Circulating Troponin As Measured by a Sensitive Assay for Cardiovascular Risk Assessment in Primary Prevention

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BACKGROUND: Measuring circulating cardiac troponin using novel sensitive assays has revealed that even minute elevations are associated with increased mortality in patients with coronary artery disease or even in the general population. Less well defined, however, is the incremental value of measuring circulating cardiac troponin I (cTnI) by a sensitive assay for risk assessment in primary prevention.

METHODS: We measured circulating concentrations of cTnI, N-terminal pro–B-type natriuretic peptide (NT-proBNP), and high-sensitivity C-reactive protein (hsCRP) in 5388 individuals free of known cardiovascular disease recruited into the DETECT study, a prospective longitudinal population-based cohort study. We determined the prognostic implications for incident major adverse cardiovascular events (MACE) during 5 years of follow-up.

RESULTS: Circulating cTnI was detectable in 19% of the subjects. Increased cTnI concentrations were associated with established risk factors for atherosclerosis and demonstrated a graded relationship with all-cause mortality and incident MACE during 5-year follow-up. A single measurement of cTnI significantly improved risk prediction over established risk factors, and also added prognostic information, when adjusted for serum concentrations of NT-proBNP and hsCRP.

CONCLUSIONS: Minute increases in cTnI are associated with increased mortality and incident MACE in a large primary prevention cohort and, thus, identify contributors to cardiovascular risk not fully captured by traditional risk factor assessment.

The release of cardiac troponin into the circulation is a hallmark for diagnosis of acute myocardial syndromes and risk stratification in patients with acute coronary syndromes (1, 2). Occasionally, troponin has also been detected in the blood of individuals from the general population; when detectable, it is associated with a profoundly increased risk for subsequent major adverse cardiovascular events (MACE)[7] (3, 4). Owing to the low prevalence of detectable troponin using standard assays, however, its usefulness for cardiovascular risk assessment in the general population has been low (5).

Recently, high-sensitivity cardiac troponin assays with a limit of detection 10-fold lower than the standard assays have become available for clinical use (6). These sensitive assays not only have improved the accuracy for early diagnosis of acute myocardial infarction (7–9) in patients with acute coronary syndromes, but also have revealed detectable circulating cardiac troponin concentrations in almost all patients with chronic coronary heart disease (10, 11), as well as in patients with heart failure (12). A recent study also reported measureable cardiac troponin T (cTnT) concentrations as assessed by high-sensitivity assays in >25% of the general population (13), which conferred a significantly increased risk for subsequent all-cause mortality. An analysis of the Women's Health Study emphasized the prognostic value of cTnT for cardiovascular risk stratification in women with diabetes mellitus (14).

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Nevertheless, the incremental value of measuring cardiac troponin using a sensitive assay for risk prediction over currently available risk assessment in broad population-based primary prevention of cardiovascular disease is still ill defined.

Therefore, we measured circulating cTnI in 5388 individuals free of known cardiovascular disease who were recruited into the Diabetes Cardiovascular Risk Evaluation Targets and Essential Data for Commitment of Treatment (DETECT) study and determined the prognostic implications for incident MACE.

Materials and Methods

STUDY POPULATION

The DETECT study is a large multistage prospective-longitudinal study. The baseline study consisted of a nationwide representative sample of physicians with primary care functions (medical practitioners, general practitioners, general internists), who recruited 55 518 unselected consecutive subjects, >95% white, in 3188 primary care offices in Germany on 2 predefined half-day cutoff dates (15). A representative sample of 7519 participants was randomly chosen in 1000 primary care offices for additional laboratory tests and evaluated for 5 years (15) (see Supplementary Table 1, which accompanies the online version of this article at http://www.clinchem.org/content/vol58/issue1).

