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JAMA | Original Investigation

Prognostic Value of Cardiovascular Biomarkers in the Population

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IMPORTANCE Identification of individuals at high risk for atherosclerotic cardiovascular disease within the population is important to inform primary prevention strategies.

OBJECTIVE To evaluate the prognostic value of routinely available cardiovascular biomarkers when added to established risk factors.

DESIGN, SETTING, AND PARTICIPANTS Individual-level analysis including data on cardiovascular biomarkers from 28 general population–based cohorts from 12 countries and 4 continents with assessments by participant age. The median follow-up was 11.8 years.

EXPOSURE Measurement of high-sensitivity cardiac troponin I, high-sensitivity cardiac troponin T, N-terminal pro-B-type natriuretic peptide, B-type natriuretic peptide, or high-sensitivity C-reactive protein.

MAIN OUTCOMES AND MEASURES The primary outcome was incident atherosclerotic cardiovascular disease, which included all fatal and nonfatal events. The secondary outcomes were all-cause mortality, heart failure, ischemic stroke, and myocardial infarction. Subdistribution hazard ratios (HRs) for the association of biomarkers and outcomes were calculated after adjustment for established risk factors. The additional predictive value of the biomarkers was assessed using the C statistic and reclassification analyses.

RESULTS The analyses included 164 054 individuals (median age, 53.1 years [IQR, 42.7-62.9 years] and 52.4% were women). There were 17 211 incident atherosclerotic cardiovascular disease events. All biomarkers were significantly associated with incident atherosclerotic cardiovascular disease (subdistribution HR per 1-SD change, 1.13 [95% CI, 1.11-1.16] for high-sensitivity cardiac troponin I; 1.18 [95% CI, 1.12-1.23] for high-sensitivity cardiac troponin T; 1.21 [95% CI, 1.18-1.24] for N-terminal pro-B-type natriuretic peptide; 1.14 [95% CI, 1.08-1.22] for B-type natriuretic peptide; and 1.14 [95% CI, 1.12-1.16] for high-sensitivity C-reactive protein) and all secondary outcomes. The addition of each single biomarker to a model that included established risk factors improved the C statistic. For 10-year incident atherosclerotic cardiovascular disease in younger people (aged <65 years), the combination of high-sensitivity cardiac troponin I, N-terminal pro-B-type natriuretic peptide, and high-sensitivity C-reactive protein resulted in a C statistic improvement from 0.812 (95% CI, 0.8021-0.8208) to 0.8194 (95% CI, 0.8089-0.8277). The combination of these biomarkers also improved reclassification compared with the conventional model. Improvements in risk prediction were most pronounced for the secondary outcomes of heart failure and all-cause mortality. The incremental value of biomarkers was greater in people aged 65 years or older vs younger people.

CONCLUSIONS AND RELEVANCE Cardiovascular biomarkers were strongly associated with fatal and nonfatal cardiovascular events and mortality. The addition of biomarkers to established risk factors led to only a small improvement in risk prediction metrics for atherosclerotic cardiovascular disease, but was more favorable for heart failure and mortality.

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Early identification of individuals in the general population at high risk for atherosclerotic cardiovascular disease shapes primary preventive strategies to reduce the risk of developing atherosclerotic cardiovascular disease.[1,2] Risk scores based on traditional risk factors for atherosclerotic cardiovascular disease (eg, the European Society of Cardiology Systematic Coronary Risk Evaluation 2 [SCORE2], the American Heart Association/American College of Cardiology Pooled Cohort Equations, and the American Heart Association Predicting Risk of Cardiovascular Disease Events [PREVENT] equations) are widely available to estimate an individual's risk for future cardiovascular events.[1-4]

Cardiovascular biomarkers, such as cardiac troponin, natriuretic peptides, and C-reactive protein (CRP), are established in clinical care. Using newer, high-sensitivity cardiac troponin assays, concentrations became measurable in the general population, opening up the prospects for a broader application of this biomarker.[5] Several studies have reported (1) strong associations of these biomarkers with incident atherosclerotic cardiovascular disease events in individuals with known atherosclerotic cardiovascular disease, but also, and most importantly, in apparently healthy individuals and (2) an improvement in risk stratification when these biomarkers were added to established risk prediction models.[5-12]

Notwithstanding the achievements of earlier studies, the actual application of routinely available cardiovascular biomarkers for risk stratification in primary prevention has not become routine clinical practice. In addition, it remains uncertain which of the established biomarkers might be best suited to predict each outcome and how such associations are influenced by age.

Therefore, this study brings together the largest multinational individual-level dataset, to date, to investigate the comparative predictive value of cardiovascular biomarkers for incident atherosclerotic cardiovascular disease events in the general population and to elucidate their differential effects according to age.

Key Points

Question What is the value of cardiovascular biomarkers when added to established risk factors to predict incident cardiovascular events in the population?

Findings In this large, individual-level data analysis from 28 general population–based cohorts from 12 countries, high-sensitivity cardiac troponins I and T, B-type natriuretic peptide, and high-sensitivity C-reactive protein were associated with fatal and nonfatal events.

Meaning The addition of biomarkers to established risk factors leads to only a small improvement in risk prediction metrics for atherosclerotic cardiovascular disease, but was more favorable for heart failure and mortality.

Methods

Study Cohorts

Details on the selection of study cohorts appear in the eMethods in Supplement 1. This individual-level analysis included data from 28 multinational population-based cohorts (eTable 1 in Supplement 1). Eligible cohorts were those that included (1) individuals from the general population, in which most participants were apparently healthy (ie, had not had any major atherothrombotic cardiovascular events); (2) individuals who had at least 1 measurement of high-sensitivity cardiac troponin I, high-sensitivity cardiac troponin T, B-type natriuretic peptide (BNP), N-terminal pro-BNP (NT-proBNP), or high-sensitivity CRP; and (3) individuals with follow-up for at least 2 years. Data from all cohorts were collected and harmonized in a database. Individuals with a history of atherosclerotic cardiovascular disease events or heart failure were excluded from the analyses (**Figure 1**).

