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High-Sensitivity Troponin-T and Cardiovascular Outcomes in the Community: Differences Between Women and Men

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Abstract

Objective: To evaluate associations of high-sensitivity cardiac troponin-T (cTnT) with cardiovascular disease (CVD), heart failure (HF), and mortality in community-dwelling women and men.

Participants and Methods: A total of 8226 adults from the Prevention of Renal and Vascular End-stage Disease (PREVEND) cohort (1997–1998) were enrolled in a prospective observational study (mean age: 49 years; 50.2% women). Sex-specific associations of cTnT levels with future clinical outcomes were evaluated using adjusted Cox-regression models.

Results: Measurable cTnT levels (≥ 3 ng/L) were detected in 1102 women (26.7%) and in 2396 men (58.5%). Baseline cTnT levels were associated with a greater risk of developing CVD in women than men [Hazard ratio (HR)_{women}, 1.48 per unit increase in $\log_2$ -cTnT; 95% CI, 1.21 to 1.81 vs HR_{men}, 1.20; 95% CI, 1.07 to 1.35; $P_{interaction} < .001$]. Similar sex-related differences were observed for HF ($P_{interaction} = .005$) and mortality ($P_{interaction} = .008$). Further, compared with referent category (cTnT < 3 ng/L), women with cTnT levels greater than or equal to 6 ng/L had a significantly increased risk for CVD (HR, 2.30; 95% CI, 1.45 to 3.64), HF (HR, 2.86; 95% CI, 1.41 to 5.80), and mortality (HR, 2.65; 95% CI, 1.52 to 4.61), whereas men with cTnT levels greater than or equal to 6 ng/L had a significantly increased risk only for CVD (HR, 1.51; 95% CI, 1.07 to 2.13).

Conclusion: Baseline cTnT levels were associated with future CVD, HF, and mortality in both sexes, and these associations were stronger in women. Future studies are needed to determine the value of cTnT in early diagnosis of CVD, particularly in women.

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Cardiac troponins (cTns) have revolutionized the diagnosis of myocardial infarction (MI), particularly with the introduction of high-sensitivity assays.¹⁻³ It is now known that even minor elevations in plasma cTn levels reflect subtle myocardial damage, increasing the risk of progression to overt cardiovascular disease (CVD).^{4,5}

Traditionally, CVD has been considered to be a male-predominant disease; however, females are equally affected with the burden

of CVD, particularly in later stages of life.^{6,7} In fact, CVD is the leading cause of mortality in women, surpassing cancer.^{8,9} Therefore, preventing heart disease is of paramount importance, particularly in women.

Current evidence strongly highlights the value of cTns in prevention of CVD, for instance, in predicting the risk of developing cardiovascular events¹⁰ and heart failure (HF).¹¹ Two previous studies examined associations of high-sensitivity cardiac troponin-I (cTnI) with cardiovascular outcomes in the

general population, showing stronger associations with incident MI and cardiovascular mortality in women.^{12,13} However, there is a lack of studies evaluating sex-related differences in associations of cTnT with clinical outcomes.

We postulated that baseline cTnT measurements would differentially relate to CVD, HF, and all-cause mortality in community-dwelling women and men. The objective of our study was therefore to investigate sex-specific associations of cTnT with incident CVD, HF, and all-cause mortality, focusing on women.

PARTICIPANTS AND METHODS

The Prevention of Renal and Vascular End-stage Disease (PREVEND) study (1997–1998) is a Dutch cohort taken from the general population of Groningen, the Netherlands. This study was designed to prospectively evaluate whether increased urinary albumin excretion (UAE > 10 mg/L) in community-dwelling individuals was associated with cardiovascular and renal disease.^{14–16} In brief, all inhabitants from Groningen, aged 28 to 75 years were asked to respond to a short questionnaire and provide early-morning urine samples (N=85,421), and 40,856 individuals (47.8%) responded. Responders with UAE greater than or equal to 10 mg/L (n=7786) as well as a randomly selected control group with UAE less than 10 mg/L (n=3395) were invited to the outpatient clinic for comprehensive health assessment including filling out questionnaires, anthropometry, fasting blood draw, and urine sampling. Individuals with type-1 diabetes (defined as insulin requirement), pregnant women (self-reported), and unwilling subjects were excluded from the study. A final total of 6000 individuals with UAE greater than or equal to 10 mg/L and 2592 individuals with UAE less than 10 mg/L underwent further investigation and constitute the baseline PREVEND cohort (N=8592). From the baseline cohort, 366 participants with missing cTnT measurements were excluded, leaving 8226 participants for final analysis. The current study conformed to the principles drafted in the Helsinki

declaration. Local medical ethical committee approval was obtained and informed consent was provided by all participants.

