High-Sensitivity Cardiac Troponin-T and N-Terminal Prohormone of B-Type Natriuretic Peptide in Relation to Cardiovascular Outcomes in Type 1 Diabetes

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OBJECTIVE

High-sensitivity cardiac troponin-T (hs-cTnT) and N-terminal prohormone of B-type natriuretic peptide (NT-proBNP), biomarkers of cardiovascular disease (CVD) and heart failure, respectively, have not been widely studied in type 1 diabetes (T1D). We evaluated whether their assessment in T1D enhances the prediction of CVD and major adverse cardiovascular events (MACE).

RESEARCH DESIGN AND METHODS

hs-cTnT and NT-proBNP were analyzed on the Roche Cobas E601 using the first available stored specimen (n = 581; mean age 29 years and diabetes duration 21 years). CVD was defined as CVD death, myocardial infarction, coronary revascularization, angina, ischemia, or stroke, and MACE as CVD death, myocardial infarction, or stroke.

RESULTS

Median hs-cTnT (5.0 ng/L; interquartile range <3.0, 10.0) was higher among men (P < 0.0001), whereas median NT-proBNP (22.0 ng/L; 7.0, 61.0) did not differ by sex. In Cox models, log hs-cTnT (hazard ratio [HR] 1.38, P = 0.0006) and log NT-proBNP (HR 1.24, P = 0.0001) independently predicted CVD during 21 years of follow-up. However, their addition to models, singly or together, did not significantly improve CVD prediction. Furthermore, a marginally significant sex interaction was observed (P = 0.06), indicating that the hs-cTnT prediction was limited to men. hs-cTnT and NT-proBNP also predicted MACE, although only NT-proBNP remained significant (HR 1.27, P = 0.0009) when the biomarkers were included in a model simultaneously. Nonetheless, their addition to multivariable models did not enhance MACE prediction.

CONCLUSIONS

Sex differences were observed in the concentration and predictive ability of hs-cTnT and NT-proBNP in T1D. Overall, their addition to traditional risk factor models increased the area under the curve for neither CVD nor MACE.

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Cardiovascular disease (CVD) is the leading cause of death in both the general population and in individuals with diabetes; however, it disproportionately affects patients with childhood-onset type 1 diabetes, in whom risk is increased >30-fold in young adulthood (1). This greatly elevated cardiovascular risk in type 1 diabetes compared with the general population constitutes a paradox, because it appears to defy the generally more favorable risk factor (i.e., lipid) profile of such individuals when under reasonable glycemic control (2). Thus, although traditional risk factors in the general population, such as smoking, hypertension, and dyslipidemia, do not lose their predictive value in individuals with type 1 diabetes (3,4), their more favorable distribution fails to explain the greatly increased disease burden this population experiences.

The identification of factors, beyond dysglycemia and traditional risk factors, which contribute to the excess cardiovascular risk in type 1 diabetes compared with the general population, appears long overdue. Such knowledge would not only advance our understanding of the underpinnings of CVD in the type 1 diabetes population and improve patient risk stratification but would perhaps also identify novel targets for preventive or therapeutic interventions. High-sensitivity cardiac troponin-T (hs-cTnT), a biomarker whose measurement is recommended for the diagnosis of acute myocardial infarction (5), and N-terminal prohormone of B-type natriuretic peptide (NT-proBNP), a biomarker of heart failure, have received considerable attention in aiding cardiovascular outcome prediction (6,7). Evidence for the prognostic ability of these two biomarkers, in terms of cardiovascular morbidity and mortality, has also been provided among individuals with type 2 diabetes (8,9). However, only two studies have prospectively assessed the presence of an association between these biomarkers and cardiovascular and all-cause mortality in type 1 diabetes, focusing on patients with existing kidney disease (10,11). We therefore investigated whether the assessment of hs-cTnT and NT-proBNP enhances the prediction of cardiovascular and major adverse cardiovascular events (MACE) in a large cohort of individuals with childhood-onset type 1 diabetes. Because the concentration of these biomarkers is known to vary by sex, we further evaluated whether the predictive ability of these markers is sex dependent.

RESEARCH DESIGN AND METHODS

Analyses were based on data from the Epidemiology of Diabetes Complications (EDC) study, a prospective investigation of a childhood-onset (<17 years) type 1 diabetes cohort diagnosed, or seen within 1 year of diagnosis, at Children's Hospital of Pittsburgh between 1950 and 1980 (12). This cohort, which has been previously shown to be representative of the type 1 diabetes population of Allegheny County, Pennsylvania, was first examined for the EDC study in 1986–1988 ($n = 658$; mean age 28 years and diabetes duration 19 years) and subsequently followed biennially with surveys for 25 years. For the first 10 years, biennial clinical examinations also occurred and were repeated at 18 and 25 years of follow-up. The University of Pittsburgh Institutional Review Board approved the study protocol.

Self-administered surveys documented demographic, health care, diabetes self-care, and medical history information. An "ever smoker" was defined as a person who smoked ≥100 cigarettes over their lifetime. During the clinical examinations, participants underwent evaluations to assess anthropometrics and provided fasting blood and urine samples, which were stored in −70°F freezers. Two waist circumference measurements were taken at the midpoint between the upper iliac crest and the lower costal margin in the midaxillary line, and two hip measurements were made at the maximum hip circumference. The waist-to-hip ratio (WHR) was calculated as the mean of two waist measurements divided by the mean of two hip measurements. BMI was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured with a random zero sphygmomanometer, according to the Hypertension Detection and Follow-up Program protocol, after a 5-min rest (13), and hypertension was defined as blood pressure ≥140/90 mmHg or use of antihypertensive medications.

