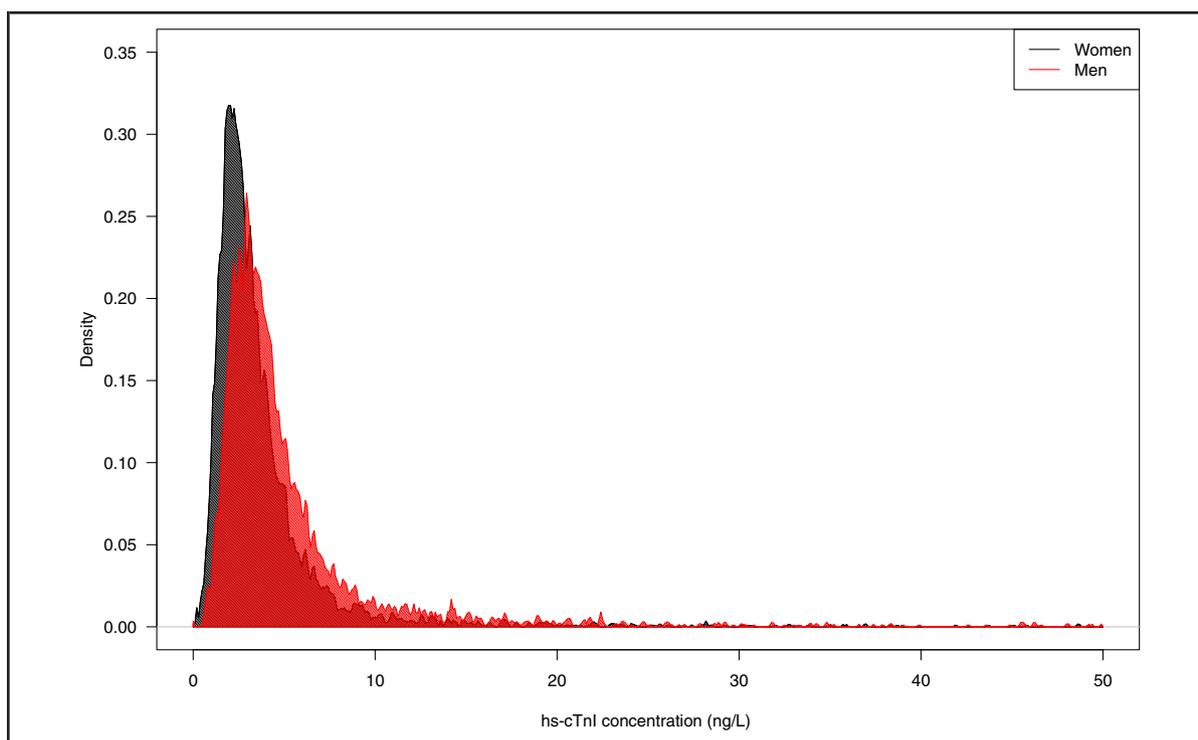


Fig. 1. Distributions of hs-cTnI in women and men in the general population.

hs-cTnI distributions differed significantly between men and women. The peak density in women was observed at a lower hs-cTnI concentration than in men.

tive incidence plots according to categories of hs-cTnI were generated. A P value <0.05 was considered to be statistically significant, and all tests were 2-sided. The SAS analysis system version 9.2, SPSS version 20.0, STATA version 12.0, and R version 3.0.2 were used for analyses. T. Omland, J.S. Benth, and S. Nygård had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Results

CHARACTERISTICS AT BASELINE

We measured circulating hs-cTnI concentrations in 4431 men and 5281 women. Concentrations at or above the limit of detection (i.e., 1.2 ng/L) were observed in 4366 (98.5%) men and 5003 (94.7%) women. The distributions of hs-cTnI concentrations in women and men are presented in Fig. 1. The 99th percentile concentrations of hs-cTnI in women and men without a history of cardiovascular disease, stroke, diabetes, or hypertension (4429 women and 3670 men) were 18.7 (95% CI 14.8–23.1) ng/L and 34.8 (95% CI 26.3–49.4) ng/L, respectively.

Patient characteristics according to sex-specific quartiles of hs-cTnI are summarized in Table 1. Increas-

ing values were positively associated with age, systolic blood pressure, total cholesterol, and CRP and inversely associated with eGFR and HDL cholesterol. The prevalence of diabetes mellitus increased from 1.1% in the lowest quartile to 5.9% in the highest quartile. Likewise, the prevalence of hypertension and prior AMI increased from 2.1% to 25.6% and from 0.5% to 8.5%, respectively, across quartiles.