For inclusion in the present analysis, study participants had to be free of any history of myocardial infarction, known coronary artery disease (CAD), documented stroke, clinical signs of systolic or diastolic heart failure, or chronic kidney disease requiring hemodialysis at baseline. In addition, participants included in the present analysis needed to have complete data on clinical outcome as well as valid measures of cTnI, N-terminal pro–B-type natriuretic peptide (NT-proBNP), and high-sensitivity C-reactive protein (hsCRP) plasma concentrations. These criteria resulted in the exclusion of 2131 patients (see online Supplementary Table 1). Thus, a total of 5388 patients were eligible for the analyses. Information about the baseline data in the total sample has been published (15).

The DETECT survey received the approval of the Ethics Committee of the Carl Gustav Carus Medical Faculty at the Technical University of Dresden (AZ: EK149092003; September 16, 2003) and was registered at clinicaltrials.gov (NCT01076608).

BASELINE EXAMINATIONS AND BIOMARKER MEASUREMENT

The details of the standardized methods used in the DETECT study have been described (15). All participants signed an informed consent form and completed a self-report questionnaire, as well as a structured clinical interview and examination by the treating physi-

cian. The physicians also filled out a questionnaire documenting symptoms, diagnoses, treatments, and health behavior of the individual subjects. Additionally, a comprehensive laboratory assessment was performed. The venous blood samples obtained in 2003 were immediately frozen after collection and stored at −80 °C until the time of analysis, performed in 2009.

Circulating troponin I was measured with the sensitive Troponin I Ultra assay (Advia Centaur TnI-Ultra™ immunoassay system, Siemens Medical Solutions Diagnostics), which has a limit of detection of 6 ng/L, a 99th-percentile cutoff of 4 ng/L, and a CV of <10% at 7 ng/L, as reported previously (6, 16). Measurements were performed by Siemens Healthcare Diagnostics Products (Marburg, Germany) according to the manufacturer's quality control specification (Advia Centaur TnI-Ultra Assay Specifications, 2007). In addition, measurements of NT-proBNP (Elecsys2010 analyzer, F. Hoffmann-La Roche Diagnostics) and hsCRP (Roche Modular, F. Hoffmann-La Roche Diagnostics) were performed.

END POINTS

State of health and medical history during follow-up were ascertained at conclusion of the study in 2008. The following end points were documented during the 5-year follow-up period: all-cause mortality, mortality of cardiovascular cause, occurrence of a myocardial infarction, and manifestation of CAD as evidenced by the necessity for coronary revascularization by either bypass graft (CABG) surgery or percutaneous coronary intervention (PCI). All information on end points was taken from a standardized assessment form by the primary care physician or the institution in which the patient was previously treated. Further information from the cause of death registry was taken into account. For prediction and reclassification analyses, we used a combined end point of MACE, including death from cardiovascular causes, nonfatal myocardial infarction, and necessity for coronary revascularization.

STATISTICAL ANALYSIS

We analyzed the cross-sectional association of cTnI concentrations with different established cardiovascular risk factors by odds ratios, which were determined by univariate multinomial logistic regression analysis. Furthermore, independent clinical predictors were determined by multivariate multinomial logistic regression analysis.

We investigated associations between 5-year outcome and cTnI concentrations with the use of Cox proportional hazards regression (17). Besides crude analyses, hazard ratios were adjusted for age, sex, hsCRP, and NT-proBNP serum concentrations, for renal function as determined by estimated glomerular filtration

rate (eGFR), and for established cardiovascular risk factors such as arterial hypertension, hyperlipidemia, diabetes mellitus, family history of CAD, smoking status, and body mass index (BMI). The proportional hazard assumptions were confirmed by Schoenfeld residuals.

We evaluated the associations of the biomarkers and their combinations with outcomes by considering tertiles of cTnI over the detection limit of the assay (6 ng/L), as well as by using a cutoff point that was identified to achieve optimal discrimination for each end point in our study *(18)*. We determined the optimal cutoff of cTnI, NT-pro BNP, and hsCRP values by selecting the maximum of sensitivity and specificity *(18)*. The integrated discrimination improvement (IDI) measure *(19)* was considered for evaluating the incremental value of biomarkers over established cardiovascular risk factors with respect to classification performance.