Study Outcomes

The primary outcome was incident atherosclerotic cardiovascular disease, which included all fatal and nonfatal events. Incident atherosclerotic cardiovascular disease was defined by the first possible or definite coronary heart disease event, possible or definite ischemic stroke event, coronary revascularization, coronary heart disease death, ischemic stroke death, or unclassifiable death.[13] The secondary outcomes were all-cause mortality, incident heart failure, incident ischemic stroke, and incident myocardial infarction. Additional information about the outcomes investigated appear in eTable 2 in Supplement 1.

Biomarkers

For all cohorts reported by the Biomarker for Cardiovascular Risk Assessment across Europe (BiomarCaRE) consortium, serum high-sensitivity cardiac troponin I concentration was determined in the BiomarCaRE core laboratory in Hamburg, Germany, using a highly sensitive cardiac troponin I immunoassay for stored samples (Architect i2000SR; Abbott Diagnostics). The limit of detection for the immunoassay was 1.9 ng/L (range, 0-50 000 ng/L) and the assay had a coefficient of variation of 10% at a concentration of 5.2 ng/L. Measurement of NT-proBNP concentration was performed using an electrochemiluminescence immunoassay (ELECSYS 2010 and Cobas e411; Roche Diagnostics); the analytic range is 0 ng/L to 35 000 ng/L.

Measurement of high-sensitivity CRP concentration was performed using the Vario immunoassay and the Architect c8000 system (Abbott Diagnostics). For the cohorts not part of the BiomarCaRE consortium, measurements of high-sensitivity cardiac troponin I, high-sensitivity cardiac troponin T, NT-proBNP, BNP, and high-sensitivity CRP were performed as part of the local cohort-specific procedures (details on the specific assays used in each cohort appear in eTable 3 in Supplement 1).

Statistical Analyses

Associations Between Cardiac-Specific Biomarkers and Study Outcomes

To examine the unadjusted association of the biomarkers and the primary outcome, cumulative incidence curves were computed according to biomarker quintiles. Death from causes

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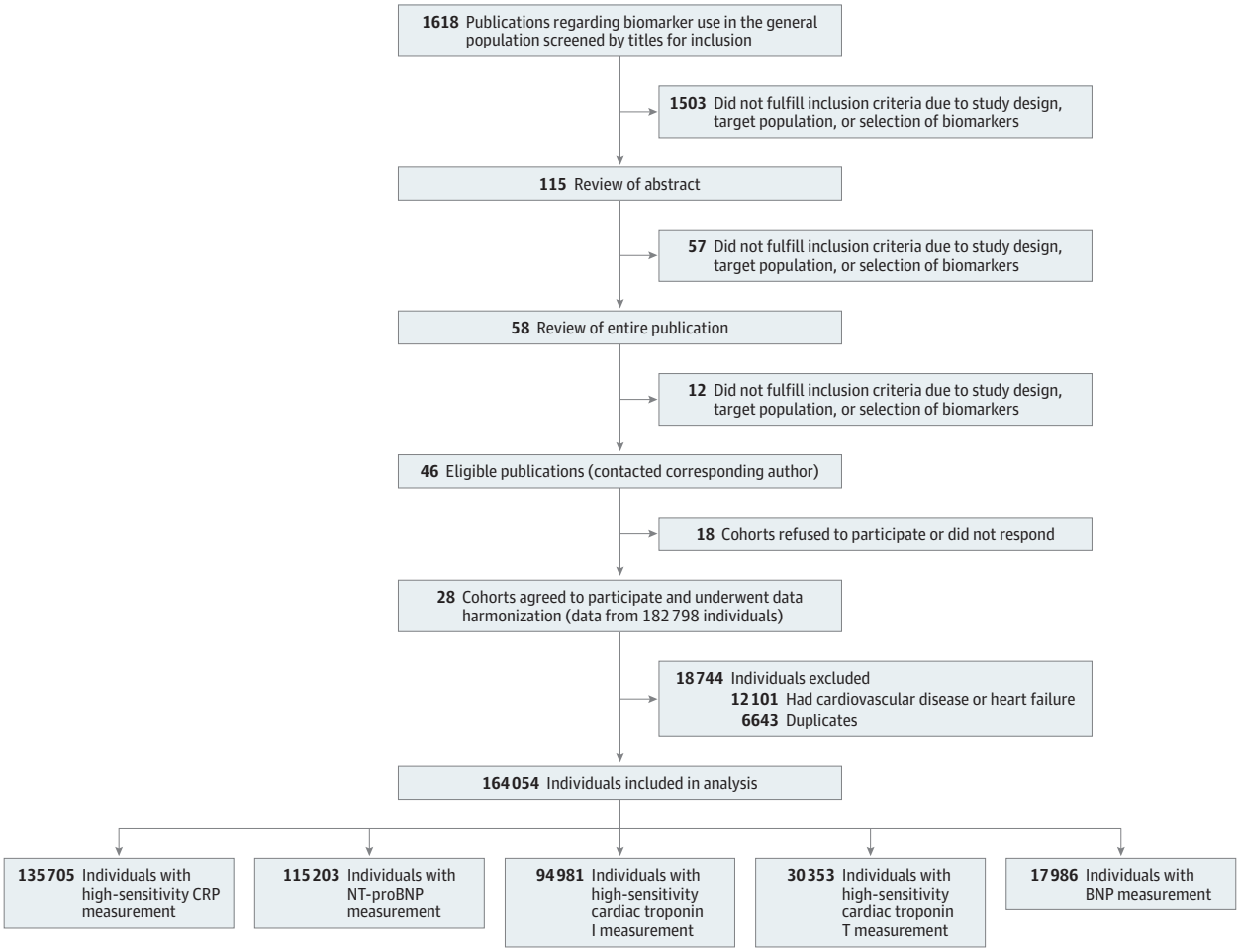
Figure 1. Flow of Publications, Cohorts, and Individuals by Exclusion Criteria



BNP indicates B-type natriuretic peptide; CRP, C-reactive protein; NT-proBNP, N-terminal pro-BNP.