Table 2 shows baseline patient characteristics stratified by sex. Mean systolic blood pressure and eGFR were higher in men than in women, whereas serum total and HDL cholesterol, as well as CRP, were slightly but significantly higher in women than in men. The prevalence of prior AMI was markedly higher in men than in women, whereas the prevalence of diabetes was only marginally higher in men. No difference in the prevalence of treated hypertension was observed.

SEX EFFECTS ON THE ASSOCIATION OF hs-cTnI AND CARDIOVASCULAR DEATH

During a mean follow-up of 13.9 years, 708 cardiovascular deaths were registered. In the overall study cohort, there was a strong and graded association between concentrations of hs-cTnI and the incidence of cardiovascular death. After adjustment for age, sex, total and HDL

Table 1. Baseline characteristics across increasing sex-specific quartiles of cTnI.

| Characteristic | Quartile 1 | | Quartile 2 | | Quartile 3 | | Quartile 4 | | P ^a | P for trend ^b |
|---|------------|------------------|------------|------------------|------------|------------------|------------|------------------|----------------|--------------------------|
| | n | Value | n | Value | n | Value | n | Value | | |
| cTnI range, ng/L | | | | | | | | | | |
| Men | 1087 | 0.0-2.6 | 1087 | 2.7-3.7 | 1120 | 3.8-5.6 | 1137 | 5.7-610.8 | | |
| Women | 1275 | 0.0-1.9 | 1264 | 2.0-2.7 | 1407 | 2.8-4.1 | 1335 | 4.2-363.1 | | |
| Mean age, years (SD) | 2360 | 39.2 (12.6) | 2351 | 44.7 (14.0) | 2527 | 52.0 (14.6) | 2472 | 63.2 (15.3) | <0.001 | <0.001 |
| Clinical characteristics | | | | | | | | | | |
| Diabetes mellitus, n (%) | 2360 | 26 (1.1) | 2349 | 31 (1.3) | 2522 | 73 (2.9) | 2459 | 146 (5.9) | <0.001 | <0.001 |
| Hypertension, n (%) | 2357 | 50 (2.1) | 2344 | 117 (5.0) | 2522 | 273 (10.8) | 2463 | 631 (25.6) | <0.001 | <0.001 |
| Myocardial infarction, n (%) | 2356 | 12 (0.5) | 2348 | 16 (0.7) | 2519 | 46 (1.8) | 2455 | 208 (8.5) | <0.001 | <0.001 |
| Current smoker, n (%) | 2345 | 807 (34.4) | 2330 | 689 (29.6) | 2500 | 746 (29.8) | 2434 | 492 (20.2) | <0.001 | 0.013 |
| Mean systolic blood pressure, mmHg (SD) | 2353 | 126.1 (15.4) | 2341 | 131.1 (17.6) | 2571 | 137.8 (20.1) | 2459 | 150.3 (24.9) | <0.001 | <0.001 |
| Laboratory measurements | | | | | | | | | | |
| Mean eGFR, mL · min ⁻¹ · (1.73 m ²) ⁻¹ (SD) | 2360 | 77.4 (12.0) | 2351 | 74.3 (12.1) | 2527 | 70.9 (12.2) | 2472 | 65.2 (14.4) | <0.001 | <0.001 |
| Mean cholesterol, mg/dL (SD) ^c | 2360 | 197 (40) | 2351 | 219 (41) | 2527 | 239 (44) | 2472 | 249 (50) | <0.001 | <0.001 |
| Mean HDL cholesterol, mg/dL (SD) | 2360 | 56 (15) | 2351 | 54 (15) | 2524 | 53 (15) | 2472 | 53 (16) | <0.001 | <0.001 |
| Geometric mean CRP, mg/L (95% CI) | 2360 | 0.61 (0.57-0.66) | 2350 | 0.81 (0.75-0.86) | 2525 | 0.96 (0.91-1.02) | 2469 | 1.32 (1.24-1.40) | <0.001 | <0.001 |

^a χ^2 test was used for categorical variables, ANOVA for continuous variables.

^b Cochran-Armitage test was used for categorical variables. For continuous variables, each case was assigned a median inside of each quartile, and the correlation was calculated between the new variable and the category number.