Baseline Measurements and Covariate Definitions

Baseline plasma samples were aliquoted and stored immediately after collection at -80°C until analysis.^{17–20} Plasma cTnT was measured using a fifth-generation high-sensitivity assay (Roche modular E170, Roche Diagnostics, Mannheim, Germany), which has a 99th percentile concentration of 14 ng/L with a corresponding coefficient of variation less than 10% at 13 ng/L.^{21,22} Limit of blank (LoB) and limit of detection (LoD) have been determined to be 3 ng/L and 5 ng/L, respectively.²¹ Plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured on the Roche Modular E170 (Roche Diagnostics) with commercially available electrochemiluminescent sandwich immunoassay.^{17,23} UAE was measured by nephelometry, with a threshold of 2.3 mg/L (BNII; Dade Behring Diagnostics, Marburg, Germany).^{17,18} Further details on assays relevant to the current study are found elsewhere,^{17,18,24} and also in [Supplementary Data](http://www.mayoclinicproceedings.org) (available online at <http://www.mayoclinicproceedings.org>).

Body-mass index (BMI) was calculated as the ratio between weight and height-squared (kg/m²). Smoking was defined as self-reported current smoking or smoking cessation within the previous year. Blood pressure (BP) was measured 10 times during 10 min using an automatic Dinamap XL Model 9300 series; BP was calculated as the mean of the last two measurements. Hypertension was defined as systolic BP greater than 140 mm Hg, diastolic BP greater than 90 mm Hg, or self-reported antihypertensive medication usage. Type-2 diabetes was defined as a fasting plasma glucose greater than or equal to 7.0 mmol/L (126 mg/dL), random plasma glucose greater than or equal to 11.1 mmol/L (200 mg/dL), self-reporting of a physician diagnosis, or record of glucose-lowering medication use obtained from central pharmacy registry. Hypercholesterolemia was defined as total

cholesterol greater than or equal to 6.5 mmol/L (251 mg/dL) or total cholesterol greater than or equal to 5.0 mmol/L (193 mg/dL) if a history of MI was present or when lipid-lowering medication was used. History of MI and stroke (CVD history) were based on subject's medical history derived from a structured questionnaire (ie, hospitalization ≥ 3 days as a result of this condition); this was complemented by a review of the medical report. Left ventricular hypertrophy (LVH) was defined using the Cornell (electrocardiogram) criteria: $RaVL + SV3$ (6 mm added in women) $\times$ QRS duration; a threshold of 2440 mm $\times$ ms was used to classify LVH.¹⁸ The estimated glomerular filtration rate (eGFR) was calculated using the chronic kidney disease epidemiology collaboration equation.²⁵

Follow-up

The follow-up duration was calculated as the time between the baseline visit to the last contact date, death, or December 31, 2010, whichever came first.

Ascertainment of Clinical Endpoints

Primary endpoint was incident CVD which was defined as cardiovascular events, HF, or death due to cardiovascular causes. In secondary analyses, associations of cTnT with HF and all-cause mortality were evaluated. In additional secondary analyses, associations of cTnT with HF subtypes were evaluated. Information on hospitalization for cardiovascular morbidity was retrieved from the Dutch national registry of hospital discharge diagnoses (PRISMANT). Data were coded according to the International Classification of Diseases, Ninth Revision (ICD-9). Cardiovascular events included acute MI (ICD-9 code 410), acute and subacute ischemic heart disease (411), hemorrhagic stroke (430, 431, and 432), ischemic stroke (433 and 434), and vascular interventions such as coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, bypass grafting of aorta, and peripheral vessels. HF endpoint was adjudicated by a committee of HF experts. Based on left ventricular ejection fraction (LVEF), HF cases

were further categorized into reduced (HFrEF, LVEF < 40%) or preserved (HFpEF, LVEF $\geq 50\%$) ejection fraction. Further details can be found elsewhere²⁴ and also in [Supplementary Data](#) (available online at <http://www.mayoclinicproceedings.org>). Data concerning mortality were obtained by record linkage with the Dutch Central Bureau of Statistics.