unrelated to atherosclerotic cardiovascular disease was treated as a competing event. The curves were estimated using the Aalen-Johansen estimator. The quintiles were computed using linear quantile mixed models.[14,15]

Fine and Gray subdistribution hazard models were calculated. Death from causes unrelated to atherosclerotic cardiovascular disease or the secondary outcomes were treated as a competing event, respectively.[16] Cox proportional hazards regression models were used for all-cause mortality. The biomarkers were used as continuous variables after applying $\log_e$ transformation with hazard ratios (HRs) or subdistribution HRs computed additionally per 1-SD change to allow for comparisons of the effect size among different biomarkers. The models with high-sensitivity cardiac troponin concentration as a continuous variable were augmented with a binary variable indicating if the measured value was above or below the limit of detection.[17]

The regression models for all the study outcomes were adjusted for sex and cohort as stratification variables. The models were also adjusted for age, total cholesterol, high-density lipoprotein (HDL) cholesterol, current smoking, prevalent diabetes, systolic blood pressure, and self-reported use of antihypertensive drugs. For the outcomes of all-cause mortality and heart failure, the models were additionally adjusted for body mass index (calculated as weight in kilograms divided by height in meters squared). In separate analyses, high-sensitivity cardiac troponin I, NT-proBNP, and high-sensitivity CRP were combined in a multivariable model because these biomarkers represent different pathophysiological pathways and the data were readily available in the cohorts. The time-to-event models were extended by modeling the biomarkers using penalized cubic splines.

Added Predictive Value

The C statistic and net reclassification improvement (NRI) were used to quantify the added predictive value of each biomarker beyond that from the adjusted model described above. In the presence of competing risks, the calculations of the C statistic and NRI were adapted.[18,19] Internal-external cross-validation was applied to control for the overoptimism of calculating performance measures on the same dataset from which the models were computed.[20] Namely, each

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Table. Baseline Characteristics of the Study Population

	Study population (N = 164 054)
Demographics	
Sex, No. (%)[a]	
Female	85 972 (52.4)
Male	78 000 (47.6)
Age at biomarker collection, median (IQR), y	53.1 (42.7-62.9)
Recruitment time span of included studies, y	1982-2011
History	
Hypertension, No. (%)[b]	67 719 (41.6)
Diabetes, No. (%)	9977 (6.1)
Daily smoking, No. (%)[c]	40 226 (24.8)
Self-reported use of antihypertensive drugs, No. (%)[d]	30 970 (19.1)
Risk scores	
SCORE2 10-y risk of atherosclerotic cardiovascular disease, median (IQR), %[e,f]	4.1 (1.7-8.6)
Pooled Cohorts Risk Equation, median (IQR), %[f,g]	4.9 (1.4-13.1)
Physical and laboratory findings	
Systolic blood pressure, median (IQR), mm Hg	130.0 (118.0-145.0)
Body mass index, median (IQR)[h]	26.3 (23.6-29.4)
Cholesterol, median (IQR), mmol/L	
Total	5.5 (4.8-6.3)
High-density lipoprotein	1.4 (1.1-1.7)
Low-density lipoprotein	4.1 (3.4-4.9)
Level was <3.4 mmol/L, No. (%)	38 223 (25.6)
Estimated glomerular filtration rate, median (IQR), mL/min/1.73 m^2	93.1 (78.7-104.8)
High-sensitivity cardiac troponin I	
Median (IQR), ng/L	2.5 (1.9-4.1)
Below limit of detection, No. (%)	35 704 (37.6)
High-sensitivity cardiac troponin T	
Median (IQR), ng/L	3.1 (3.0-6.0)
Below limit of detection, No. (%)	13 379 (49.5)
N-terminal pro-B-type natriuretic peptide, median (IQR), ng/L	43.8 (20.6-86.2)
B-type natriuretic peptide, median (IQR), ng/L	14.9 (7.9-28.6)
High-sensitivity C-reactive protein, median (IQR), mg/L	1.4 (0.7-3.2)

Abbreviation: SCORE2, European Society of Cardiology Systematic Coronary Risk Evaluation 2.

SI conversion factors: To convert high-density, low-density, and total cholesterol to mg/dL, divide by 0.0259.

[a] Information on sex was available for 163 972 individuals.

[b] Information on hypertension was available for 162 947 individuals.

[c] Information on smoking was available for 162 139 individuals.

[d] Information on use of antihypertensive drugs was available for 162 181 individuals.

[e] Recommended by the European Society of Cardiology to calculate the individual 10-year risk of an incident cardiovascular event. This score considers age, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, sex, and smoking as risk factors.

[f] Indicates the absolute risk, but was computed for descriptive purposes because not all individuals in the dataset fall within the intended scope of the corresponding score.

[g] Recommended by the American Heart Association/American College of Cardiology. In addition to the risk factors in the SCORE2, this risk equation considers race, treatment for hypertension, and diabetes.

[h] Calculated as weight in kilograms divided by height in meters squared.

study was in turn left out and the Cox model or the Fine and Gray model was estimated in the remaining studies. Next, the models were used to estimate the event probabilities in the excluded study. The category-based NRI and the continuous NRI were calculated. The 95% CIs for the C statistic and NRI were computed by bootstrapping 500 times the internal-external cross-validation.

All statistical analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing).[21] Additional information about the statistical analyses appears in the eMethods in Supplement 1.

Results

Study Population

There were 28 general population–based cohorts included (from 12 countries and 4 continents) with data on 164 054 individuals (median age, 53.1 years [IQR, 42.7-62.9 years]; 85 972 [52.4%] were women; and 9977 [6.1%] had diabetes) (Figure 1, **Table**, and eTable 4 in Supplement 1). Of the 162 947 individuals with data for the hypertension variable, 67 719 (41.6%) had hypertension. Of the 162 139 individuals with data for the smoking variable, 40 226 (24.8%) smoked daily. The median 10-year atherosclerotic cardiovascular disease risk SCORE2 was 4.1% (IQR, 1.7%-8.6%) and the corresponding 10-year risk using the Pooled Cohort Risk Equation was 4.9% (IQR, 1.4%-13.1%).