Stable glycated hemoglobin (HbA_1) was measured by ion exchange chromatography (Isolab, Akron, OH) for the first 18 months and subsequently by automated high-performance liquid chromatography (DIAMAT; Bio-Rad, Hercules, CA). The two assays were highly correlated ($r = 0.95$). The original HbA_1 values were converted to Diabetes Control and Complications Trial (DCCT)-aligned HbA_{1c} values using regression formulas derived from duplicate analyses (DCCT $HbA_{1c} = [0.83 \times \text{EDC } HbA_1] + 0.14$). HDL cholesterol (HDL-C) was determined using ultracentrifugation precipitation techniques (14). Total cholesterol and triglycerides were measured enzymatically (15,16), and non–HDL-C was calculated as total cholesterol minus HDL-C. Serum and urinary albumin were measured using immunonephelometry (17), and serum creatinine was assayed using an Ektachem 400 Analyzer (Eastman Kodak Co., Rochester, NY). The glomerular filtration rate was estimated (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration equation (18). White blood cell (WBC) count was obtained using a Coulter Counter S-plus IV (Coulter Electronics, Hialeah, FL).

hs-cTnT and NT-proBNP were analyzed on the Roche Cobas E601 (Roche Diagnostics Corporation, Indianapolis, IN) via electrochemiluminescence immunoassays using the first available stored specimen (before incident coronary artery disease, the original end point studied, or end of follow-up for noncase subjects) from the EDC study. A sample was available for 82% from 1986 to 1990, whereas a sample was available for 18% at later examinations. No differences were observed in the median values of the two biomarkers by time of assessment. The intra- and interassay precision (% coefficient of variation [CV]) for hs-cTnT with this assay is 2.4% and 6.2% at 7.6 ng/L, respectively, and 1.2% and 2.9% at 22.2 ng/L. Sex-specific 99th percentiles are 9 ng/L for females and 16 ng/L for males. The limit of detection (LoD) for the hs-cTnT assay is 5.0 ng/L, and the limit of blank is 3 ng/L. For NT-proBNP, the interassay CVs are 4.9% at a mean concentration of 45.6 ng/L, 3.0% at a mean concentration of 144.7 ng/L, and 3.4% at a mean concentration of 4,337 ng/L. The LoD is 5.0 ng/L.

CVD was defined as cardiovascular death, myocardial infarction confirmed by Q-waves on electrocardiogram (Minnesota codes 1.1 or 1.2) or hospital records, revascularization, angina determined by the EDC study physician, ischemia (Minnesota codes 1.3, 4.1–4.3, 5.1–5.3, 7.1), or stroke confirmed by

medical records. MACE was defined as cardiovascular death, myocardial infarction, or stroke.

Statistical Analysis

All covariates used in the analyses were extracted from the examination cycle in which hs-cTnT and NT-proBNP were analyzed. For hs-cTnT, individuals with values below the limit of blank were assigned a value below the limit (i.e., 2) and used in the analyses because excluding them would bias results. Statistical analyses were conducted using SAS 9.4 software (SAS Institute, Cary, NC). Descriptive statistics were used to evaluate the distribution of variables used in the analyses. As neither hs-cTnT nor NT-proBNP was normally distributed, Spearman correlation coefficients were used to assess the presence of an association between these two biomarkers and continuous risk characteristics, and their distribution across levels of classification variables was compared using the Wilcoxon two-sample test. Univariate associations between continuous variables and incident CVD or MACE were determined using the Student *t* test or the Wilcoxon two-sample test for normally and nonnormally distributed continuous variables, respectively; the χ^2 or Fisher exact test, as appropriate, were used for categorical variables. Given that the distribution of the two biomarkers differed significantly by sex, the association between quartiles of their concentrations and the cardiovascular outcomes studied by sex was assessed to evaluate whether risk differed between men and women at similar biomarker concentrations.

Cox proportional hazards models with backward elimination were first constructed allowing for traditional risk factors only. The final models comprising significant independent risk factor predictors were compared with identical models that further included hs-cTnT and/or NT-proBNP. Because the concentration of the two biomarkers is affected by kidney function, eGFR was forced in all models. The integrated time-dependent area under the curve was estimated using the option ROCOPTIONS in the PROC PHREG statement and specifying the inverse probability of the censoring weighting method to compute the receiver operating characteristic curves. The Uno concordance statistic (via the CONCORDANCE option) was further used to assess whether the addition of the two biomarkers improved outcome prediction. The presence of modification of the effect of the two biomarkers on each outcome studied by sex was also assessed, and analyses stratifying by sex were conducted. Survival time was defined as the time in years from biomarker assessment to the date of a first incident event or, for noncase subjects, the last available follow-up.

RESULTS

Of 581 study participants with data on these two biomarkers, 572 were free of CVD or MACE and had data on major risk factors at the analytic baseline. A description of this cohort overall and by sex is given in Supplementary Table 1.

hs-cTnT

The median concentration of hs-cTnT in the total EDC cohort was 5.0 ng/L (interquartile range [IQR] <3.0, 10.0) and greater among men (7.9; IQR 5.0, 13.0) compared with women (3.4; IQR <3.0, 6.0; $P < 0.0001$), with almost 10% of men and 45% of women, having a concentration of hs-cTnT <3.0 ng/L. Overall, 15.7% (17.9% of men and 13.6% of women, $P = 0.16$) exhibited hs-cTnT concentrations higher than the sex-specific 99th percentile upper reference limits in the general population of 16 ng/L for men and 9 ng/L women, respectively. hs-cTnT concentrations positively correlated with age, diabetes duration, WHR, HbA_{1c}, blood pressure, non–HDL-C, triglycerides, WBC count, and albumin excretion rate (AER) and inversely with insulin dose per body weight, HDL-C, and eGFR (Supplementary Table 2).