Statistical Analyses

Normally distributed data are presented as means $\pm$ SD and non-normally distributed data as medians, Q1–Q3 (50th percentile, 25th–75th percentile). Categorical variables are represented as percentages. cTnT was modeled as a continuous as well as a categorical variable. In continuous models, a value of 2.5 was assigned for cTnT concentrations less than LoB.^{24,26} Continuous variables were compared using analysis of variance (normal distribution) or the Kruskal-Wallis test (non-normal distribution). Categorical variables were compared using Pearson's χ^2 test.

Outcome analyses were performed separately in males and females. We used three Cox-regression models to relate cTnT levels with clinical outcomes: (1) univariate analyses; (2) adjusting for age, smoking, hypertension, hypercholesterolemia, type-2 diabetes, BMI, CVD history, and UAE; and (3) also adjusting for NT-proBNP. Sex-pooled models also adjusted for sex, and there was a significant sex $\times$ cTnT interaction for all endpoints. To account for overselection of subjects with increased UAE (>10 mg/L) in the PREVEND cohort, a design-based analysis was performed using statistical weights, which allows conclusions to be generalized to the general population.^{24,27,28} The proportionality assumption was checked by calculating the Schoenfeld residuals, and where needed time-varying covariates were included to avoid proportionality violations.²⁹ Skewed variables including cTnT, UAE, and NT-proBNP were log₂ transformed. Results are expressed as hazard ratios (HRs) with 95% CIs based on robust standard error estimates.

In exploratory analyses, Akaike information criteria (AIC) and *P* values based on likelihood-ratio tests were used to evaluate the incremental value of cTnT beyond predictor variables in the Framingham risk score (FRS) as well as in the PREVENT model for the primary outcome ie, whether addition of cTnT improved global model fit and whether this resulted in a parsimonious model.

Statistical analyses were performed using STATA version-14, and a *P* value less than .05 was considered to be significant.

RESULTS

Our study included 8226 participants, and 50.2% (n=4133) were women. Mean age in women was slightly lower compared with men (48±12 vs 50±13 years; *P*<.001). Baseline cTnT levels (median; Q1–Q3) were lower in women than in men (2.5; 2.5–3.0 vs 4.0; 2.5–6.0 ng/L; *P*<.001) (Supplementary Figure 1, available online at <http://www.mayoclinicproceedings.org>). Prevalence of measurable cTnT (≥3 ng/L) was also lower in women than men (26.7% versus 58.5%; *P*<.001).

Baseline Characteristics According to cTnT Category in Men and Women

We sex-stratified the population and evaluated associations of baseline characteristics across pre-specified cTnT categories (<3 ng/L, 3 to 6 ng/L and ≥6 ng/L) (Table 1). Individuals (ie, men and women) in higher cTnT categories were older, had a higher prevalence of CVD risk factors (except smoking), reduced renal function, and higher NT-proBNP, high-sensitivity C-reactive protein (hs-CRP), and UAE levels.

Sex-Specific Associations of cTnT With Longitudinal Outcomes

CVD. Total follow-up duration for CVD was 89,219 person-years. During a median (Q1–Q3) follow-up of 12.5 (10.8–12.9) years, 1093 individuals developed CVD, of which 348 (31.8%) were women. Sex-specific associations of individual predictor variables with the primary endpoint are

TABLE 1. Baseline Characteristics in Women and Men According to Troponin-T Category^{a,b}