To assess model discrimination, we calculated estimates of the *c* statistic after Cox regression models (with 95% CIs) *(20)* for conventional cardiovascular risk factors, with and without the biomarkers. We also investigated whether the addition of the combination of 2 or 3 different biomarkers improved the discrimination of the models *(21, 22)*.

Additionally, we evaluated the ability of biomarkers to reclassify risk in comparison to a risk stratification by Framingham risk score, following methods suggested previously *(19, 23–25)*. Using multivariable risk models with the clinical covariates listed above, participants were initially classified into low, intermediate, or high risk, if their predicted 10-year Framingham risk of a cardiovascular event was <6%, 6% to <20%, or 20% or greater, respectively. Subjects were then reclassified into different categories according to the addition of biomarker concentrations. The number of subjects reclassified was assessed by the net reclassification improvement (NRI) and IDI. The categorical NRI was calculated according to Framingham risk categories of <6%, 6% to <20%, and 20% or greater. In addition, continuous NRI was estimated as recently suggested by Pencina et al. *(26)* relying on upward and downward reclassification instead of considering risk thresholds.

P values of <0.05 from 2-sided tests were considered to indicate statistical significance. All statistical analyses were conducted with the use of STATA 10 *(27)*.

Results

PREVALENCE OF DETECTABLE cTnI IN THE STUDY POPULATION

The characteristics of the study population are summarized in online Supplementary Table 2. The prevalence of detectable cTnI was 19.0% using the sensitive cTnI assay; 7.3% of the subjects had a cTnI concentration >10 ng/L.

ASSOCIATION OF cTnI WITH RISK FACTORS FOR CARDIOVASCULAR DISEASE

As summarized in Table 1, cTnI concentrations were increased with advanced age, male sex, increased systolic and diastolic blood pressure, increased triglyceride concentrations, higher BMI, the presence of hyperlipidemia and diabetes mellitus, and decreased eGFR. Likewise, cTnI concentrations demonstrated a gradual increase with higher Framingham risk scores.

In a multivariate logistic regression model, increased cTnI was independently associated with age, male sex, hypertension, increased BMI, and reduced eGFR (see online Supplementary Table 3).

ASSOCIATION OF cTnI WITH ALL-CAUSE MORTALITY AND INCIDENT CARDIOVASCULAR EVENTS

During the follow-up period of 5 years, we documented 138 deaths (2.6%) and 111 (2.1%) MACE, including 24 cardiovascular deaths, 33 myocardial infarctions, and 54 revascularization procedures (41 PCIs, 13 CABGs).

Unadjusted all-cause mortality was 1.5% in the cohort of subjects with cTnI concentrations below the detection limit (<6 ng/L) and increased to 4.9% in the first cTnI tertile (6–7 ng/L) and 10.8% in the highest tertile (cTnI 12–22 640 ng/L) of detectable cTnI concentrations (*P* < 0.0001). Likewise, the occurrence of incident major cardiovascular events within the 5-year follow-up period profoundly increased (*P* < 0.0001) from 1.2% in subjects with undetectable cTnI concentrations to 4.1% in the first cTnI tertile and 9.3% in the third cTnI tertile.

For subjects in the highest tertile of cTnI (>12 ng/L), unadjusted hazard ratios were 7.4 for all-cause mortality and 7.7 for incident major cardiovascular events (Table 2). Similar results were obtained using a study-specific optimal cutoff threshold of >17 ng/L (see online Supplementary Table 4). By Cox proportional hazard models adjusting for traditional risk factors including age, sex, arterial hypertension, hyperlipidemia, diabetes mellitus, family history of CAD, BMI, smoking status, and eGFR, hazard ratios were 2.7 for all-cause mortality (*P* < 0.001) and 2.7 for MACE (*P* < 0.001) (Table 2). Finally, further adjustment for NT-proBNP and hsCRP serum concentrations, in addition to traditional risk factors and eGFR, resulted in hazard ratios of 2.3 for all-cause mortality (*P* < 0.001) and 2.1 for MACE (*P* = 0.009) in the highest tertile of cTnI (Table 2).