^c To convert cholesterol concentrations from mg/dL to mmol/L, multiply by 0.02586.

| Table 2. Characteristics according to sex. | | | | | |
|---|-------|------------------|------|------------------|----------------|
| Characteristic | Women | | Men | | P ^a |
| | n | Value | n | Value | |
| Age, years | 5281 | 50.2 (17.1) | 4429 | 49.7 (16.4) | 0.218 |
| Clinical characteristics | | | | | |
| Diabetes mellitus, n (%) | 5273 | 136 (2.6) | 4417 | 140 (3.2) | 0.047 |
| Hypertension, n (%) | 5266 | 600 (11.4) | 4420 | 471 (10.7) | 0.131 |
| Myocardial infarction, n (%) | 5270 | 73 (1.4) | 4408 | 209 (4.7) | <0.001 |
| Current smoking, n (%) | 5218 | 1528 (29.3) | 4391 | 1206 (27.5) | 0.026 |
| Mean systolic blood pressure, mmHg (SD) | 5261 | 134.8 (23.9) | 4409 | 136.5 (21.9) | <0.001 |
| Laboratory measurements | | | | | |
| Mean eGFR, mL · min ⁻¹ · (1.73 m ²) ⁻¹ (SD) | 5281 | 68.1 (12.7) | 4429 | 76.3 (13.0) | <0.001 |
| Mean cholesterol, mg/dL (SD) ^b | 5281 | 228 (50) | 4429 | 224 (46) | <0.001 |
| Mean HDL cholesterol, mg/dL (SD) | 5281 | 58 (15) | 4426 | 50 (12) | <0.001 |
| Geometric mean C-reactive protein, mg/L (95% CI) | 5275 | 0.96 (0.92-1.00) | 4429 | 0.82 (0.78-0.86) | <0.001 |

^a χ^2 test was used for categorical variables, ANOVA for continuous variables.
^b To convert cholesterol concentrations from mg/dL to mmol/L, multiply by 0.02586.

cholesterol, systolic blood pressure, treatment of hypertension, smoking status, and diabetes status, the association remained highly significant [hazard ratio (HR) 1.27 per 1 SD in log hs-cTnI (95% CI 1.19–1.35)], and it was only slightly attenuated after further adjustment for prior AMI, eGFR, and CRP [HR 1.23 (1.15–1.31)] (Table 3).

Although a graded association between hs-cTnI concentrations and the incidence of cardiovascular death was evident in both women and men (Fig. 2), a significant interaction between sex and continuous hs-cTnI concentrations was observed in both unadjusted ($P_{\text{interaction}} < 0.001$) and fully adjusted ($P_{\text{interaction}} < 0.001$) models.

Accordingly, in participants with hs-cTnI ≤ 3 ng/L, the risk in women was significantly lower than the risk in men ($P < 0.001$, log-rank test). Conversely, in participants with hs-cTnI > 9 ng/L, the risk was higher in women than in men ($P < 0.001$, log-rank test) (Fig. 2). The pattern with lower risk in women in the low concentration range and higher risk in the high concentration range was also evident when participants were divided in 4 categories according to the cutoffs 4, 16, and 30 ng/L (see Supplemental Fig. 1, which accompanies the online version of this article at <http://www.clinchem.org/content/vol61/issue4>). This difference was reflected in

| Table 3. Associations between baseline cTnI concentrations and outcomes. | | | | |
|--|----------------------|------------------|------------------|------------------|
| Outcome | HR (95% CI) | | | |
| | Model 1 ^a | Model 2 | Model 3 | Model 4 |
| Cardiovascular death | | | | |
| Both sexes | 1.93 (1.85-2.01) | 1.31 (1.23-1.40) | 1.27 (1.19-1.35) | 1.23 (1.15-1.31) |
| Women | 2.13 (2.02-2.25) | 1.51 (1.38-1.65) | 1.49 (1.36-1.64) | 1.44 (1.31-1.58) |
| Men | 1.73 (1.62-1.84) | 1.18 (1.08-1.29) | 1.14 (1.04-1.25) | 1.10 (1.00-1.20) |
| All-cause mortality | | | | |
| Both sexes | 1.80 (1.74-1.85) | 1.21 (1.28-1.45) | 1.19 (1.14-1.25) | 1.17 (1.12-1.22) |
| Women | 1.96 (1.88-2.03) | 1.36 (1.28-1.45) | 1.36 (1.27-1.46) | 1.33 (1.24-1.42) |
| Men | 1.64 (1.57-1.72) | 1.11 (1.04-1.17) | 1.10 (1.03-1.17) | 1.08 (1.01-1.15) |

^a Model 1, unadjusted; model 2, adjusted for sex and age; model 3, adjusted for sex, age, total and HDL cholesterol, systolic blood pressure, treatment of hypertension, smoking status, and diabetes status; model 4, adjusted for sex, age, total and HDL cholesterol, systolic blood pressure, treatment of hypertension, smoking status, diabetes status, estimated glomerular filtration rate, history of myocardial infarction, and C-reactive protein.