The median biomarker concentrations were 2.5 ng/L (IQR, 1.9-4.1 ng/L) for high-sensitivity cardiac troponin I, 3.1 ng/L (IQR, 3.0-6.0 ng/L) for high-sensitivity cardiac troponin T, 43.8 ng/L (IQR, 20.6-86.2 ng/L) for NT-proBNP, 14.9 ng/L (IQR, 7.9-28.6 ng/L) for BNP, and 1.4 mg/L (IQR, 0.7-3.2 mg/L) for high-sensitivity CRP (Table and eFigure 1 in Supplement 1). Except for NT-proBNP, there was a linear relationship between age and the median biomarker concentrations (eFigure 2 in Supplement 1).

During a median follow-up of 11.8 years (IQR, 6.2-18.0 years; maximum follow-up, 28.2 years), there were 17 211 incident atherosclerotic cardiovascular disease events, 25 346

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deaths from any cause, 6766 cases of heart failure, 4794 incident cases of incident ischemic stroke, and 8024 incident cases of myocardial infarction (eTable 5 in Supplement 1).

Primary Outcome: Association of Biomarkers With Incident Atherosclerotic Cardiovascular Disease Events

After adjusting for sex and cohort and the conventional risk factors of age, total cholesterol, HDL cholesterol, smoking status, diabetes, systolic blood pressure, and self-reported use of antihypertensive drugs, the biomarker concentrations were associated with incident atherosclerotic cardiovascular disease events (subdistribution HR per 1-SD change, 1.13 [95% CI, 1.11-1.16] for high-sensitivity cardiac troponin I; 1.18 [95% CI, 1.12-1.23] for high-sensitivity cardiac troponin T; 1.21 [95% CI, 1.18-1.24] for NT-proBNP; 1.14 [95% CI, 1.08-1.22] for BNP; and 1.14 [95% CI, 1.12-1.16] for high-sensitivity CRP; **Figure 2** and **Figure 3**). For all 5 biomarkers, there were more events per 1000 person-years in individuals with biomarker concentrations above the median compared with those with biomarker concentrations below the median (Figure 3). Additional data appear in eTable 6 in Supplement 1.

In separate analyses, high-sensitivity cardiac troponin I, NT-proBNP, and high-sensitivity CRP were included in the same model and proved to be predictors of atherosclerotic cardiovascular disease events (adjusted subdistribution HR, 1.07 [95% CI, 1.04-1.10] for high-sensitivity cardiac troponin I; 1.19 [95% CI, 1.15-1.23] for NT-proBNP; and 1.14 [95% CI, 1.10-1.17] for high-sensitivity CRP). When stratified by biomarker quintiles, the cumulative atherosclerotic cardiovascular disease incidence gradually increased with increasing biomarker concentrations (eFigure 3 in Supplement 1).

The addition of the biomarkers to the base model, which included only conventional risk factors, was associated with an increase in the C statistics for atherosclerotic cardiovascular disease events after 1 year, 5 years, and 10 years (**Figure 4** and eTable 7 in Supplement 1). The strongest increase was observed when high-sensitivity cardiac troponin I, NT-proBNP, and high-sensitivity CRP were combined in 1 model. In the reclassification analyses, the categorical NRI for the combination of high-sensitivity cardiac troponin I, NT-proBNP, and high-sensitivity CRP was 0.044 (95% CI, 0.023-0.069) (eTable 8 in Supplement 1).

The continuous NRI was 0.241 (95% CI, 0.193-0.309) for high-sensitivity cardiac troponin I, 0.201 (95% CI, 0.008-0.364) for high-sensitivity cardiac troponin T, 0.06 (95% CI, 0.016-0.093) for NT-proBNP, 0.077 (95% CI, 0.000-0.144) for BNP, 0.192 (95% CI, 0.162-0.222) for high-sensitivity CRP, and 0.23 (95% CI, 0.162-0.283) for the combination of high-sensitivity cardiac troponin I, NT-proBNP, and high-sensitivity CRP (eTable 9 in Supplement 1).

Association of Biomarkers With Secondary Outcomes

All biomarkers were associated with all-cause mortality, incident heart failure, incident ischemic stroke, and incident myocardial infarction (Figure 3 and eTables 10-13 in Supplement 1). The associations of biomarkers with all-cause mortality and incident heart failure were larger than those for atherosclerotic cardiovascular disease. The highest subdistribution HRs were observed for incident heart failure with high-sensitivity cardiac troponin T (HR, 1.44; 95% CI, 1.38-1.51), NT-proBNP (HR, 1.62; 95% CI, 1.56-1.68), and BNP (HR, 1.59; 95% CI, 1.43-1.77). The addition of the biomarkers also improved the C statistics (Figure 4) and the appropriate classification of risk (eTables 8-9 in Supplement 1) when added to the base model for the secondary outcomes. The largest risk classification improvements were for heart failure and all-cause mortality.

Sensitivity Analyses

When stratified according to the age cutoff of 65 years, older individuals (n = 34 143; aged ≥65 years) more often had diabetes and hypertension, but smoked less often than younger individuals (n = 129 456; aged <65 years) (eTable 14 in Supplement 1). Concentrations of high-sensitivity cardiac troponin I, high-sensitivity cardiac troponin T, NT-proBNP, BNP, and high-sensitivity CRP were higher, on average, in older individuals.