NT-proBNP

The median concentration of NT-proBNP (22.0 ng/L; IQR 7.0, 59.0) was lower among men (11.0 ng/L; IQR <5.0, 29.0) compared with women (36.0 ng/L; IQR 16.0, 81.0; $P < 0.0001$). NT-proBNP concentrations were above the clinical cutoff of 125 ng/L for individuals <75 years in 11.7% of EDC participants. Women, however, were significantly more likely to have concentrations higher than this cutoff compared with men (16.7% vs. 6.4%, $P = 0.0001$). No correlation was observed between the concentrations of hs-cTnT and NT-proBNP in this cohort (Supplementary Table 2). However, NT-proBNP positively correlated with age, diabetes duration, blood pressure, HDL-C, non–HDL-C, triglycerides, WBC count, and AER and inversely with BMI, WHR, insulin dose per body weight and eGFR.

Cardiovascular Disease

Of 540 participants free of CVD at the time of biomarker assessment, 197 (36.5%) developed an incident event during a median follow-up of 18.6 years, for an incidence density of 21.9 per 1,000 person-years. Participant characteristics at the time of biomarker assessment by incident CVD status are presented in Table 1. Incident case subjects were older, with a longer duration of diabetes, higher BMI, WHR, blood pressure, non–HDL-C, triglycerides, WBC count, AER, hs-cTnT, and NT-proBNP concentrations, and lower insulin dose per body weight and eGFR compared with noncase subjects; they were also more likely to report having ever smoked.

The incidence of CVD increased incrementally with increasing quartile of hs-cTnT in men, although risk among women peaked in the second quartile (Cochran-Armitage trend test $P < 0.0001$ for both sexes) (Fig. 1*A*). CVD incidence also increased significantly across quartiles of NT-proBNP in both sexes (Cochran-Armitage Trend Test $P < 0.0001$ in men and $P = 0.0006$ in women) (Fig. 1*B*). Significant trends toward a higher incidence with increasing quartile of each biomarker were also observed when sex-specific cutoff points were used (not shown).

In Cox proportional hazards models, adjusting for diabetes duration, significant independent predictors of incident CVD among traditional risk factors comprised BMI, smoking, non–HDL-C, and AER (Table 2). Both hs-cTnT and NT-proBNP significantly predicted CVD incidence when added to this model, separately or simultaneously, although adding them did not significantly improve the prediction of CVD. The comparison of models with and without hs-cTnT produced an Uno *P* value of 0.40, whereas similar comparisons for the addition of NT-proBNP produced an Uno *P* value of 0.15; comparison with a model including both hs-cTnT and NT-proBNP yielded a *P* value of 0.22. It is important to note, however, that including or excluding any other single traditional risk factor also did not significantly affect the model's prediction performance (Uno $P = 0.63$ for

Table 1—Participant characteristics at the time of biomarker assessment by incident CVD or MACE*

	Incident CVD			Incident MACE		
	No (n = 343)	Yes (n = 197)	P value	No (n = 443)	Yes (n = 127)	P value
Age (years)	25.0 (20.7, 30.7)	32.5 (27.1, 37.2)	<0.0001	25.6 (21.4, 32.9)	33.5 (28.5, 39.4)	<0.0001
Age at diabetes onset (years)	8.0 (4.7, 11.6)	9.0 (5.7, 11.6)	0.15	8.6 (5.1, 11.8)	8.6 (5.6, 11.5)	0.79
Diabetes duration (years)	16.9 (12.9, 21.8)	24.1 (18.8, 29.1)	<0.0001	17.8 (13.6, 23.8)	25.6 (20.2, 29.6)	<0.0001
Follow-up time (years)	21.4 (15.7, 24.9)	11.9 (6.2, 17.7)	<0.0001	21.8 (16.9, 25.0)	11.9 (6.5, 16.1)	<0.0001
Females, % (n)	51.6 (177)	49.2 (97)	0.60	51.9 (230)	49.6 (63)	0.65
BMI (kg/m^2)	23.5 (3.2)	24.4 (3.5)	0.002	23.8 (3.2)	24.0 (3.7)	0.38
WHR	0.81 (0.75, 0.86)	0.84 (0.77 0.90)	0.0009	0.82 (0.76, 0.87)	0.84 (0.78, 0.90)	0.01
Ever smoker, % (n)	29.9 (101)	46.7 (92)	<0.0001	32.6 (143)	48.8 (62)	0.0008
Insulin dose (units/body weight)	0.78 (0.64, 0.95)	0.70 (0.57, 0.89)	0.003	0.76 (0.62, 0.94)	0.68 (0.56, 0.86)	0.009
HbA_{1c} (%)	8.5 (7.7, 9.8)	8.8 (7.9, 9.8)	0.06	8.6 (7.8, 9.8)	9.0 (8.2, 10.3)	0.004
Blood pressure						
Systolic (mmHg)	108 (102, 115)	115 (108, 127)	<0.0001	110 (103, 117)	116 (108, 133)	<0.0001
Diastolic (mmHg)	70 (65, 76)	75 (66, 82)	<0.0001	70 (65, 77)	77 (66, 85)	<0.0001
Hypertension medications, % (n)	5.0 (16)	16.9 (33)	<0.0001	6.7 (28)	25.4 (32)	<0.0001
Pulse rate (bpm)	76 (68, 82)	78 (72, 84)	0.02	76 (68, 82)	80 (72, 86)	0.002
Hypertension, % (n)	8.2 (28)	26.4 (52)	<0.0001	10.4 (46)	36.2 (46)	<0.0001
HDL-C (mg/dL)	51.8 (45.5, 60.8)	50.7 (43.9, 61.0)	0.31	52.0 (45.2, 60.8)	50.7 (42.9, 61.7)	0.45
Men	48.8 (42.3, 55.0)	46.5 (40.5, 55.1)	0.20	47.2 (41.8, 54.5)	47.0 (40.6, 53.9)	0.60
Women	56.0 (49.2, 67.0)	57.7 (48.3, 65.9)	0.96	57.0 (49.2, 67.4)	57.9 (47.7, 67.3)	0.75
Non–HDL-C (mg/dL)	121.7 (101.3, 142.6)	146.4 (125.9, 172.6)	<0.0001	125.0 (104.2, 147.8)	149.0 (123.4, 181.6)	<0.0001
Lipid medications, % (n)	0.62 (2)	1.5 (3)	0.37	0.71 (3)	1.6 (2)	0.32
Triglycerides (mg/dL)	76.0 (56.0, 107.5)	96.0 (69.0, 135.0)	<0.0001	78.5 (57.0, 114.0)	107.5 (76.5, 143.0)	<0.0001
ACE/ARB, % (n)	4.3 (14)	7.1 (14)	0.17	4.5 (19)	6.4 (8)	0.39
WBC count ($\times 10^3$/mm^2)	6.1 (5.2, 7.6)	6.6 (5.8, 8.2)	0.0005	6.2 (5.2, 7.7)	6.9 (5.8, 8.7)	<0.0001
AER (μg/min)	10.7 (6.3, 33.6)	27.8 (9.6, 409.0)	<0.0001	11.5 (6.5, 44.4)	116.5 (12.8, 584.8)	<0.0001
eGFR (mL/min/1.73 m^2)	111.7 (91.8, 127.6)	100.7 (79.9, 119.0)	<0.0001	108.7 (89.8, 126.0)	93.1 (73.7, 120.5)	0.0001
hs-cTnT (ng/L)						
Overall	4.0 (<3.0, 7.0)	6.8 (4.2, 12.0)	<0.0001	5.0 (<3.0, 8.0)	8.0 (4.6, 13.9)	<0.0001
Men	6.0 (4.0, 10.0)	10.1 (6.4, 16.5)	<0.0001	7.0 (4.0, 11.0)	11.8 (7.1, 20.9)	<0.0001
Women	<3.0 (<3.0, 5.0)	4.5 (3.1, 7.0)	<0.0001	<3.0 (<3.0, 5.0)	4.8 (3.0, 8.7)	<0.0001
NT-proBNP (ng/L)						
Overall	17.0 (4.0, 42.0)	27.0 (12.0, 76.0)	<0.0001	19.0 (5.0, 46.0)	40.0 (13.0, 109.0)	<0.0001
Men	7.0 (4.0, 20.0)	14.5 (7.0, 37.0)	<0.0001	9.0 (4.0, 23.0)	18.5 (9.0, 77.5)	<0.0001
Women	28.0 (13.0, 62.0)	51.0 (22.0, 107.0)	0.0003	30.0 (14.0, 72.0)	73.0 (25.0, 155.0)	<0.0001