Table 1. Cross-sectional association of cTnI and cardiovascular risk factors within the study cohort.

	cTnI				
	Below detection level (<6 ng/L)	First tertile (6–7 ng/L)	Second tertile (8–11 ng/L)	Third tertile (12–22 640 ng/L)	P^a
n	4364	365	326	333	
Mean age, years (SD)	53.5 (13.2)	65.0 (11.0)	66.0 (11.4)	65.9 (12.4)	<0.001
Male sex, n (%)	1473 (33.8)	191 (52.3)	191 (58.6)	180 (54.1)	<0.001
Mean Framingham score, % (SD)	9.1 (8.6)	15.7 (10.2)	17.1 (9.9)	16.0 (11.1)	<0.001
Arterial hypertension, n (%)	1307 (30.0)	174 (47.7)	167 (51.2)	200 (60.1)	<0.001
Mean systolic blood pressure, mmHg (SD)	129.9 (17.5)	137.0 (17.6)	139.3 (18.6)	139.7 (20.0)	<0.001
Mean diastolic blood pressure, mmHg (SD)	79.8 (9.9)	80.3 (9.2)	81.6 (9.1)	81.3 (9.4)	0.006
Diabetes mellitus, n (%)	419 (9.6)	73 (20.0)	89 (27.3)	81 (24.3)	<0.001
Insulin-dependent diabetes mellitus, n (%)	103 (2.4)	21 (5.8)	34 (10.4)	20 (6.0)	<0.001
Mean Hb A_{1c}, % (SD)	5.4 (0.7)	5.7 (1.0)	5.9 (1.1)	5.8 (0.9)	<0.001
Hyperlipidemia, n (%)	1131 (25.9)	123 (33.7)	122 (33.4)	122 (36.6)	<0.001
Mean LDL cholesterol, mg/dL (SD)	128.5 (33.3)	133.9 (31.4)	133.7 (33.4)	130.6 (33.2)	0.258
Mean triglycerides, mg/dL (SD)	145.5 (109.4)	164.0 (132.7)	173.3 (252.0)	163.9 (154.8)	0.003
Mean BMI, kg/m^2 (SD)	26.7 (4.9)	28.0 (4.8)	27.7 (4.0)	28.1 (4.9)	<0.001
Current smoker, n (%)	917 (22.6)	49 (14.9)	35 (12.5)	51 (17.1)	<0.001
Mean eGFR, mL · min^{-1} · (1.73m^2)$^{-1}$ (SD)	58.2 (10.6)	56.6 (10.8)	56.9 (12.2)	54.3 (12.6)	<0.001
Mean hsCRP, mg/L (SD)	4.27 (6.88)	4.59 (7.47)	4.37 (6.30)	4.92 (7.88)	0.095
Mean NT-proBNP, ng/L (SD)	88.8 (166.4)	179.7 (269.4)	173.0 (223.2)	451.7 (951.8)	<0.001

[a] P value for odds ratio, increase of 1 SD for metric risk factors; participants with cTnI concentrations below detection level as reference group.

CARDIOVASCULAR RISK STRATIFICATION BY cTnI CONCENTRATIONS

Accordingly, the addition of cTnI to traditional risk factors significantly ($P = 0.002$) improved the c statistic from 0.800 to 0.839 for prediction of incident major cardiovascular events. As illustrated in Fig. 1, the area under the ROC curve (AUC) increased from 0.809 for established cardiovascular risk factors to 0.823 when high-sensitivity cTnI was added. As a result, IDI and NRI were significantly ($P = 0.001$) improved (Fig. 1; Table 3).