The association of biomarkers with atherosclerotic cardiovascular disease events remained significant in both individuals younger than 65 years of age and in those aged 65 years or older (eTable 15 in Supplement 1). The subdistribution HRs for high-sensitivity cardiac troponin I, high-sensitivity cardiac troponin T, and NT-proBNP were higher in older individuals. The subdistribution HR was lower for high-sensitivity CRP in older people. In older people, the C statistic of the base model was substantially lower compared with younger people and the addition of the biomarkers provided higher absolute increases of the C statistic in older people (eTable 16 in Supplement 1). For example, the combination of high-sensitivity cardiac troponin I, NT-proBNP, and high-sensitivity CRP increased the C statistic for 10-year atherosclerotic cardiovascular disease events from 0.812 (95% CI, 0.8021-0.8208) to 0.8194 (95% CI, 0.8089-0.8277) in younger people and from 0.6323 (95% CI, 0.5945-0.6570) to 0.6602 (95% CI, 0.6224-0.6834) in older people. Furthermore, the overall NRI with the combined biomarkers for atherosclerotic cardiovascular disease was higher in older people (NRI, 0.062; 95% CI, 0.013-0.120) compared with younger people (NRI, 0.028; 95% CI, 0.010-0.070) (eTable 17 in Supplement 1).

The HRs for all-cause mortality were also higher for NT-proBNP and BNP in older people, but slightly lower for high-sensitivity CRP and high-sensitivity cardiac troponin T (eTable 15 in Supplement 1). A similar pattern was also observed for the other outcomes of heart failure, ischemic stroke, and myocardial infarction. The overall NRI using the combination of high-sensitivity cardiac troponin I, NT-proBNP, and high-sensitivity CRP was higher in older people for the secondary outcomes of heart failure, ischemic stroke, and myocardial infarction, but lower for all-cause mortality (eTable 17 in Supplement 1).

In sensitivity analyses, the regression analyses were repeated for 10-year atherosclerotic cardiovascular disease events while removing 1 risk factor from the base model (eTable 18 in Supplement 1). The addition of high-sensitivity cardiac troponin I, NT-proBNP, and high-sensitivity CRP resulted in the highest increase in the C statistic when age was removed from the base model (C statistic difference of 0.0312; 95% CI,

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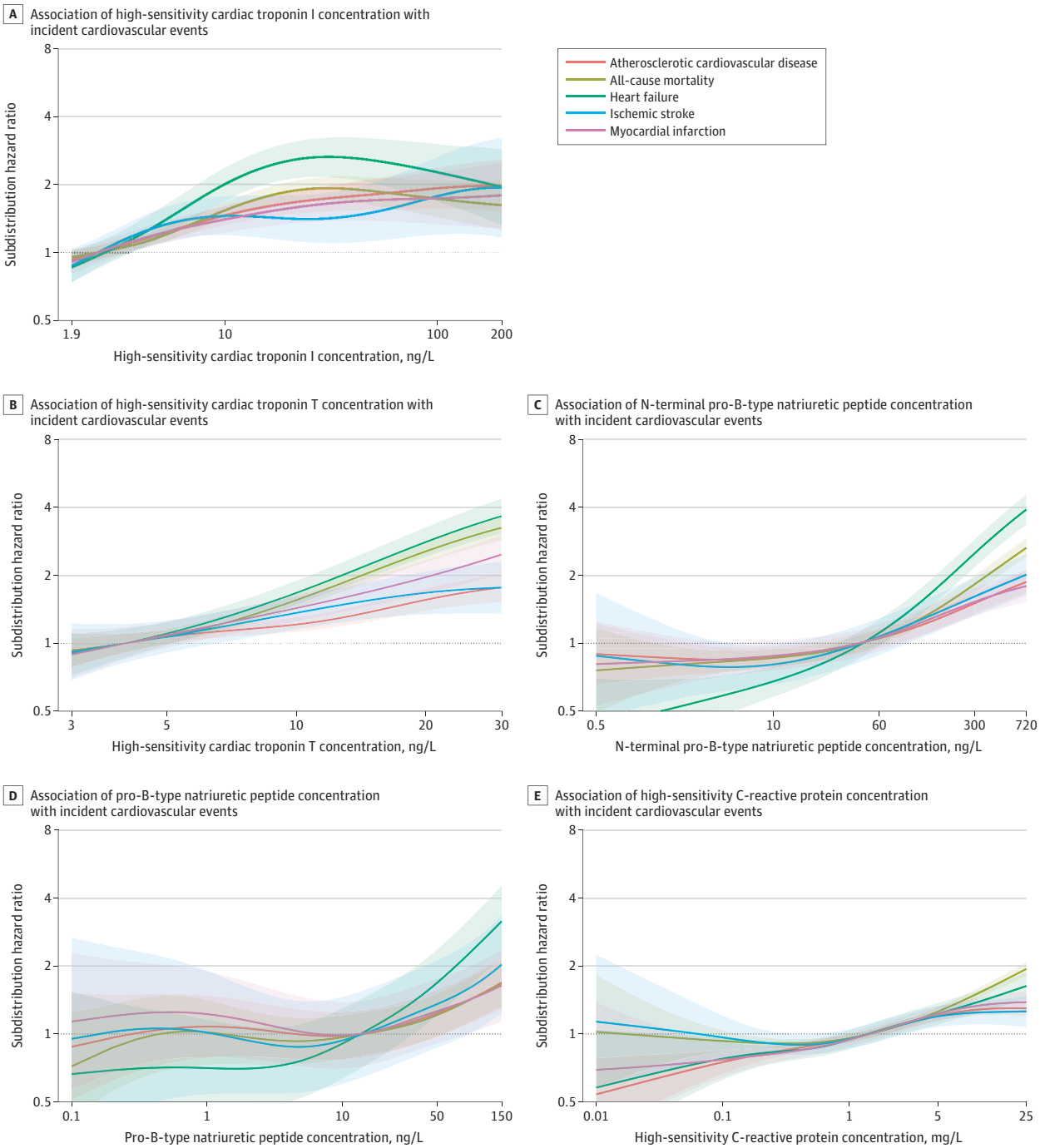
Figure 2. Association of Biomarkers With Incident Cardiovascular Events



The data were plotted based on results from adjusted Cox models or Fine and Gray subdistribution hazard models for the $\log_e$-transformed biomarker concentrations using penalized cubic splines. The x-axes contain the back-transformed values on a log scale (range, lowest reported value [or the limit of detection in the case of high-sensitivity cardiac troponin I and T] to the 99th percentile). The shading indicates the 95% CIs. The corresponding reference values vary per graph and are used specifically for each biomarker and event combination. The median follow-up time was 11.8 years (IQR, 6.2-18.0 years) for atherosclerotic cardiovascular disease, 13.0 years (IQR, 7.9-19.2 years) for all-cause mortality, 12.8 years (IQR, 6.2-19.3 years) for heart failure, 11.9 years (IQR, 6.3-17.7 years) for ischemic stroke, and 11.6 years (IQR, 6.2-17.8 years) for myocardial infarction. Additional data appear in eTable 6 and eTables 10-13 in Supplement 1.