Continuous data are presented as mean (SD) or median (IQR) and categorical data as indicated. ARB, angiotensin receptor blocker. *For analyses relating to CVD the sample size was 539 (197 events) for BMI, 463 (171 events) for WHR, 535 (197 events) for having ever smoked, 509 (195 events) for insulin dose per weight, 516 (195 events) for hypertension medications, 520 (196 events) for lipid medications and ACE/ARB, 511 (187 events) for triglycerides, 534 (197 events) for WBC, and 538 (197 events) for AER. For analyses relating to MACE, the sample size was 569 (127 events) for BMI, 490 (107 events) for WHR, 565 (127 events) for having ever smoked, 537 (125 events) for insulin dose per weight, 545 (126 events) for hypertension medications, 549 (126 events) for lipid medications, 538 (124 events) for triglycerides, 565 (127 events) for WBC count, 548 (125 events) for ACE/ARB, and 567 (126 events) for AER.

BMI, $P = 0.67$ for smoking, $P = 0.79$ for non–HDL-C, $P = 0.74$ for AER, and $P = 0.67$ for eGFR).

In assessing effect modification by sex, a marginally significant interaction was observed for hs-cTnT ($P = 0.06$). Analyses were therefore repeated stratifying by sex (Table 2). Both hs-cTnT and NT-proBNP significantly predicted CVD risk in men, whereas only NT-proBNP was a significant predictor of CVD among women. However, simultaneously including both biomarkers in a model with traditional risk factors rendered both insignificant. Moreover, addition (separately or simultaneously) of hs-cTnT and NT-proBNP to a model already including traditional risk factors did not significantly improve the model's prediction performance for either sex.

MACE

Of 570 individuals free of MACE, 127 (22.3%) developed an incident event during a median follow-up of 20.3 years, for an incidence density of 12.4 per 1,000 person-years. Incident case subjects were older, with a longer diabetes duration, larger WHR, higher HbA_{1c}, blood pressure, non–HDL-C, triglycerides, WBC count, and AER levels, and lower insulin dose per weight and eGFR compared with noncase subjects (Table 1). Those with a subsequent event were also more likely to have ever smoked and to have elevated concentrations of hs-cTnT and NT-proBNP.

The incidence of MACE increased with increasing quartile of hs-cTnT (Cochran-Armitage trend test $P \leq 0.0001$) (Fig. 1*C*) and NT-proBNP (Cochran-Armitage trend test $P = 0.0001$ in men and $P = 0.002$ in