Troponin-T categories	Women			Men		
	< 3 ng/L	3–6 ng/L	≥6 ng/L	<3 ng/L	3–6 ng/L	≥6 ng/L
n (%)	3031 (73)	708 (17)	394 (10)	1697 (41)	1212 (30)	1184 (29)
Troponin T, ng/L (Q1–Q3)	2.5 (2.5–2.5)	4.0 (3.0–4.0)	8.0 (6.0–10.0)	2.5 (2.5–2.5)	4.0 (3.0–5.0)	8.0 (7.0–11.0)
Age, years (SD)	45 (11)	54 (12)	63 (10)	45 (10)	49 (12)	60 (12)
Smoking (last 1 year), n (%)	1148 (38.0)	275 (39.1)	126 (32.1)	663 (39.2)	479 (39.8)	412 (34.9)
Hypertension, n (%)	600 (19.9)	274 (38.8)	285 (72.3)	409 (24.3)	451 (37.7)	743 (63.2)
Hypercholesterolemia, n (%)	611 (20.4)	260 (37.3)	189 (48.3)	392 (23.4)	329 (27.4)	376 (32.4)
Type-2 diabetes, n (%)	66 (2.2)	36 (5.1)	41 (10.5)	23 (1.4)	52 (4.3)	104 (8.9)
BMI, kg/m ² (SD)	25.4 (4.5)	27.0 (5.1)	27.9 (4.8)	25.7 (3.6)	26.1 (3.5)	27.3 (3.7)
CVD history, n (%)	118 (3.9)	33 (4.7)	41 (10.4)	75 (4.4)	90 (7.4)	196 (16.6)
LVH, n (%)	36 (1.2)	8 (1.1)	15 (3.8)	38 (2.2)	48 (4.0)	67 (5.7)
eGFR (mL/min per 1.73m ²) (SD)	99 (15)	89 (16)	78 (18)	101 (14)	95 (15)	82 (19)
UAE (mg/24 h) (Q1–Q3)	8 (6–13)	9 (6–15)	11 (7–26)	9 (7–15)	10 (7–20)	17 (8–43)
hs-CRP, mg/L (Q1–Q3)	1.2 (0.5–2.9)	1.6 (0.8–3.8)	2.1 (0.9–4.8)	1.0 (0.5–2.2)	1.1 (0.5–2.5)	1.8 (0.8–3.8)
NT-proBNP, ng/L (Q1–Q3)	46 (27–79)	56 (31–99)	89 (45–184)	16 (7–33)	23 (10–48)	53 (22–129)
<i>P</i> value	—	—	—	—	—	—

^aBMI = body-mass index; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; hs-CRP = high-sensitivity C-reactive protein; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B-type natriuretic peptide; UAE = urinary albumin excretion.

^bData are represented as mean (SD), median (Q1–Q3), or proportion n (%).

TABLE 2. Sex-Specific Associations of Continuous Troponin-T With Incident Outcomes^{a,b}

	No. of events	Unadjusted models		Adjusted for age and clinical risk factors ^c		Additionally adjusted for NT-proBNP		<i>P</i> _{interaction}
		HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value	
Cardiovascular disease								
Total	1093	1.82 (1.56-2.12)	<.001	1.37 (1.24-1.51)	<.001	1.25 (1.13-1.38)	<.001	<.001
Women	348	2.94 (2.47-3.50)	<.001	1.65 (1.36-2.00)	<.001	1.48 (1.21-1.81)	<.001	—
Men	745	1.72 (1.47-2.00)	<.001	1.30 (1.16-1.45)	<.001	1.20 (1.07-1.35)	.002	—
Heart failure								
Total	358	2.32 (2.00-2.70)	<.001	2.03 (1.75-2.35)	<.001	1.57 (1.25-1.96)	<.001	.005
Women	128	3.32 (2.75-4.01)	<.001	2.89 (1.33-6.27)	.007	1.88 (1.16-3.06)	.01	—
Men	230	2.13 (1.84-2.46)	<.001	1.85 (1.53-2.23)	<.001	1.53 (1.13-2.08)	.006	—
All-cause mortality								
Total	799	1.95 (1.72-2.20)	<.001	1.55 (1.24-1.95)	<.001	1.38 (1.09-1.73)	.006	.008
Women	249	2.96 (2.54-3.45)	<.001	2.36 (1.39-4.01)	.001	2.25 (1.33-3.81)	.002	—
Men	550	1.83 (1.63-2.06)	<.001	1.46 (1.09-1.96)	.01	1.25 (0.93-1.67)	.14	—

^aCI = confidence interval; HR = hazard ratio; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

^bHRs are presented per unit increase in log₂-transformed troponin-T.