0.0254-0.0373). The magnitude of change in the C statistic after adding the biomarkers to the full base model was comparable with the effect of systolic blood pressure and self-reported use of antihypertensive medication.

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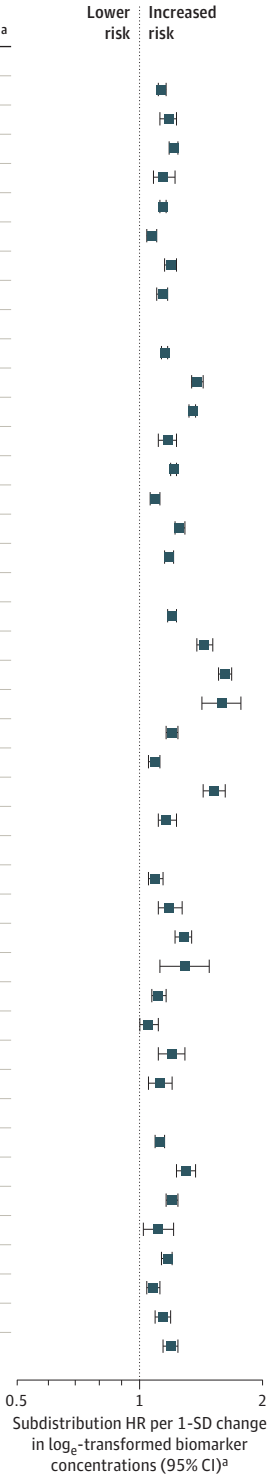
Figure 3. Association of the Biomarkers of Interest With Incident Cardiovascular Events

	Laboratory value below median, events/1000 person-years (95% CI)	Laboratory value above median, events/1000 person-years (95% CI)	Subdistribution HR per 1-SD change in $\log_e$-transformed biomarker concentrations (95% CI)[a]
Atherosclerotic cardiovascular disease[b,c]			
High-sensitivity cardiac troponin I concentration, ng/L	10.92 (10.64-11.21)	28.36 (26.79-30.01)	1.13 (1.11-1.16)
High-sensitivity cardiac troponin T concentration, ng/L	12.14 (11.5-12.8)	44.86 (39.97-50.32)	1.18 (1.12-1.23)
NT-proBNP concentration, ng/L	14.99 (14.66-15.33)	31.6 (30.07-33.21)	1.21 (1.18-1.24)
B-type natriuretic peptide concentration, ng/L	15.99 (15.21-16.8)	26.62 (23.77-29.8)	1.14 (1.08-1.22)
High-sensitivity C-reactive protein concentration, mg/L	16.61 (16.32-16.9)	30 (28.82-31.23)	1.14 (1.12-1.16)
High-sensitivity cardiac troponin I concentration, ng/L[d]	9.61 (9.29-9.95)	24.63 (22.86-26.53)	1.07 (1.04-1.10)
NT-proBNP concentration, ng/L[d]	12.7 (12.33-13.07)	22.41 (20.99-23.93)	1.19 (1.15-1.23)
High-sensitivity C-reactive protein concentration, mg/L[d]	12.82 (12.46-13.18)	22.71 (21.29-24.22)	1.14 (1.10-1.17)
All-cause mortality[c]			
High-sensitivity cardiac troponin I concentration, ng/L	5.25 (5.06-5.44)	14.51 (13.42-15.7)	1.15 (1.13-1.17)
High-sensitivity cardiac troponin T concentration, ng/L	7.27 (6.89-7.66)	21.27 (18.92-23.89)	1.38 (1.34-1.43)
NT-proBNP concentration, ng/L	6.9 (6.7-7.11)	16.72 (15.66-17.85)	1.35 (1.32-1.37)
B-type natriuretic peptide concentration, ng/L	6.62 (6.14-7.13)	13.2 (11.16-5.6)	1.17 (1.11-1.23)
High-sensitivity C-reactive protein concentration, mg/L	8.19 (7.99-8.39)	15.15 (14.35-15.99)	1.21 (1.19-1.23)
High-sensitivity cardiac troponin I concentration, ng/L[d]	4.51 (4.3-4.73)	12.31 (11.1-13.64)	1.09 (1.06-1.12)
NT-proBNP concentration, ng/L[d]	5.54 (5.32-5.78)	11.69 (10.65-12.83)	1.25 (1.22-1.29)
High-sensitivity C-reactive protein concentration, mg/L[d]	6.08 (5.84-6.32)	11.3 (10.34-12.36)	1.18 (1.15-1.21)
Heart failure[c]			
High-sensitivity cardiac troponin I concentration, ng/L	12.29 (11.95-12.63)	30.9 (29.09-32.82)	1.20 (1.17-1.23)
High-sensitivity cardiac troponin T concentration, ng/L	14.26 (13.72-14.81)	40.1 (36.84-43.64)	1.44 (1.38-1.51)
NT-proBNP concentration, ng/L	15.15 (14.79-15.51)	32.96 (31.26-34.75)	1.62 (1.56-1.68)
B-type natriuretic peptide concentration, ng/L	13.62 (12.86-14.41)	27.55 (24.25-31.28)	1.59 (1.42-1.77)
High-sensitivity C-reactive protein concentration, mg/L	16.72 (16.4-17.04)	30.79 (29.47-32.16)	1.20 (1.16-1.24)
High-sensitivity cardiac troponin I concentration, ng/L[d]	10.91 (10.49-11.34)	26.78 (24.61-29.14)	1.09 (1.05-1.12)
NT-proBNP concentration, ng/L[d]	13.09 (12.65-13.54)	25.91 (24.01-27.96)	1.52 (1.43-1.62)
High-sensitivity C-reactive protein concentration, mg/L[d]	14.17 (13.73-14.63)	25.47 (23.68-27.39)	1.16 (1.11-1.23)
Ischemic stroke[c]			
High-sensitivity cardiac troponin I concentration, ng/L	10.48 (10.2-10.76)	28.89 (27.28-30.59)	1.09 (1.05-1.14)
High-sensitivity cardiac troponin T concentration, ng/L	14.33 (13.79-14.87)	41.38 (38.06-44.99)	1.18 (1.11-1.27)
NT-proBNP concentration, ng/L	14.1 (13.8-14.41)	32.52 (31.01-34.1)	1.28 (1.22-1.34)
B-type natriuretic peptide concentration, ng/L	14.13 (13.41-14.88)	27.41 (24.39-30.79)	1.29 (1.12-1.48)
High-sensitivity C-reactive protein concentration, mg/L	16.27 (15.98-16.55)	29.91 (28.75-31.12)	1.11 (1.07-1.16)
High-sensitivity cardiac troponin I concentration, ng/L[d]	8.95 (8.64-9.27)	24.2 (22.42-26.12)	1.05 (1.00-1.11)
NT-proBNP concentration, ng/L[d]	11.4 (11.06-11.75)	22.84 (21.35-24.43)	1.20 (1.11-1.29)
High-sensitivity C-reactive protein concentration, mg/L[d]	12.25 (11.9-12.6)	22.33 (20.93-23.83)	1.12 (1.05-1.20)
Myocardial infarction[c]			
High-sensitivity cardiac troponin I concentration, ng/L	10.24 (9.97-10.52)	27.15 (25.61-28.78)	1.12 (1.09-1.15)
High-sensitivity cardiac troponin T concentration, ng/L	14.7 (14.16-15.26)	40.84 (37.58-44.37)	1.30 (1.23-1.37)
NT-proBNP concentration, ng/L	13.91 (13.61-14.22)	31.34 (29.84-32.91)	1.20 (1.16-1.24)
B-type natriuretic peptide concentration, ng/L	13.97 (13.23-14.74)	24.81 (21.95-28.02)	1.11 (1.02-1.21)
High-sensitivity C-reactive protein concentration, mg/L	16.07 (15.78-16.35)	29.23 (28.07-30.43)	1.17 (1.13-1.20)
High-sensitivity cardiac troponin I concentration, ng/L[d]	8.7 (8.39-9.01)	22.71 (21.01-24.54)	1.08 (1.04-1.12)
NT-proBNP concentration, ng/L[d]	11.34 (11-11.69)	20.81 (19.43-22.29)	1.14 (1.09-1.19)
High-sensitivity C-reactive protein concentration, mg/L[d]	11.66 (11.32-12.01)	20.88 (19.52-22.32)	1.19 (1.14-1.24)