CARDIOVASCULAR RISK STRATIFICATION BY BIOMARKER COMBINATIONS

Because adding NT-proBNP serum concentrations to traditional risk factors also significantly improved the c statistics, we analyzed the potential role of combining established biomarkers as a multimarker-panel for risk prediction. As illustrated in Table 4, none of the measured biomarkers hsCRP, NT-proBNP, and cTnI, considered individually without taking into account traditional risk factors, was superior to traditional risk factors to predict incident MACE. The addition of all individual serum biomarkers to the traditional risk fac-

tors, however, was associated with a small but significant improvement in c statistics for predicting incident MACE (Table 4). Nevertheless, combining all 3 biomarkers did not significantly improve risk prediction for incident MACE compared with using only 2 of the biomarkers in combination.

Discussion

The results of the present study demonstrate that circulating troponin I measured by a contemporary sensitive assay is detectable in almost 20% of adults in a general primary prevention population. Higher concentrations of cTnI were found to be associated with classic risk factors for coronary artery disease and demonstrated a graded association with all-cause mortality as well as incident major adverse cardiovascular events during a 5-year follow-up period. Importantly, a single measurement of cTnI significantly improved risk stratification for MACE even after adjustment for traditional risk factors in primary prevention.

The results of the present study are remarkably similar to data of the few studies published to date investigating circulating troponin concentrations as

Table 2. Hazard ratios (HRs) for all-cause mortality and MACE according to cTnI concentrations.

	All-cause mortality		MACE	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Crude				
Detectable cTnI (>6 ng/L)	4.82 (3.45–6.74)	<0.001	4.59 (3.16–6.66)	<0.001
Undetectable cTnI	0.21 (0.15–0.29)	<0.001	0.22 (0.15–0.32)	<0.001
First tertile (cTnI 6–7 ng/L)	3.27 (1.93–5.54)	<0.001	3.33 (1.87–5.91)	<0.001
Second tertile (cTnI 8–11 ng/L)	4.03 (2.44–6.65)	<0.001	2.90 (1.55–5.42)	<0.001
Third tertile (cTnI 12–22 640 ng/L)	7.37 (4.91–11.08)	<0.001	7.76 (4.98–12.08)	<0.001
Adjusted for age, sex, and eGFR				
Detectable cTnI	2.09 (1.46–2.98)	<0.001	1.92 (1.23–2.98)	0.004
Undetectable cTnI	0.48 (0.34–0.68)	<0.001	0.52 (0.34–0.81)	0.004
First tertile	1.63 (0.97–2.74)	0.065	1.59 (0.86–2.94)	0.138
Second tertile	1.73 (1.02–2.91)	0.045	1.19 (0.62–2.28)	0.602
Third tertile	2.97 (1.90–4.64)	<0.001	3.04 (1.79–5.17)	<0.001
Adjusted for hsCRP and NT-proBNP[a]				
Detectable cTnI	3.50 (2.49–4.94)	<0.001	3.22 (2.19–4.73)	<0.001
Undetectable cTnI	0.29 (0.20–0.40)	<0.001	0.31 (0.21–0.46)	<0.001
First tertile	2.44 (1.44–4.13)	<0.001	2.54 (1.43–4.51)	<0.001
Second tertile	3.07 (1.83–5.15)	<0.001	2.13 (1.13–4.00)	0.019
Third tertile	5.09 (3.36–7.72)	<0.001	4.99 (3.12–7.98)	<0.001
Adjusted for age, sex, eGFR, and risk factors[b]				
Detectable cTnI	1.94 (1.35–2.79)	<0.001	1.78 (1.15–2.75)	0.009
Undetectable cTnI	0.51 (0.36–0.74)	<0.001	0.56 (0.36–0.87)	0.009
First tertile	1.58 (0.93–2.66)	0.089	1.59 (0.87–2.90)	0.133
Second tertile	1.60 (0.94–2.72)	0.081	1.11 (0.58–2.11)	0.759
Third tertile	2.69 (1.71–4.25)	<0.001	2.65 (1.55–4.52)	<0.001
Adjusted for age, sex, eGFR, hsCRP, NT-proBNP,[a] and risk factors[b]				
Detectable cTnI	1.68 (1.16–2.43)	0.006	1.48 (0.96–2.29)	0.075
Undetectable cTnI	0.60 (0.41–0.86)	0.006	0.67 (0.44–1.04)	0.075
First tertile	1.38 (0.82–2.32)	0.221	1.40 (0.76–2.55)	0.279
Second tertile	1.41 (0.82–2.44)	0.212	0.96 (0.51–1.81)	0.893
Third tertile	2.29 (1.43–3.65)	<0.001	2.06 (1.20–3.53)	0.009