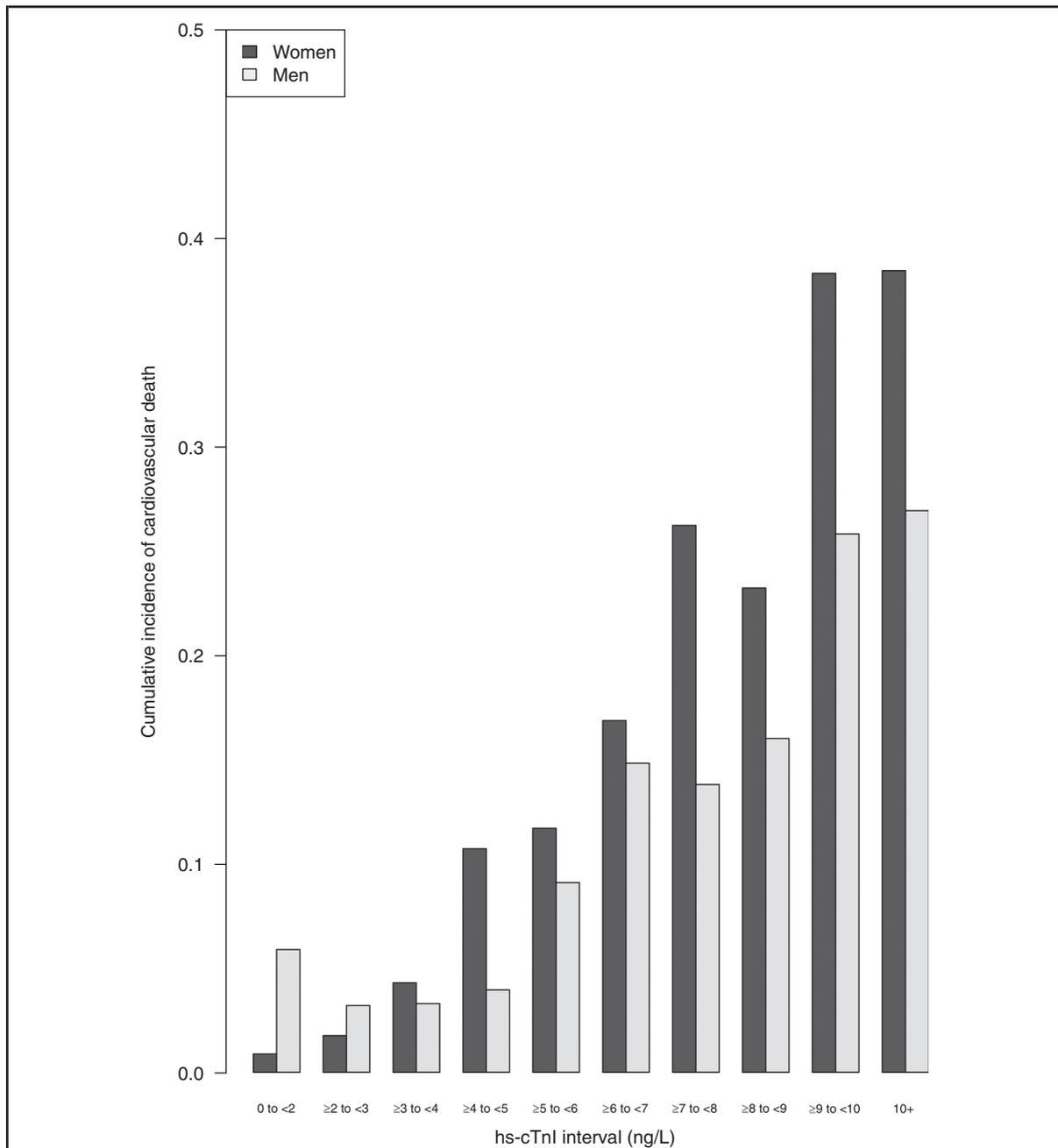


Fig. 2. Cardiovascular death in men vs women, stratified by categories of hs-cTnI.

The risk in the 2 lowest categories (hs-cTnI ≤ 3 ng/L) was significantly higher in men than in women ($P < 0.001$, log-rank test). Conversely, in the 2 highest hs-cTnI concentration categories (hs-cTnI > 9 ng/L), the risk was significantly higher in women than in men ($P < 0.001$, log-rank test). Note that the categories are not specific for sex.

the results of Cox regression analyses stratified by sex, in which the unadjusted risk of cardiovascular death associated with a 1SD increase in the log of hs-cTnI was higher for women than for men [HR 2.13 (2.02–2.25) vs 1.73 (1.62–1.84)] (Table 3, Model 1). This difference per-

sisted after multivariate adjustment [HR 1.44 (1.31–1.58) in women vs 1.10 (1.00–1.20) in men] (Table 3, Model 4). Cumulative incidence plots by hs-cTnI quartiles in men and women are shown in Fig. 3. Raw data on the cumulative incidence of cardiovascular