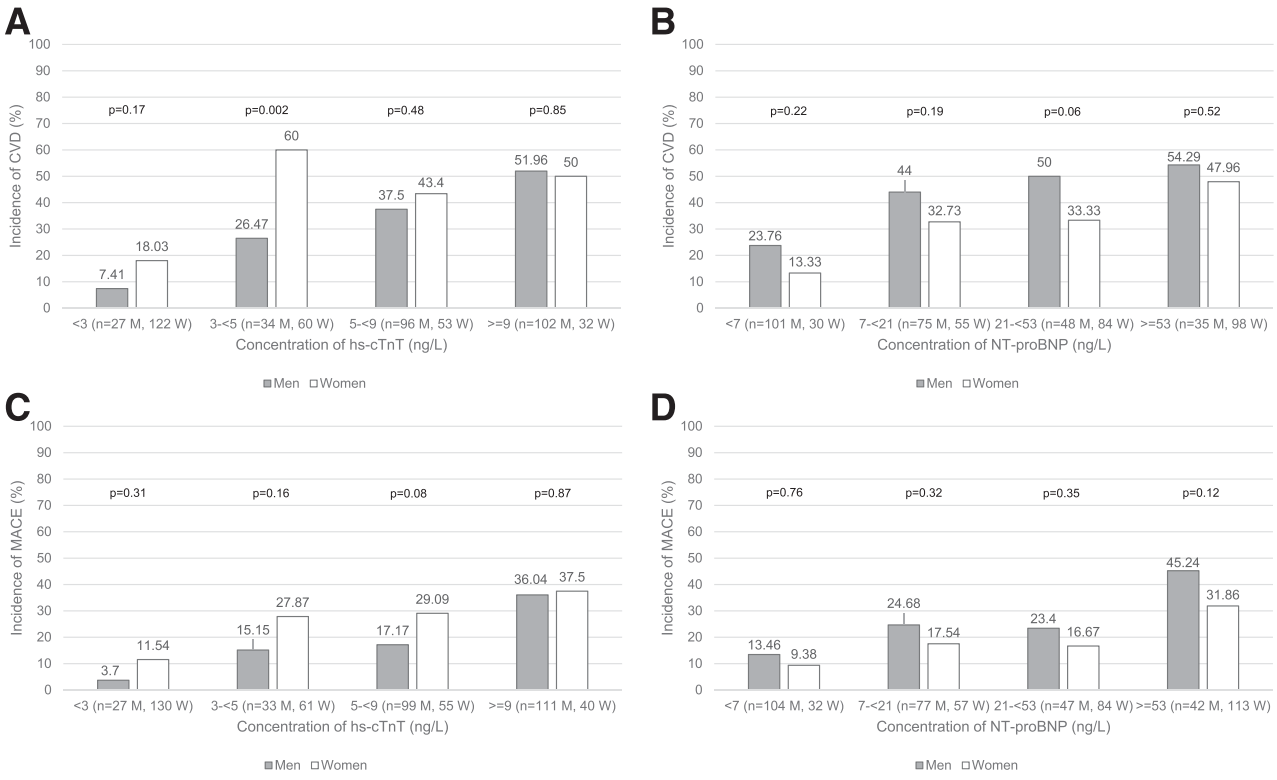

Figure 1—Incidence of CVD and MACE by biomarker quartile and sex (M, men; W, women). *A*: CVD incidence by quartiles of hs-cTnT and sex (Cochran-Armitage trend test $P < 0.0001$ in both sexes). *B*: CVD incidence by quartiles of NT-proBNP and sex (Cochran-Armitage trend test $P < 0.0001$ in men and $P = 0.0006$ in women). *C*: MACE incidence by quartiles of hs-cTnT and sex (Cochran-Armitage trend test $P < 0.0001$ in men and $P = 0.0001$ in women). *D*: MACE incidence by quartiles of NT-proBNP and sex (Cochran-Armitage trend test $P = 0.0001$ in men and $P = 0.002$ in women).

women) (Fig. 1*D*) in both sexes. Significant trends toward a higher incidence with increasing quartile of each biomarker were also observed when sex-specific cutoff points were used (data not shown). In Cox proportional hazards models, adjusting for diabetes duration, significant independent predictors of incident MACE among traditional risk factors comprised HbA_{1c}, hypertension status, non–HDL-C, WBC count, and AER (Table 3). Both hs-cTnT and NT-proBNP significantly predicted CVD incidence when added to this model separately, although their addition did not improve the prediction of MACE (Uno $P = 0.38$ for hs-cTnT and $P = 0.89$ for NT-proBNP). When the two biomarkers were simultaneously added to the model, NT-proBNP was a better predictor of MACE than hs-cTnT; however, their addition did not improve the prediction of MACE (Uno $P = 0.31$). As was the case for CVD, including or excluding any single traditional risk factor also did not significantly affect the model's prediction performance for MACE (Uno $P = 0.76$ for HbA_{1c}, $P = 0.32$ for hypertension, $P = 0.38$ for non–HDL-C, 0.21 for WBC count, $P = 0.25$ for AER, and $P = 0.43$ for eGFR).

There was no significant modification of the effect of either biomarker by sex (the *P* value for interaction was 0.12 for hs-cTnT and 0.42 for NT-proBNP). Nevertheless, repeating analyses separately for men and women revealed that hs-cTnT was a stronger predictor of MACE compared with NT-proBNP among men, whereas a stronger association was observed for the latter among women. However, the addition of the two biomarkers to models already including traditional risk factors, did not significantly affect the models' prediction performance for MACE in either sex.

CONCLUSIONS

In a cohort of young adults with childhood-onset type 1 diabetes who were free of heart disease, the concentrations of hs-cTnT and NT-proBNP differed significantly by sex, with women presenting lower hs-cTnT and higher NT-proBNP concentrations compared with men. Moreover, although hs-cTnT and NT-proBNP concentrations directly predicted the incidence of cardiovascular events and MACE ~21 years later in the overall cohort, sex differences were observed in the strength of these associations. Thus, hs-cTnT more strongly predicted CVD and MACE among men, whereas NT-proBNP was a stronger predictor of MACE among women. Nevertheless, the addition of either or both of these biomarkers to models that included traditional risk factors improved the models' predictive ability for neither CVD nor MACE, although it is important to note that the addition or exclusion from final models of any of the traditional risk factors also failed to enhance the prediction of the outcomes studied.