^cClinical risk factors include smoking, hypertension, hypercholesterolemia, type-2 diabetes, body-mass index, history of cardiovascular disease, and urinary albumin excretion.

All sex-pooled models were adjusted for sex; *P*_{interaction} represents *P* value for interaction (sex*troponin-T) on a multiplicative scale in sex-pooled models.

provided in [Supplementary Table 1](#) (available online at <http://www.mayoclinicproceedings.org>). Associations of cTnT with incident CVD using crude as well as adjusted Cox-regression models are presented in [Table 2](#). In fully adjusted models, cTnT levels remained strongly associated with incident CVD in the total population (HR, 1.25; 95% CI, 1.13 to 1.38) and displayed a significant cTnT*sex interaction (*P*_{interaction}<.001). Effect sizes were greater in women (HR_{women}, 1.48; 95% CI, 1.21 to 1.81) compared with men (HR_{men}, 1.20; 95% CI, 1.07 to 1.35) ([Table 2](#)).

We performed several sensitivity analyses ([Supplementary Table 2](#), available online at <http://www.mayoclinicproceedings.org>). First, excluding individuals with cTnT greater than or equal to 50 ng/L (n=10) did not materially change our results. Second, additional adjustment for LVH, hs-CRP, and eGFR did not also materially change the results. Third, individuals with cTnT concentrations less than LoB were assigned a value of (1) 1.5 ng/L (as suggested by D'Angelo et al^{30,31}; and (2) 1.5 ng/L in women and 2.5 ng/L in men. Essentially, similar results were obtained.

In exploratory analyses, we used likelihood-based measures to evaluate the sex-specific incremental value of cTnT beyond the Framingham CVD risk prediction model. Adding cTnT improved the Framingham model in both sexes, as evidenced by reduction in AIC indices. Reduction in prediction error was slightly greater in women compared with men ($\Delta\text{AIC}_{\text{women}} = -23.1$; *P*<.001 versus $\Delta\text{AIC}_{\text{men}} = -18.5$; *P*<.001) ([Supplementary Table 3](#), available online at <http://www.mayoclinicproceedings.org>). We further evaluated the incremental value of cTnT added to the PREVENT model that also included NT-proBNP. Again, reduction in AIC was greater in women compared with men ($\Delta\text{AIC}_{\text{women}} = -21.1$; *P*<.001 versus $\Delta\text{AIC}_{\text{men}} = -12.5$; *P*<.001) ([Supplementary Table 3](#)).

HF. Total follow-up duration for HF was 92,678 person-years. During a median (Q1-Q3) follow-up of 12.6 (12.2-12.9) years, 358 individuals developed HF, of which 128 (35.8%) were women. Among incident HF cases, 229 were classified as HFREF, of which 60 (26.2%) were women, and 122

were classified as HFpEF, of which 64 (52.5%) were women. Higher cTnT levels were associated with a ~two-fold increased risk of developing HF in women compared with a 53% increased risk in men ($HR_{\text{women}}, 1.88$; 95% CI, 1.16 to 3.06 versus $HR_{\text{men}}, 1.53$; 95% CI, 1.13 to 2.08; $P_{\text{interaction}} = .005$). Among HF subtypes, associations of cTnT levels with incident HFrEF were stronger in women than men ($P_{\text{interaction}} = .004$). Sex-related differences were not observed for HFpEF ($P_{\text{interaction}} = .53$).

Mortality. Total follow-up duration for all-cause mortality was 94,044 person-years. During a median (Q1-Q3) follow-up of 12.6 (12.3-12.9) years, 799 deaths were recorded, of which 249 deaths (31.2%) occurred in women. cTnT levels were significantly associated with all-cause mortality in the general population ($P = .006$), and these associations were stronger in women than men ($P_{\text{interaction}} = .008$) (Table 2).