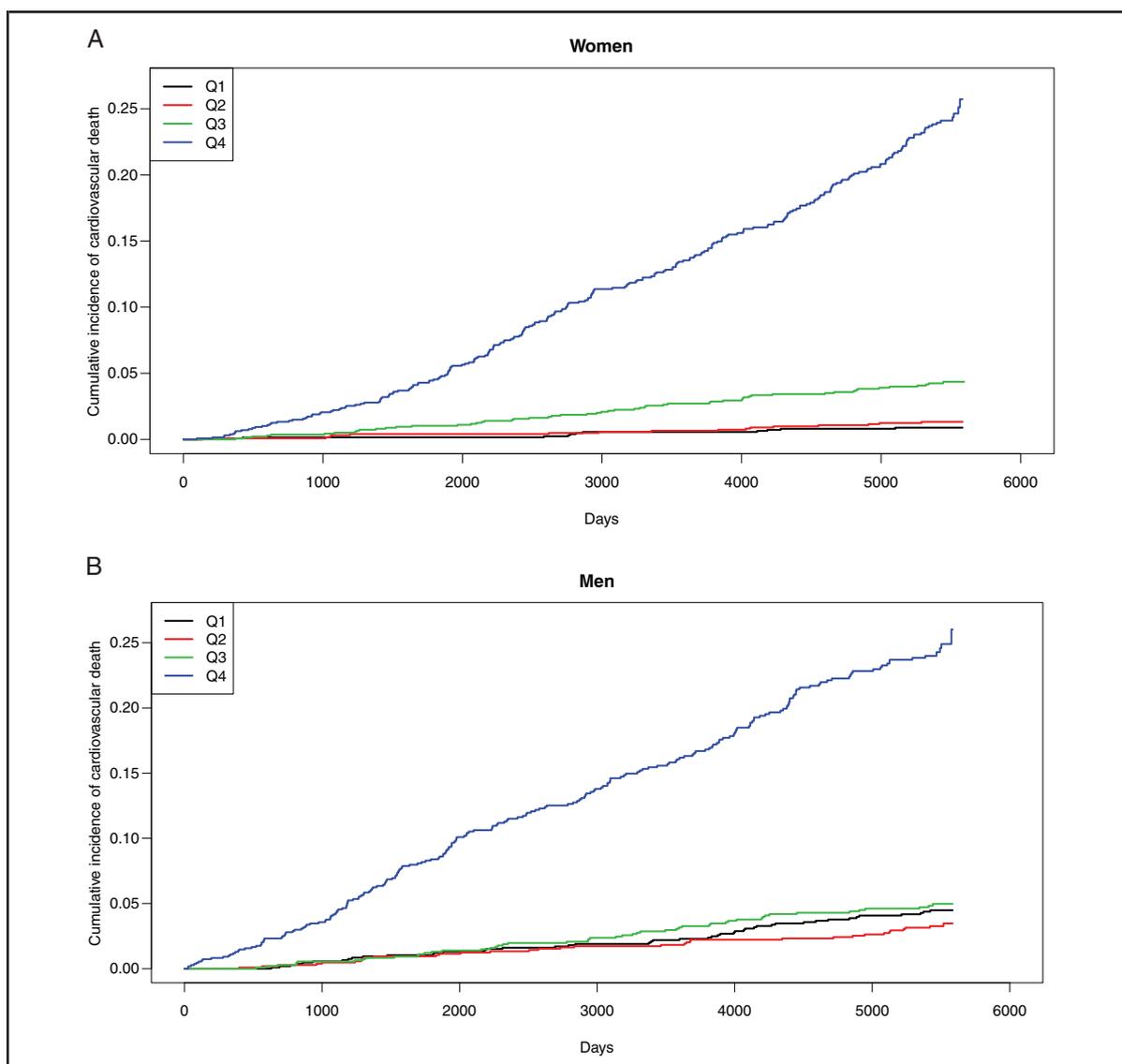


Fig. 3. Cumulative incidence of cardiovascular death in women (A) and men (B) on the basis of the Nelson-Aalen estimator.

Concentrations of hs-cTnI were divided into quartile 1 (<2.0 ng/L in women, <2.7 ng/L in men), quartile 2 (2.0–2.8 ng/L in women, 2.7–3.8 ng/L in men), quartile 3 (2.8–4.2 ng/L in women, 3.8–5.7 ng/L in men), and quartile 4 (>4.2 ng/L in women, >5.7 ng/L in men).

death and hs-cTnI concentrations in different age strata in men and women are presented in online Supplemental Table 1.