[a] Over optimal DETECT discriminatory cutoff value. NT-proBNP: all-cause mortality, >85.85 ng/L; MACE, >121.9 ng/L. hsCRP: all-cause mortality, >1.43 mg/L; MACE, >1.4 mg/L.
[b] Risk factors include the following variables: hypertension (binary), hyperlipidemia (binary), diabetes (binary), familial predisposition for diabetes (binary), smoking status (binary), and BMI (continuous).

measured by high-sensitivity assays in a population-based cohort, free of known cardiovascular disease. The Dallas Heart Study *(13)* was a slightly smaller study measuring circulating troponin T concentrations using a high-sensitivity assay (hs-cTnT) in 3546 individuals recruited from Dallas County residents and followed up for a median of 6.4 years. In 26% of the individuals without known CAD, hs-cTnT concentrations ≥3 ng/L (the lower detection limit of the assay) were observed; these concentrations correlated with multiple traditional risk factors for CAD and demonstrated significant associations with all-cause and cardiovascular mortality *(13)*. Thus, our results essentially confirm that measurement of cTnI with a sensitive assay adds value to the assessment of traditional cardiovascular risk factors in an entirely different population of primary prevention subjects. Compared with the Dallas Heart Study cohort, individuals of the DETECT cohort

Fig. 1. ROC curves showing increased AUCs when cTnI and the combination of cTnI, NT-proBNP, and hsCRP were added to established cardiovascular risk factors for prediction of incident major cardiovascular events within the study cohort, compared to a model with only the established cardiovascular risk factors.
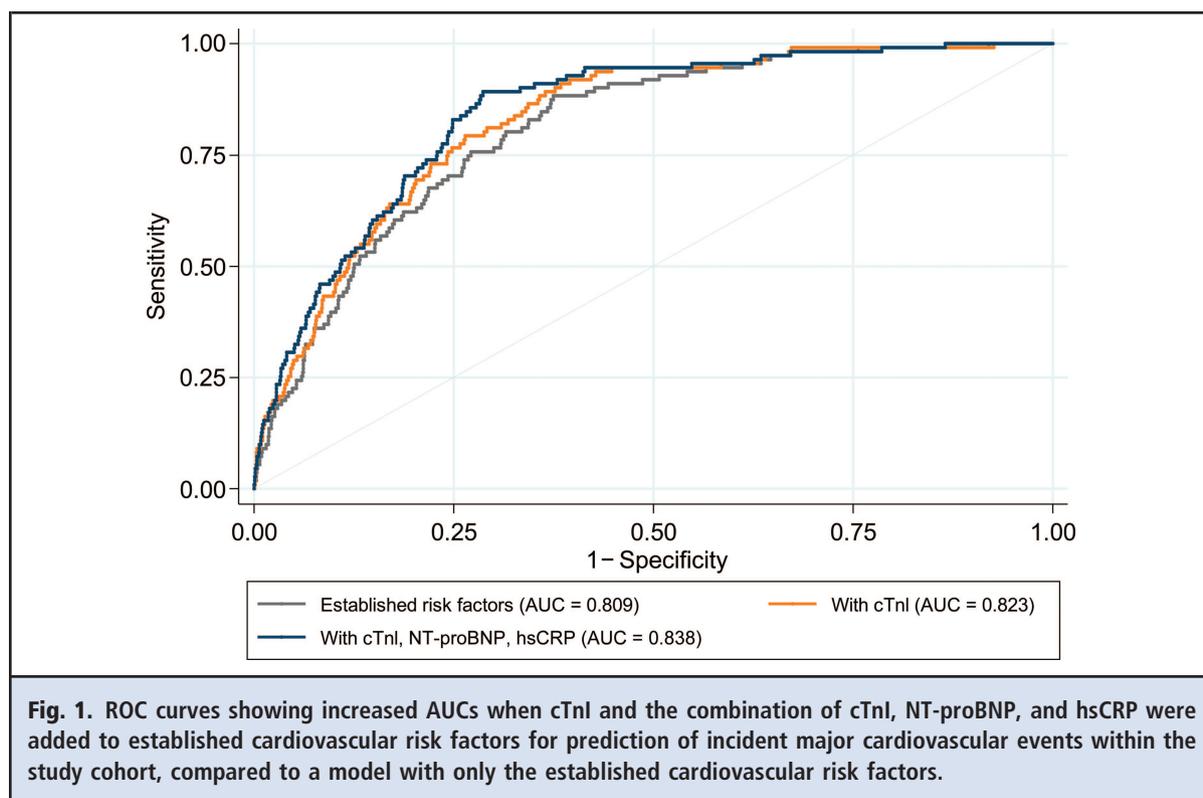
spanned a much wider age range and had significantly higher LDL cholesterol concentrations but lower BMI values; the DETECT trial did not use a predefined sampling strategy including intentional oversampling of specific individuals.