Cardiac troponins are regulatory proteins found in muscle fibers and are fundamental to muscular contraction. Their release into the circulation signals myocardial cell injury and/or myocyte necrosis. Thus, the criterion for the diagnosis of myocardial injury includes cardiac troponin concentrations elevated above the sex-specific 99th percentiles, and cardiac troponin further comprises one of the diagnostic criteria for acute myocardial infarction (19). In addition to their use in clinical practice for diagnosis, however, elevated concentrations of hs-cTnT, in particular, have been proposed

Table 2—Cox models for the prediction of incident CVD during 25 years of follow-up

Participant characteristics	Model 1	Model 2	Model 3	Model 4
Overall cohort (n = 526; 197 events)				
Duration	1.09 (1.07–1.11)	1.09 (1.06–1.11)	1.09 (1.07–1.11)	1.09 (1.06–1.11)
BMI	1.05 (1.01–1.10)	1.06 (1.01–1.11)	1.07 (1.02–1.11)	1.07 (1.02–1.12)
Ever smoker	1.54 (1.15–2.05)	1.51 (1.13–2.01)	1.60 (1.20–2.13)	1.57 (1.17–2.10)
Non–HDL-C	1.008 (1.005–1.01)	1.008 (1.004–1.01)	1.008 (1.005–1.01)	1.008 (1.004–1.01)
Log AER	1.20 (1.11–1.29)	1.15 (1.06–1.25)	1.17 (1.09–1.26)	1.13 (1.04–1.22)
eGFR	0.998 (0.99–1.003)	1.00 (0.99–1.005)	1.00 (0.995–1.005)	1.003 (0.997–1.01)
hs-cTnT (log)	Not allowed	1.38 (1.16–1.66)	Not allowed	1.38 (1.15–1.65)
NT-proBNP (log)	Not allowed	Not allowed	1.25 (1.12–1.40)	1.24 (1.11–1.39)
AIC	2,092.660	2,082.372	2,079.502	2,092.660
AUC	0.8162	0.8305	0.8184	0.8328
Uno concordance statistic for models with vs. without the biomarker(s)				
Estimate (SE)		−0.03 (0.04)	−0.01 (0.008)	−0.03 (0.03)
P value		0.40	0.15	0.22
Men (n = 259; 100 events)				
Duration	1.07 (1.04–1.10)	1.07 (1.04–1.10)	1.07 (1.03–1.10)	1.07 (1.04–1.10)
Hypertension	1.81 (1.05–3.12)	1.70 (0.98–2.92)	1.68 (0.98–2.89)	1.62 (0.94–2.79)
Non–HDL-C	1.01 (1.005–1.015)	1.01 (1.005–1.015)	1.01 (1.007–1.02)	1.01 (1.006–1.02)
Log AER	1.22 (1.08–1.36)	1.12 (0.99–1.28)	1.15 (1.03–1.30)	1.08 (0.95–1.23)
eGFR	1.004 (0.995–1.01)		1.005 (0.996–1.01)	1.01 (0.997–1.02)
hs-cTnT (log)	Not allowed	1.63 (1.23–2.15)	Not allowed	1.56 (1.16–2.09)
NT-proBNP (log)	Not allowed	Not allowed	1.33 (1.11–1.58)	1.28 (1.07–1.53)
AIC	910.643	910.715	912.691	905.638
AUC	0.8059	0.8351	0.8047	0.8325
Uno concordance statistic for models with vs. without the biomarker(s)				
Estimate (SE)		−0.04 (0.07)	−0.01 (0.02)	−0.05 (0.07)
P value		0.52	0.58	0.47
Women (n = 267; 97 events)				
Duration	1.10 (1.07–1.13)	1.10 (1.07–1.13)	1.10 (1.07–1.13)	1.10 (1.07–1.13)
Ever smoker	1.67 (1.11–2.50)	1.66 (1.10–2.49)	1.58 (1.05–2.39)	1.59 (1.05–2.39)
Non–HDL-C	1.008 (1.003–1.01)	1.008 (1.003–1.01)	1.008 (1.003–1.01)	1.008 (1.003–1.01)
Log AER	1.14 (1.02–1.27)	1.13 (1.01–1.26)	1.12 (0.997–1.25)	1.11 (0.99–1.24)
eGFR	0.996 (0.99–1.003)	0.998 (0.99–1.01)	0.998 (0.99–1.005)	0.998 (0.99–1.01)
hs-cTnT (log)	Not allowed	1.19 (0.88–1.60)	Not allowed	1.06 (0.77–1.47)
NT-proBNP (log)	Not allowed	Not allowed	1.22 (1.01–1.46)	1.20 (0.98–1.46)
AIC	907.091	907.864	904.735	906.599
AUC	0.8141	0.8196	0.8226	0.8235
Uno concordance statistic for models with vs. without the biomarker(s)				
Estimate (SE)		−0.004 (0.01)	−0.02 (0.02)	−0.02 (0.02)
P value		0.65	0.41	0.38

Data are hazard ratio (95% CI) unless otherwise indicated. Model 1 adjusted for eGFR and allowed for diabetes duration, BMI, having ever smoked, HbA_{1c}, hypertension status, HDL-C and non–HDL-C, WBC count, and AER. This model also allowed for sex in analyses of the entire cohort. Model 2 included significant predictors from model 1 in addition to eGFR and hs-cTnT. Model 3 included significant predictors from model 1 in addition to eGFR and NT-proBNP. Model 4 included significant predictors from model 1 in addition to eGFR, hs-cTnT, and NT-proBNP. AIC, Akaike information criterion; AUC, integrated time-dependent area under the curve.

as a biomarker of risk for future CVD events as well as prognosis. Indeed, a meta-analysis of studies in the general population recently provided support that increases in hs-cTnT concentrations even <99th percentile strongly and independently predict subsequent CVD (6).