Lending further support to the impact of sex on the prognostic value of hs-cTnI, the *c*-index for the prediction of cardiovascular death by hs-cTnI was 0.836 (0.815–0.858) in women and 0.725 (0.694–0.756) in men ($P < 0.0001$). ROC curves for the ability of hs-cTnI to discriminate between survivors and nonsurvivors are presented in Fig. 4. hs-cTnI concentrations were significantly higher in men than in women among participants without the end point cardiovascular death [median

(Q1–Q3): 3.7 (2.6–5.3) vs 2.7 (1.9–3.9) ng/L, $P < 0.0001$], whereas there was no significant difference between men and women in those with the end point cardiovascular death [6.8 (4.0–12.2) vs 6.1 (4.1–10.0) ng/L, $P = 0.22$]. The cutoffs providing optimal discrimination concerning the incidence of cardiovascular death on the basis of the Youden index were 3.85 ng/L in women and 5.65 ng/L in men (Fig. 4). With a cutoff suggested by findings in patients with acute chest pain (23), the unadjusted HR of participants with hs-cTnI concentrations <4 ng/L vs ≥ 4 ng/L was 11.7 (95% CI 9.0–15.3) in women and 3.9 (95% CI 3.1–5.0) in men.

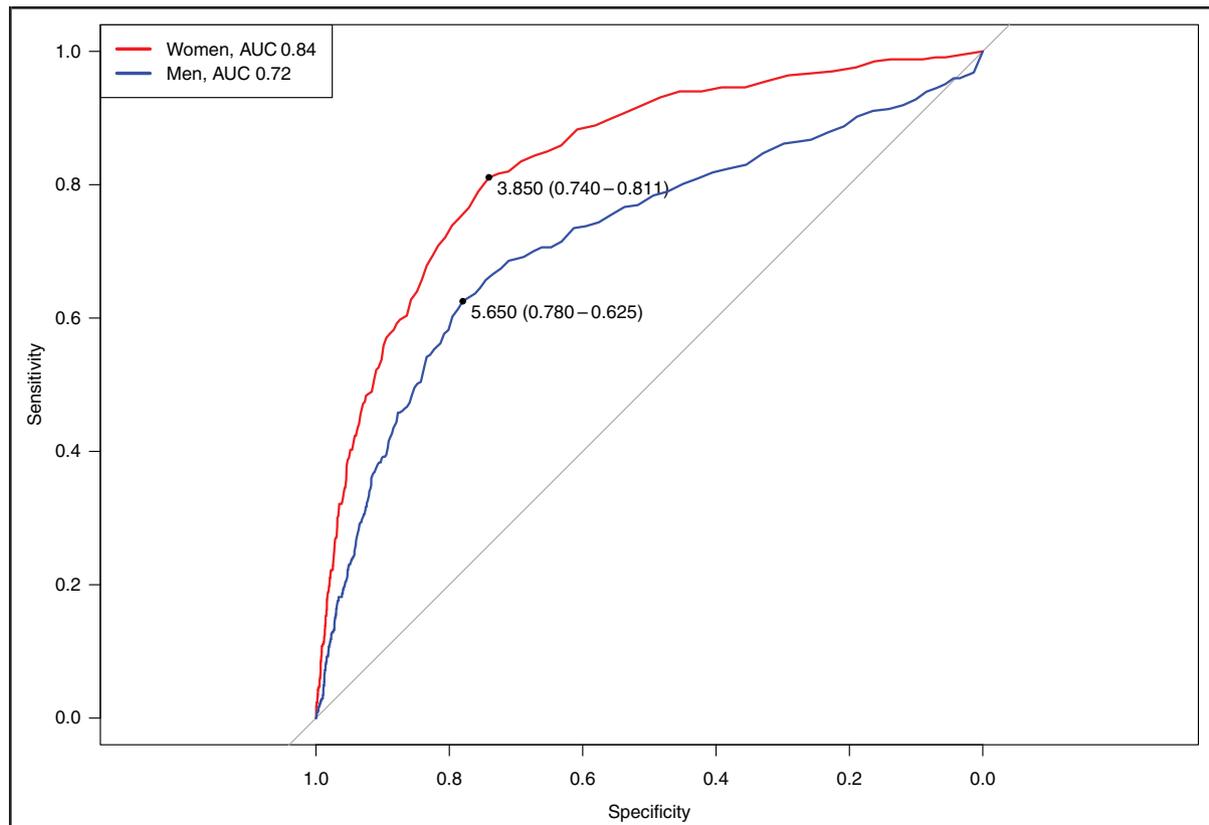


Fig. 4. ROC curves for the ability of hs-cTnI to predict cardiovascular death in men and women.

Areas under the curves were 0.84 (0.81–0.86) in women and 0.72 (0.69–0.75) in men ($P < 0.0001$). The cutoffs providing optimal discriminatory power were 3.85 ng/L (specificity 0.740, sensitivity 0.811) in women and 6.65 ng/L (specificity 0.780, sensitivity 0.625) in men.