Importantly, even in the model fully adjusted for traditional cardiovascular risk factors, the addition of a single measurement of cTnI increased the *c* statistic and significantly improved discrimination, suggesting that the measurement of low concentrations of circulating TnI is indeed clinically meaningful. Moreover, in accordance with data from the Dallas Heart Study *(13)*, adjustment for NT-proBNP concentrations also significantly improved the *c* statistic, indicating that cTnI and NT-proBNP might provide partly overlapping information on risk prediction in asymptomatic individuals. It should be noted, however, that the troponin assay used in the present study falls short of the recently developed high-sensitivity assays, given its 10% CV at cTnI concentrations of 70 ng/L *(28)*. Specifically, in settings other than diagnosis of myocardial infarction, classification of the applied assay for troponin measurements is crucial for interpretation of the results *(29)*. In fact, the use of a high-sensitivity assay, as applied in the Dallas Heart Study *(13)*, would have most likely resulted in a higher proportion of patients with measureable troponin I concentrations in our primary

prevention cohort, given that circulating troponin concentrations correlate with age and the present population was significantly older than the Dallas Heart Study population. In line with this reasoning are recently published results with respect to the incremental value of measuring cTnT by use of a high-sensitivity assay (hs-cTnT) for risk prediction in the Atherosclerosis Risk in Communities (ARIC) study cohort, a general population of middle-aged to older adults *(30)*. The ARIC cohort is significantly older than our cohort, and the prevalence of measurable hs-cTnT was 66.5%, indicating that the association of hs-cTnT concentrations with age translated into a significantly higher prevalence of measurable hs-cTnT *(31)*. Finally, subjects lost to follow-up in the present study were significantly older, more frequently men, and had lower eGFR, all of which might have contributed to a lower prevalence of measurable cTnI in the study cohort available for analysis.

Nevertheless, although cTnI and NT-proBNP demonstrated independent and additive associations with cardiovascular risk prediction, further studies are required to determine whether combinations of these 2 markers will perform better than either marker alone in the identification of contributors to cardiovascular risk not fully captured by traditional risk factor assessment. In addition, heart failure end points were not assessed