Interestingly, through the use of a new generation of highly sensitive troponin assays, it has become evident that increases in the levels of cardiac troponins are not specific to ischemic myocyte injury or necrosis, because concentrations >99th percentile also present in a variety of nonischemic, chronic diseases (20). Thus, the concentration of hs-cTnT was previously shown to be elevated in individuals with type 2 diabetes compared with normal glucose tolerance individuals (21). The median concentration of hs-cTnT in our cohort of young adults with childhood-onset type 1 diabetes was similar to that reported in studies of type 1 (10) and type 2 diabetes (21,22) and elevated compared with normal glucose tolerance individuals free of overt CVD (21). Notwithstanding the generally higher concentrations observed in the presence of diabetes, however, hs-cTnT was still shown to predict the subsequent development of cardiovascular morbidity and mortality in type 2 diabetes, regardless of kidney disease status (22–24), which could potentially impair its clearance. This association was also evaluated in a study of type 1 diabetes in which investigators noted that higher hs-cTnT concentrations independently predicted the incidence of cardiovascular events, but only among individuals with diabetic nephropathy (10). In our large cohort of young adults with long-standing childhood-onset type 1 diabetes, increased levels of hs-cTnT were associated with the development of CVD and MACE

Table 3—Cox models for the prediction of incident MACE during 25 years of follow-up

Participant characteristics	Model 1	Model 2	Model 3	Model 4
Overall cohort (n = 555; 126 events)				
Duration	1.09 (1.06–1.12)	1.09 (1.06–1.12)	1.09 (1.06–1.12)	1.09 (1.06–1.12)
HbA_{1c}	1.15 (1.02–1.30)	1.15 (1.02–1.30)	1.14 (1.02–1.29)	1.14 (1.02–1.28)
Hypertension	1.83 (1.15–2.93)	1.73 (1.08–2.76)	1.68 (1.05–2.70)	1.59 (0.99–2.56)
Non–HDL-C	1.006 (1.001–1.01)	1.005 (1.001–1.01)	1.006 (1.002–1.01)	1.005 (1.001–1.01)
WBC count	1.16 (1.07–1.27)	1.17 (1.07–1.28)	1.16 (1.07–1.27)	1.17 (1.07–1.27)
Log AER	1.18 (1.06–1.30)	1.14 (1.03–1.27)	1.16 (1.04–1.28)	1.13 (1.02–1.26)
eGFR	1.002 (0.99–1.01)	1.003 (0.996–1.01)	1.005 (0.998–1.01)	1.006 (0.999–1.01)
hs-cTnT (log)	Not allowed	1.27 (1.01–1.60)	Not allowed	1.23 (0.97–1.55)
NT-proBNP (log)	Not allowed	Not allowed	1.29 (1.12–1.49)	1.27 (1.10–1.47)
AIC	1,381.024	1,378.869	1,370.659	1,369.802
AUC	0.8499	0.8509	0.8622	0.8633
Uno concordance statistic for models with vs. without the biomarker(s)				
Estimate (SE)		−0.005 (0.005)	−0.0008 (0.006)	−0.007 (0.007)
P value		0.38	0.89	0.31
Men (n = 270; 63 events)				
Duration	1.05 (1.01–1.10)	1.06 (1.01–1.10)	1.05 (1.01–1.09)	1.05 (1.01–1.10)
Hypertension	2.71 (1.39–5.28)	2.76 (1.42–5.35)	2.46 (1.25–4.87)	2.54 (1.29–5.00)
Non–HDL-C	1.007 (1.001–1.01)	1.006 (1.00–1.01)	1.007 (1.002–1.01)	1.006 (1.00–1.01)
WBC count	1.17 (1.03–1.32)	1.19 (1.05–1.35)	1.17 (1.03–1.32)	1.18 (1.04–1.34)
Log AER	1.22 (1.06–1.40)	1.15 (0.99–1.33)	1.18 (1.03–1.36)	1.14 (0.99–1.32)
eGFR	1.01 (0.998–1.02)	1.01 (1.00–1.02)	1.01 (1.001–1.02)	1.01 (1.003–1.03)
hs-cTnT (log)	Not allowed	1.60 (1.12–2.27)	Not allowed	1.45 (1.00–2.11)
NT-proBNP (log)	Not allowed	Not allowed	1.32 (1.07–1.63)	1.24 (0.996–1.55)
AIC	600.790	596.008	596.153	594.347
AUC	0.8436	0.8537	0.8610	0.8659
Uno concordance statistic for models with vs. without the biomarker(s)				
Estimate (SE)		−0.009 (0.009)	−0.003 (0.009)	−0.01 (0.01)
P value		0.29	0.76	0.27
Women (n = 285; 63 events)				
Duration	1.11 (1.07–1.15)	1.11 (1.07–1.15)	1.11 (1.07–1.15)	1.11 (1.07–1.15)
Ever smoker	1.76 (1.05–2.96)	1.78 (1.06–2.99)	1.63 (0.97–2.74)	1.63 (0.96–2.74)
HbA_{1c}	1.30 (1.11–1.53)	1.30 (1.10–1.52)	1.26 (1.07–1.47)	1.26 (1.07–1.47)
Hypertension	2.03 (0.98–4.20)	1.90 (0.89–4.06)	1.56 (0.73–3.34)	1.58 (0.73–3.44)
WBC count	1.19 (1.05–1.35)	1.19 (1.04–1.35)	1.19 (1.05–1.35)	1.19 (1.05–1.36)
Log AER	1.19 (1.05–1.37)	1.17 (1.01–1.36)	1.17 (1.01–1.35)	1.17 (1.01–1.36)
eGFR	1.00 (0.99–1.01)	1.00 (0.99–1.01)	1.002 (0.99–1.01)	1.00 (0.99–1.01)
hs-cTnT (log)	Not allowed	1.13 (0.77–1.66)	Not allowed	0.97 (0.65–1.46)
NT-proBNP (log)	Not allowed	Not allowed	1.35 (1.04–1.76)	1.36 (1.03–1.79)
AIC	607.536	609.164	604.089	606.072
AUC	0.8652	0.8646	0.8792	0.8795
Uno concordance statistic for models with vs. without the biomarker(s)				
Estimate (SE)		−0.003 (0.008)	−0.009 (0.01)	−0.009 (0.01)
P value		0.75	0.46	0.51

Data are hazard ratio (95% CI) unless otherwise indicated. Model 1 adjusted for eGFR and allowed for diabetes duration, BMI, having ever smoked, HbA_{1c}, hypertension status, HDL-C and non–HDL-C, WBC count, AER, and eGFR. This model also allowed for sex in analyses of the entire cohort. Model 2 included significant predictors from model 1, in addition to eGFR and hs-cTnT. Model 3 included significant predictors from model 1, in addition to eGFR and NT-proBNP. Model 4 included significant predictors from model 1, in addition to eGFR, hs-cTnT, and NT-proBNP. AIC, Akaike information criterion; AUC, integrated time-dependent area under the curve.

independently of traditional risk factors, including markers of kidney disease and function.