The cumulative incidences of cardiovascular death in men and women stratified by this cutoff are depicted in online Supplemental Fig. 2. Adding log hs-cTnI to the multivariate model that included the variables male sex, age, total and HDL cholesterol, systolic blood pressure, treatment of hypertension, smoking status, diabetes status, eGFR, history of myocardial infarction, and CRP resulted in a small but statistically significant increase in the c -index [0.937 (0.929–0.946) vs 0.934 (0.925–0.943); $P = 0.011$] in women, whereas no significant effect on the c -index was observed in men.

We also evaluated the impact of hs-cTnI on the association between sex and cardiovascular mortality. In unadjusted analysis, male sex was associated with a significantly higher risk of cardiovascular death [HR 1.28 (1.11–1.49)], but after adjustment for hs-cTnI, male sex was no longer associated with increased risk [HR 0.87 (0.75–1.02)].

ASSOCIATION WITH DEATH FROM ALL CAUSES

During follow-up, there were 1689 deaths from all causes. In the total sample, hs-cTnI was strongly associated with death from all causes, by both univariate [HR

1.80 per 1 SD in log hs-cTnI (95% CI 1.74–1.85)] and multivariate [HR 1.17 (1.12–1.22)] analyses. In line with the results for cardiovascular mortality, the strength of the association with the incidence of death from all causes tended to be stronger in women than in men (Table 3). The c -index for the prediction of mortality from all causes by hs-cTnI was 0.783 (0.771–0.795) in women and 0.702 (0.690–0.714) in men. Adding hs-cTnI to the multivariate model that included the variables sex, age, total and HDL cholesterol, systolic blood pressure, treatment of hypertension, smoking status, diabetes status, eGFR, history of myocardial infarction, and CRP resulted in a small but statistically significant increase in the c -index in women [0.878 (0.867–0.888) vs 0.875 (0.864–0.886); $P = 0.003$], but no significant effect was observed in men.

Discussion

The salient findings of the current study are that cTnI concentrations, measured with a new highly sensitive assay that permits precise quantification of concentrations

across the reference interval, are markedly higher in men than in women and that the association between hs-cTnI and the risk of cardiovascular death is significantly modified by sex. Thus, the association between hs-cTnI and the incidence of cardiovascular death was stronger in women than in men. This was reflected by a highly significant interaction in both unadjusted and adjusted analyses. The interaction by sex appeared to be driven both by lower risk of cardiovascular death in women with low hs-cTnI concentrations and by higher risk of women in the high concentration range. A similar pattern was observed for the secondary end point all-cause mortality. These findings, combined with the observation that the increased cardiovascular risk in men was attenuated after adjustment for hs-cTnI, suggest that hs-cTnI may represent an index of early subclinical differences in cardiac structure and function between men and women that translate into distinct cardiovascular risk profiles between sexes over long-term follow-up.

HIGH-SENSITIVITY CARDIAC TROPONIN ASSAYS

In clinical practice, measurement of cardiac troponins has been used to confirm the presence or absence of myocardial necrosis, typically in the setting of acute chest pain (24). Challenging the paradigm that cardiac troponins are found circulating only in pathologic states, very low concentrations of cardiac troponins have recently been found circulating in individuals in the general population without a history of acute or chronic cardiovascular disease (6–12). The mechanisms responsible for chronic low-level troponin release are not clear, but processes such as cardiomyocyte hypertrophy, apoptosis, increased physiological cell turnover, and diffuse myocardial fibrosis may contribute (5, 25). In prior population-based epidemiological studies, we have documented an association between circulating hs-cTnI and indices of left ventricular function and anatomy (6, 26), suggesting that increased left ventricular stress and mass are important determinants of circulating concentrations of cardiac troponin. These data are supported by findings in individuals with established cardiovascular disease (27).

hs-cTnI REFLECTS SEX-DEPENDENT DIFFERENCES IN CARDIOVASCULAR RISK

Several factors may contribute to the differential prognostic value of hs-cTnI in men and women. It is well established that adult men have greater left ventricular mass than women (2), and this observation has commonly been attributed to the greater body mass of men. However, men also have higher blood pressure at a given age than women (1), as well as higher sympathetic nervous system activity (28). In addition, sex steroid hormones such as estrogen may attenuate cardiomyocyte and left ventricular hypertrophy (29). Accordingly, premenopausal women will commonly have low cardiac

mass and hearts without subtle pathologic structural changes. This phenotype will be reflected in very low concentrations of circulating cardiac troponins and a correspondingly low risk of cardiovascular death. In contrast, men at the same age will tend to have both higher left ventricular mass and subtle structural abnormalities such as mild fibrotic changes as a result of higher blood pressure and possible direct effects of higher sympathetic tone and sex hormones. Combined, these factors may lead to higher concentrations of circulating cardiac troponins in men than in women. At the same time, younger men may be at increased risk of acute coronary events that are not directly linked to structural pathology of the myocardium and, thus, are not accurately reflected in circulating cardiac troponin concentrations. This theory is supported by the observation that cardiac troponins are only weakly associated with the incidence of myocardial infarction in patients with stable coronary artery disease (17, 30–32). Combined, these factors may contribute to the closer association between hs-cTnI values in the low concentration range and outcome in women than in men.