Finally, we investigated associations of cTnT as a categorical variable with longitudinal outcomes in men and women separately. Cumulative incidence of clinical outcomes across cTnT categories in men and women are depicted in Figure 1. Sex-specific sensitivity and specificity of selected cTnT cut-points for longitudinal outcomes are provided in Supplementary Table 4 (available online at <http://www.mayoclinicproceedings.org>). Associations of cTnT in women and men were evaluated using Cox-regression models, and cTnT less than 3 ng/L was set as the referent category. Although not significant after full adjustment, cTnT levels between LoB and LoD in women were associated with a 50% increased risk of developing CVD ($HR_{\text{women}}, 1.50$; 95% CI, 0.97-2.32) and a 79% increased risk of developing HF ($HR_{\text{women}}, 1.79$; 95% CI, 0.89-3.61). Such a trend was not observed in men (Table 3). Further, in fully adjusted models, women with cTnT levels above the LoD (ie, ≥ 6 ng/L) had a greater than two-fold increase in CVD risk ($HR, 2.30$; 95% CI, 1.45 to 3.64), and ~three-fold increase in rate of HF incidence

($HR, 2.86$; 95% CI, 1.41 to 5.80) and mortality ($HR, 2.65$; 95% CI, 1.52 to 4.61). In contrast, men with cTnT levels above the LoD only had a 51% increased risk of developing CVD ($HR, 1.51$; 95% CI, 1.07 to 2.13), and did not display significant associations with HF ($HR, 1.79$; 95% CI, 0.90 to 3.57) and mortality ($HR, 1.27$; 95% CI, 0.81 to 1.99) (Table 3).

DISCUSSION

It is known from previous studies that cTns are strongly associated with incident CVD in the general population,^{10,11,18,26,31,32} and also predict outcomes in patients with pre-existing CVD.³³⁻³⁵ We evaluated whether cTnT was differentially associated with incident CVD, HF, and mortality in community-dwelling women and men. In unadjusted models, higher cTnT levels were associated with a greater risk of developing longitudinal outcomes in both sexes — although the relative hazard was higher in women than men for each of these endpoints. After multivariable adjustment for clinical risk factors and NT-proBNP, associations of cTnT with all endpoints remained stronger in women (Table 2). We performed several sensitivity analyses, and the results were generally consistent with those from primary analysis.

A few previous studies also evaluated associations of cTns with incident cardiovascular outcomes in men and women separately. For instance, in the Nord-Trøndelag Health Study (HUNT), cTnI displayed stronger associations with incident MI and cardiovascular death in women.^{12,13} Associations of cTnI with mortality also tended to be stronger in women.¹² In the current study, cTnT levels were also more strongly associated with CVD and all-cause mortality in women. In the HUNT study, sex-related differences were not observed for incident HF,¹³ despite MI being a leading cause of HF.³⁶ We found that cTnT levels were associated with incident HF in both sexes, and these associations were stronger in women (Table 2). The discrepancy in results may partly be due to assay-based differences (ie, cTnI assay versus cTnT assay³⁷), and partly due to differences in HF characterization (ie, HF-adjudication

FIGURE 1. Cumulative incidence of cardiovascular disease, heart failure, and mortality according to troponin-T categories. Troponin-T levels between 3 ng/L and 6 ng/L are significantly associated with a higher risk of developing adverse outcomes in women whereas these associations are less apparent in men, particularly for cardiovascular disease and heart failure. Troponin-T levels greater than or equal to 6 ng/L are strongly associated with adverse outcomes in both sexes.

TABLE 3. Sex-Specific Associations of Categorical Troponin-T With Incident Outcomes^{a,b}