Predicted risk with established risk factors	Predicted risk with cTnI			Reclassification	
	<6%	6–20%	>20%	Up	Down
Reclassification by adding cTnI[b]					
Patients with MACE					
Categorical					
<6%	63 (88.7)	8 (11.3)	0 (0.0)	18 (16.2)	14 (12.6)
6–20%	13 (33.3)	16 (41.0)	10 (25.6)		
>20%	0 (0.0)	1 (100.0)	0 (0.0)		
Continuous				24 (21.6)	9 (8.1)
Patients without MACE					
Categorical					
<6%	4793 (98.6)	70 (1.4)	0 (0.0)	106 (2.0)	152 (2.9)
6–20%	152 (36.8)	225 (54.5)	36 (8.7)		
>20%	0 (0.0)	0 (0.0)	1 (100.0)		
Continuous				141 (2.7)	145 (2.8)
Reclassification by adding cTnI, NT-proBNP, and hsCRP[c]					
Patients with MACE					
Categorical					
<6%	60 (84.5)	10 (14.1)	1 (1.4)	21 (18.9)	9 (8.1)
6–20%	8 (20.5)	21 (53.9)	10 (25.6)		
>20%	0 (0.0)	1 (100.0)	0 (0.0)		
Continuous				31 (27.9)	15 (13.5)
Patients without MACE					
Categorical					
<6%	4703 (97.6)	111 (2.3)	6 (0.1)	146 (2.8)	184 (3.5)
6–20%	184 (44.9)	197 (48.1)	29 (7.1)		
>20%	0 (0.0)	0 (0.0)	1 (100.0)		
Continuous				228 (4.3)	333 (6.3)

in the DETECT study. Given that increased concentrations of cardiac troponin and NT-proBNP have been shown to associate with an increased risk for incident heart failure *(30)*, incorporation of heart failure as an end point may have further improved cardiovascular risk prediction. The value of recommending general screening of the primary prevention population by measuring cTnI, as well as appropriate diagnostic and therapeutic consequences, should be determined prospectively.

In summary, minute increases of circulating troponin I as measured by a sensitive assay are detectable in a significant fraction of primary prevention subjects free of known cardiovascular disease and are associated with an increase in all-cause mortality as well as incident major adverse cardiovascular events. These data extend similar results recently published in investigations of entirely different population-based cohorts *(3, 13, 14, 30, 32)* and may also provide strong support to prospectively address the potential clinical utility of more intensive diagnostic and therapeutic intervention in subjects with minor increases of circulating troponin I concentrations.

Table 4. c Statistics for Cox regression models predicting incident MACE by biomarker combinations.

	MACE	
	c Statistic	P
Established risk factors[a]	0.800	Reference
cTnI[b]	0.710	
NT-proBNP[b]	0.677	
hsCRP[b]	0.602	
cTnI + NT-proBNP	0.774	
cTnI + hsCRP	0.720	
hsCRP + NT-proBNP	0.718	
cTnI + NT-proBNP + hsCRP	0.794	
Combination with 1 biomarker		
Established risk factors + cTnI	0.839	
Estimated difference with the addition of cTnI	0.039	0.002
Established risk factors + NT-proBNP	0.843	
Estimated difference with the addition of NT-proBNP	0.043	0.000
Established risk factors + hsCRP	0.834	
Estimated difference with the addition of hsCRP	0.034	0.001
Combination with 2 biomarkers		
Established risk factors + cTnI + NT-proBNP	0.853	
Estimated difference with the addition of cTnI + NT-proBNP	0.052	0.000
Established risk factors + cTnI + hsCRP	0.844	
Estimated difference with the addition of cTnI + hsCRP	0.044	0.000
Established risk factors + hsCRP + NT-proBNP	0.851	
Estimated difference with the addition of hsCRP + NT-proBNP	0.050	0.000
Combination with 3 biomarkers		
Established risk factors + cTnI + NT-proBNP + hsCRP	0.859	
Estimated difference with the addition of cTnI + NT-proBNP + hsCRP	0.058	0.000

[a] Established risk factors: age, hypertension, smoking status, hyperlipidemia, family history of CAD, diabetes mellitus, obesity.
[b] Over optimal DETECT discriminatory cutoff value (study-specific optimal cutoff derived from ROC analysis): NT-proBNP, MACE >121.9 ng/L. hsCRP, MACE >1.4 mg/L. cTnI, MACE >17 ng/L.

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