For concentrations in the upper part of the reference interval, we observed that for a given hs-cTnI value, the risk of cardiovascular death was higher in women than in men. A potential explanation for this observation, given that left ventricular mass in general is lower in women than in men, is that in elderly women myocardial structural pathology may be more severe than in men with similar hs-cTnI values. In other words, the relative contribution of left ventricular mass per se vs left ventricular structural pathology to circulating troponin concentrations may differ between sexes. In addition, the higher incidence in elderly women of diastolic heart failure, a condition with limited therapeutic options, and the potential disparity in treatment and recognition of cardiovascular disease between men and women (33) may contribute to higher risk in women for a given hs-cTnI concentration. Notably, a similar pattern of increased risk discrimination of hs-cTnI in women than in men has recently been observed in patients with non-ST-elevation acute coronary syndrome (34) and patients presenting to the emergency department with chest pain (35).

Interestingly, this study's higher crude risk of cardiovascular death in men than in women was neutralized by adjustment for hs-cTnI concentrations. This observation lends further support to the theory that hs-cTnI concentrations in the general population represent an index of structural and functional myocardial alterations that are both associated with increased risk and more prevalent in men than in women.

STRENGTHS AND LIMITATIONS

Strengths of the current study include the population-based design, large sample size, long duration of follow-up, and the subsequent large number of end points. The

classification of cardiovascular deaths was based on diagnoses of death certificates, and only a minor fraction of these were based on autopsies. Accordingly, some misclassification of cause of death may have occurred, but this is unlikely to affect the differential strength of the associations between men and women. The study population was ethnically homogeneous, and the results may not be generalizable to other ethnicities. A long duration from blood sampling to biochemical analysis may potentially have resulted in some degree of degradation of cTnI. However, we observed a proportion of individuals with hs-cTnI concentrations above the limit of detection and sex-specific 99th hs-cTnI percentile values comparable to those previously reported in samples that were analyzed soon after blood collection (13), suggesting that no substantial degradation occurred during storage. Moreover, it is unlikely that any degradation would explain the sex-specific differences observed. A potential limitation of the current study is the lack of information concerning statin use. Statin use has been reported to slightly reduce circulating hs-cTnI concentrations and has been associated with reduced risk of cardiovascular events (36); therefore, it could theoretically be a confounder of the association between hs-cTnI concentrations and outcome. However, the rate of statin use was low (probably <5%) in the adult Norwegian population at the time of the HUNT 2 baseline examination (37), and most users were probably patients with a history of myocardial infarction or diabetes, factors that already have been adjusted for in our multivariate model. Finally, cardiac imaging data and estimation of left ventricular mass, a potential mediator of the association between hs-cTnI and outcome, would have provided further mechanistic insight into the observed differences in troponin concentrations and prognostic value between sexes.

Conclusions and Implications

The current prospective, observational, population-based study demonstrates a robust and graded association between hs-cTnI concentrations and the risk of cardiovascular death. The increment in risk was evident from concentrations starting in the lower end of the reference interval and appeared to increase linearly with increasing concentrations. Marked differences in hs-cTnI concentration were observed between sexes, and the association

between hs-cTnI concentrations and cardiovascular death was modified by sex, being stronger in women than in men. Accordingly, these findings favor the use of different cutoff values for risk stratification purposes in women and men. Although we used a new, highly sensitive assay for cardiac troponin I in the current study, it is likely that the sex differences observed can be extrapolated to other cardiac troponin assays with similar analytical sensitivity. As an equally important corollary observation in the current study, the increased cardiovascular risk associated with male sex was attenuated after adjustment for hs-cTnI, suggesting that differences in the burden of subclinical cardiac injury may explain some of the differences in long-term cardiovascular disease outcomes between men and women. New studies that include phenotypic characterization with contemporary methods of cardiac imaging, such as cardiac magnetic resonance imaging, will be needed to confirm this theory. Finally, future evaluation of high-sensitivity cardiac troponin assays as potential screening tools for identification of asymptomatic individuals at high risk of cardiovascular death should take into account the impact of sex on the prognostic value of these assays.

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