Sex-specific analysis	Troponin-T as a categorical variable	Unadjusted Models		Adjusted for age and clinical risk factors ^c		Additionally adjusted for NT-proBNP	
		HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Cardiovascular disease							
Women	< 3 ng/L	1.00		1.00		1.00	
	3-6 ng/L	3.13 (2.14-4.57)	<.001	1.53 (0.99-2.36)	.05	1.50 (0.97-2.32)	.07
	≥ 6 ng/L	9.58 (6.68-13.75)	<.001	2.67 (1.72-4.15)	<.001	2.30 (1.45-3.64)	<.001
	Trend across categories	3.10 (2.59-3.71)	<.001	1.63 (1.31-2.04)	<.001	1.52 (1.20-1.91)	<.001
Men	< 3 ng/L	1.00		1.00		1.00	
	3-6 ng/L	1.39 (1.01-1.92)	.04	0.96 (0.69-1.34)	.83	0.97 (0.69-1.35)	.85
	≥ 6 ng/L	4.55 (3.48-5.96)	<.001	1.64 (1.18-2.30)	.004	1.51 (1.07-2.13)	.02
	Trend across categories	2.24 (1.93-2.60)	<.001	1.31 (1.10-1.56)	.002	1.25 (1.04-1.49)	.02
Heart failure							
Women	< 3 ng/L	1.00		1.00		1.00	
	3-6 ng/L	4.54 (2.40-8.61)	<.001	1.91 (0.96-3.79)	.06	1.79 (0.89-3.61)	.10
	≥ 6 ng/L	16.33 (9.08-29.36)	<.001	3.61 (1.84-7.05)	<.001	2.86 (1.41-5.80)	.004
	Trend across categories	4.02 (3.03-5.32)	<.001	1.90 (1.36-2.65)	<.001	1.68 (1.19-2.38)	.003
Men	< 3 ng/L	1.00		1.00		1.00	
	3-6 ng/L	1.33 (0.66-2.67)	.43	0.87 (0.43-1.77)	.70	0.86 (0.42-1.77)	.68
	≥ 6 ng/L	7.79 (4.49-13.51)	<.001	2.02 (1.05-3.89)	.04	1.79 (0.90-3.57)	.10
	Trend across categories	3.22 (2.34-4.44)	<.001	1.52 (1.07-2.18)	.02	1.42 (0.98-2.06)	.07
All-cause mortality							
Women	< 3 ng/L	1.00		1.00		1.00	
	3-6 ng/L	2.58 (1.60-4.16)	<.001	1.18 (0.70-2.00)	.54	1.17 (0.69-1.99)	.56
	≥ 6 ng/L	11.45 (7.60-17.25)	<.001	2.71 (1.57-4.68)	<.001	2.65 (1.52-4.61)	.001
	Trend across categories	3.40 (2.73-4.23)	<.001	1.66 (1.25-2.21)	.001	1.64 (1.22-2.19)	.001
Men	< 3 ng/L	1.00		1.00		1.00	
	3-6 ng/L	1.77 (1.17-2.68)	.007	1.05 (0.69-1.60)	.82	1.06 (0.69-1.62)	.78
	≥ 6 ng/L	6.35 (4.44-9.06)	<.001	1.43 (0.92-2.29)	.11	1.27 (0.81-1.99)	.29
	Trend across categories	2.69 (2.23-3.24)	<.001	1.21 (0.98-1.51)	.08	1.14 (0.91-1.42)	.27

^aCI = confidence interval; HR = hazard ratio; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

^bHR represents the risk of developing cardiovascular disease per unit increase of troponin-T category, with troponin-T <3 ng/L taken as the referent category.

^cClinical risk factors include smoking, hypertension, hypercholesterolemia, type-2 diabetes, body-mass index, history of cardiovascular disease, and urinary albumin excretion.

committee in the PREVEND cohort²⁴ versus defining HF based only on hospitalization records in the HUNT study¹³). When we evaluated HF subtypes separately, sex-differences were present for HF_rEF ($P_{\text{interaction}} = .004$) but were absent for HF_pEF ($P_{\text{interaction}} = .53$). However, due to limited power, particularly for HF_pEF, these results should be interpreted with caution.

Nevertheless, our results are generally concordant with the HUNT study, and collectively these data suggest that cTns are more strongly associated with cardiovascular outcomes in women compared with men,

also after adjustment for potential confounders/mediators. This leads us to hypothesize that covariates not represented in our adjustment models (eg, sex hormone levels, microvascular disease, and markers of mitochondrial function³⁸⁻⁴⁰) may potentially explain stronger associations of cTn levels with CVD in women.