NT-proBNP indicates N-terminal pro-B-type natriuretic peptide.

[a]Hazard ratio (HR) per unit increase = exponential function(log[HR per 1-SD increase]/SD).

[b]First possible/definite coronary heart disease or ischemic stroke event; coronary revascularization; or died of coronary heart disease, ischemic stroke, or unclassifiable.

[c]The median follow-up was 11.8 years (IQR, 6.2-18.0 years) for atherosclerotic cardiovascular disease; all-cause mortality, 13.0 years (IQR, 7.9-19.2 years); heart failure, 12.8 years (IQR, 6.2-19.3 years); ischemic stroke, 11.9 years (IQR, 6.3-17.7 years); and myocardial infarction, 11.6 years (IQR, 6.2-17.8 years).

[d]These 3 biomarkers were combined into 1 model to investigate their independent effect on association.

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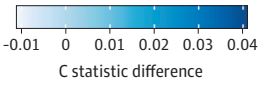
Figure 4. Heat Maps Displaying the Changes in the C Statistic After the Addition of the Biomarker to the Base Model



A Change in the C statistic for atherosclerotic cardiovascular disease after addition of individual biomarkers and in combined model of high-sensitivity cardiac troponin I concentration, N-terminal pro-B-type natriuretic peptide concentration, and high-sensitivity C-reactive protein concentration

Change in C statistic (95% CI) by year	High-sensitivity cardiac troponin I concentration	High-sensitivity cardiac troponin T concentration	N-terminal pro-B-type natriuretic peptide concentration	B-type natriuretic peptide concentration	High-sensitivity C-reactive protein concentration	Combined model of high-sensitivity cardiac troponin I concentration, N-terminal pro-B-type natriuretic peptide concentration, and high-sensitivity C-reactive protein concentration
10	0.0039 (0.0027 to 0.0053)	0.0155 (0.0092 to 0.0220)	0.0049 (0.0035 to 0.0064)	0.0023 (-0.0001 to 0.0047)	0.0031 (0.0023 to 0.0040)	0.0091 (0.0062 to 0.0121)
5	0.0067 (0.0049 to 0.0087)	0.0081 (0.0036 to 0.0132)	0.0065 (0.0047 to 0.0085)	0.0021 (-0.0015 to 0.0053)	0.0033 (0.0023 to 0.0046)	0.0138 (0.0102 to 0.0177)
1	0.0064 (0.0022 to 0.0103)	0.0097 (0.0021 to 0.0205)	0.0126 (0.0096 to 0.0163)	-0.0034 (-0.0144 to 0.0046)	0.0044 (0.0022 to 0.0061)	0.0131 (0.0070 to 0.0204)

B Change in the C statistic for all-cause mortality after addition of individual biomarkers and in combined model of high-sensitivity cardiac troponin I concentration, N-terminal pro-B-type natriuretic peptide concentration, and high-sensitivity C-reactive protein concentration