The analytical sensitivity of high-sensitivity cardiac troponin assays has further revealed differences in the concentrations of this biomarker by sex, with women presenting with lower levels compared with men. Despite this, however, the ability of hs-cTnT to independently predict cardiovascular outcomes has generally not been evaluated separately in men and women, with few exceptions (25,26). Our results suggest that compared with men, women are dramatically more likely to experience a subsequent cardiovascular event at hs-cTnT concentrations below the LoD (i.e., <5 ng/L), with no further increase in risk at higher hs-cTnT concentrations. This could be due to a lack of clinical performance and sensitivity of the hs-cTnT assay, because concentrations below the LoD are considered analytically inaccurate. Nevertheless, CVD incidence increased significantly across quartiles of hs-cTnT, including categories for the LoD and limit of blank, in both sexes, suggesting perhaps that factors other than the sensitivity of the assay may have contributed to these results. Confirmation of our results in other cohorts and/or diverse populations with or without diabetes would thus be important to determine clinical relevance because it would suggest that separate prognostic cutoff points should be established for men and women.

BNPs are primarily synthesized and released from ventricular cardiac myocytes in response to cardiac hypertrophy and pressure overload and have received considerable attention as biomarkers of heart failure (27). A substantial body of evidence supports the role of the N-terminal fragment of the prohormone (NT-proBNP), which has a longer half-life in the circulation, as a biomarker for the diagnosis (or exclusion) of and screening for heart failure (28,29). However, evidence has also been accumulating relating to the role of NT-proBNP as a prognostic marker for cardiovascular morbidity and mortality in both the general population as well as among patients with stable vascular disease (7,30,31).

Interestingly, although diabetes carries a significantly increased CVD risk, within the reference interval, higher concentrations of NT-proBNP were previously associated with a lower incidence of type 2 diabetes in adults (32,33). Questions relating to the possible causality of this association have been raised, however, given the absence of a relationship between genetic NT-proBNP variants and insulin resistance (34). Moreover, currently available evidence appears to suggest that NT-proBNP concentrations are elevated in patients with type 2 diabetes compared with control participants, both in the absence of overt CVD (35) and among individuals with dyspnea undergoing cardiac catheterization (36). Two small studies provided evidence to suggest that the concentrations of NT-proBNP are also increased in children (37) and young adults (38) with type 1 diabetes compared with control subjects. Unfortunately, it is impossible to directly compare our results to values obtained using different techniques in the above-mentioned studies because natriuretic peptide assays are not standardized (39).

As previously demonstrated in cohort studies (7,22,24), the prognostic ability of NT-proBNP for cardiovascular morbidity and mortality extends from the general population to individuals with type 2 diabetes. However, few studies have evaluated the association of NT-proBNP with cardiovascular outcomes in type 1 diabetes, and reported findings have been conflicting. Thus, although elevated concentrations of NT-proBNP were previously cross-sectionally associated with microvascular complications (i.e., nephropathy, neuropathy) and macrovascular disease among older adults with long-duration type 1 diabetes in one study (40), another small study of middle-aged adults suggested no independent association between NT-proBNP and the presence of subclinical atherosclerosis (38). With the exception of an observational study showing that increased plasma NT-proBNP concentrations independently predicted all-cause and CVD mortality only among patients with diabetic nephropathy (11), there have been no prospective publications on the prognostic value (in terms of CVD) of NT-proBNP in type 1 diabetes. In the present investigation, elevated concentrations of NT-proBNP strongly predicted the subsequent development of both CVD and MACE after adjustment for demographic and clinical risk characteristics of participants, including markers of kidney disease and function.

As reported earlier in the general population (32,33), women with type 1 diabetes in our cohort presented with higher concentrations of NT-proBNP compared with similarly aged men, although sex did not modify the association between NT-proBNP and either any CVD or MACE. Stratifying by sex revealed that the concentrations of NT-proBNP were a stronger predictor of MACE in women compared with men (in whom the effect size was smaller and nonsignificant in the final model), although the effect of this biomarker on any CVD incidence was similar by sex.

Limitations of the present work include the large proportion of participants with hs-cTnT concentrations below the LoD, raising concerns regarding the accuracy of the analyses. It may further be argued that the sample size was insufficient to allow adequate power to detect significant improvement in outcome prediction with hs-cTnT and/or NT-proBNP. However, although a previous investigation included a greater overall sample of patients with type 1 diabetes, the suggested improved prediction with the addition of hs-cTnT was based on a subsample smaller than the sample included in the present analyses (10). Indeed, the EDC comprises a relatively large cohort of individuals with childhood-onset type 1 diabetes.

In conclusion, hs-cTnT and NT-proBNP both appear to be strong, independent predictors of CVD and MACE among individuals with childhood-onset type 1 diabetes. Although we were unable to show that their assessment improves outcome prediction beyond that offered by traditional cardiovascular risk factors, it would be unlikely that a single biomarker or even a combination of two biomarkers would significantly improve disease prediction, given the multitude of factors contributing to the pathogenesis of cardiovascular complications in diabetes. Indeed, similar findings were obtained with the addition of any of the traditional CVD risk factors evaluated. Moreover, the observed differences in both the distribution of these biomarkers and the strength of their association with the outcomes studied by sex, as also seen in older community-dwelling adults in terms of mortality (25), highlight the value of disaggregating study findings by sex. Such tactics would potentially not only better inform our understanding of the pathophysiology of CVD in men and women with or without diabetes but would also further aid clinical decision making and bring the practice of medicine a step closer to the concept of personalized care.

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