In exploratory analysis, we also examined the incremental value of adding of cTnT to the Framingham CVD risk prediction algorithm using likelihood-based measures. Clearly, adding cTnT lowered AIC of FRS in both sexes; however, reduction in

prediction error was slightly greater in women compared with men — indicating that the evidence for adding cTnT to FRS was higher in women than men. We further evaluated the incremental value of cTnT on top of PREVENT model that also included NT-proBNP. Again, adding cTnT reduced AIC to a greater extent in women compared with men. These results are in line with a previous study examining associations of cTnT with coronary heart disease, HF and mortality in the Atherosclerosis Risk in Communities (ARIC) study, which showed that cTnT improved model fit based on Grønnesby-Borgan statistic to a greater extent in women compared with men, particularly for the total coronary heart disease endpoint.³¹ Although exploratory in nature, our results along with data from the ARIC study, underscore the potential value of including cTnT in CVD risk prediction models, particularly in women.

In categorical analyses, we found that even minor cTnT elevations tend to be associated with CVD and HF risk in women, but not in men (Figure 1, Table 3). A meta-analysis of three studies enrolling community-dwelling individuals showed that cTnT levels between LoB and LoD were significantly associated with increased risk of HF and cardiovascular mortality.³² Our study adds granularity to these findings, and suggests that cTnT levels between LoB and LoD may particularly be associated with a greater risk of developing adverse cardiovascular outcomes in women.

We also found that although cTnT levels above the LoD were generally associated with CVD and mortality risk in both sexes, these associations remained robust in women, also after multivariable adjustment (Table 3). Recently, it was shown that in patients with suspected acute coronary syndrome, sex-specific cTnI cutpoints identified up to five times more additional women than men with myocardial injury.⁴¹ In the same study, it was also observed that despite identifying women more effectively, outcomes were not improved in women. Our findings also suggest that a lower threshold of cTnT elevation may associate more strongly with adverse

cardiovascular outcomes in women compared with men. Whether implementation of sex-specific thresholds to predict future CVD or to identify subclinical CVD would improve cardiovascular care and reduce outcomes in women must be tested in clinical trials.

Study Strengths and Limitations

Key strengths of our study include a large number of individuals with an almost 1:1 sex ratio. Participants were well characterized and underwent detailed clinical assessment. Data on cardiovascular events were obtained from the Dutch national registry of hospital discharge diagnoses, with 84% of primary diagnoses and 87% of secondary diagnoses matching the diagnoses recorded in participant's charts.^{27,42} HF endpoint was adjudicated by a committee of experts, and was further classified on the basis of left ventricular ejection fraction into HFrEF and HFpEF. Measurement of cTnT was performed using a reliable fifth-generation high-sensitivity assay (Roche modular E170, Roche Diagnostics).

We note the following limitations: (1) Commercially available cTn assays⁴³ may have different LoB — limiting generalizability of our findings. (2) Regression dilution effects could have underestimated associations between CVD risk and baseline cTnT measurements in both sexes.⁴⁴ However, performance metrics of cTnT for clinical outcomes in the PREVENT cohort appears to be comparable to cTn measurements from other population-based cohorts such as the Framingham Heart Study (FHS) and Multi-Ethnic Study of Atherosclerosis (MESA).⁴⁵ (3) The PREVENT study, by design has a higher proportion of individuals with UAE greater than 10 mg/mL. Although we accounted for this by conducting a design-based analysis,^{24,27,28} our sample may not be completely representative of a randomly selected population cohort, and comparisons with other cohorts should be cautiously made. (4) The current study was conducted on a predominantly white population from the northern Netherlands — warranting validation of our results in other white cohorts and also in different

ethnicities. (5) PREVENT is a relatively young cohort with a mean age of 49 years. The number of events is rather small and a large proportion of individuals had cTnT levels less than LoB, which could have limited the statistical power to detect differences. And finally, (6) this is an observational study; therefore, our results cannot be used to prove causality.

CONCLUSION

In the current study we show that baseline cTnT levels were more strongly associated with CVD, HF, and mortality in women than men. Our data suggest that even very low cTnT elevations may indicate future CVD and HF risk in women. Future studies are needed to examine the value of cTns as potential screening tools to facilitate early detection of CVD, particularly in women.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://www.mayoclinicproceedings.org>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: AIC = Akaike information criterion; cTnT = high-sensitivity cardiac troponin-T; CVD = cardiovascular disease; HF = heart failure; LoB = limit of blank; LoD = limit of detection; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PREVENT = The Prevention of Renal and Vascular End-stage Disease study; UAE = urinary albumin excretion

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