Change in C statistic (95% CI) by year	High-sensitivity cardiac troponin I concentration	High-sensitivity cardiac troponin T concentration	N-terminal pro-B-type natriuretic peptide concentration	B-type natriuretic peptide concentration	High-sensitivity C-reactive protein concentration	Combined model of high-sensitivity cardiac troponin I concentration, N-terminal pro-B-type natriuretic peptide concentration, and high-sensitivity C-reactive protein concentration
10	0.0026 (0.0017 to 0.0035)	0.0117 (0.0084 to 0.0150)	0.0072 (0.0058 to 0.0088)	0.004 (0.0014 to 0.0069)	0.0039 (0.0031 to 0.0048)	0.0105 (0.0080 to 0.0132)
5	0.0048 (0.0035 to 0.0062)	0.0131 (0.0086 to 0.0177)	0.0094 (0.0075 to 0.0116)	0.0047 (0.0006 to 0.0091)	0.0059 (0.0047 to 0.0072)	0.0158 (0.0118 to 0.0197)
1	0.0092 (0.0053 to 0.0136)	0.0261 (0.0128 to 0.0416)	0.0184 (0.0126 to 0.0241)	0.0099 (-0.0027 to 0.0231)	0.0135 (0.0094 to 0.0174)	0.0313 (0.0194 to 0.0422)

C Change in the C statistic for heart failure after addition of individual biomarkers and in combined model of high-sensitivity cardiac troponin I concentration, N-terminal pro-B-type natriuretic peptide concentration, and high-sensitivity C-reactive protein concentration

Change in C statistic (95% CI) by year	High-sensitivity cardiac troponin I concentration	High-sensitivity cardiac troponin T concentration	N-terminal pro-B-type natriuretic peptide concentration	B-type natriuretic peptide concentration	High-sensitivity C-reactive protein concentration	Combined model of high-sensitivity cardiac troponin I concentration, N-terminal pro-B-type natriuretic peptide concentration, and high-sensitivity C-reactive protein concentration
10	0.0064 (0.0034 to 0.0095)	0.0267 (0.0195 to 0.0344)	0.0266 (0.0222 to 0.0313)	0.0253 (0.0163 to 0.0374)	0.0044 (0.0028 to 0.0062)	0.0303 (0.0200 to 0.0404)
5	0.0004 (-0.0028 to 0.0040)	0.0266 (0.0183 to 0.0368)	0.0266 (0.0216 to 0.0320)	0.0306 (0.0143 to 0.0495)	0.0035 (0.0018 to 0.0056)	0.0183 (0.0090 to 0.0271)
1	0.001 (-0.0080 to 0.0106)	0.0381 (0.0228 to 0.0559)	0.0399 (0.0255 to 0.0547)	0.0296 (0.0045 to 0.0662)	0.0027 (-0.0009 to 0.0070)	0.0238 (0.0022 to 0.0500)

D Change in the C statistic for ischemic stroke after addition of individual biomarkers and in combined model of high-sensitivity cardiac troponin I concentration, N-terminal pro-B-type natriuretic peptide concentration, and high-sensitivity C-reactive protein concentration

Change in C statistic (95% CI) by year	High-sensitivity cardiac troponin I concentration	High-sensitivity cardiac troponin T concentration	N-terminal pro-B-type natriuretic peptide concentration	B-type natriuretic peptide concentration	High-sensitivity C-reactive protein concentration	Combined model of high-sensitivity cardiac troponin I concentration, N-terminal pro-B-type natriuretic peptide concentration, and high-sensitivity C-reactive protein concentration
10	0.0015 (-0.0009 to 0.0037)	0.0047 (0.0000 to 0.0090)	0.0028 (0.0004 to 0.0058)	0.0059 (-0.0026 to 0.0149)	0.0033 (0.0015 to 0.0050)	0.0041 (-0.0010 to 0.0095)
5	0.0062 (0.0025 to 0.0106)	0.006 (0.0005 to 0.0116)	0.0039 (0.0003 to 0.0080)	0.0031 (-0.0081 to 0.0156)	0.003 (0.0009 to 0.0056)	0.0094 (0.0018 to 0.0166)
1	0.0077 (-0.0048 to 0.0242)	0.0106 (0.0015 to 0.0210)	0.0148 (0.0081 to 0.0223)	-0.0093 (-0.0511 to 0.0255)	0.008 (0.0036 to 0.0146)	0.0175 (0.0032 to 0.0343)

E Change in the C statistic for myocardial infarction after addition of individual biomarkers and in combined model of high-sensitivity cardiac troponin I concentration, N-terminal pro-B-type natriuretic peptide concentration, and high-sensitivity C-reactive protein concentration

Change in C statistic (95% CI) by year	High-sensitivity cardiac troponin I concentration	High-sensitivity cardiac troponin T concentration	N-terminal pro-B-type natriuretic peptide concentration	B-type natriuretic peptide concentration	High-sensitivity C-reactive protein concentration	Combined model of high-sensitivity cardiac troponin I concentration, N-terminal pro-B-type natriuretic peptide concentration, and high-sensitivity C-reactive protein concentration
10	0.0036 (0.0017 to 0.0056)	0.0147 (0.0072 to 0.0217)	0.0058 (0.0037 to 0.0082)	0.0036 (-0.0007 to 0.0084)	0.0041 (0.0027 to 0.0056)	0.0105 (0.0058 to 0.0152)
5	0.0064 (0.0035 to 0.0091)	0.0083 (0.0011 to 0.0149)	0.0072 (0.0046 to 0.0100)	0.0053 (-0.0015 to 0.0129)	0.0045 (0.0026 to 0.0065)	0.0161 (0.0103 to 0.0223)
1	0.0046 (0.0000 to 0.0095)	0.0127 (-0.0052 to 0.0283)	0.0116 (0.0071 to 0.0166)	0.0016 (-0.0143 to 0.0146)	0.0033 (0.0005 to 0.0066)	0.0113 (0.0025 to 0.0219

The changes in the C statistic were based on Cox regression models for all-cause mortality and based on Fine and Gray models for the other outcomes. The C statistics were computed based on the 1-year, 5-year, and 10-year probabilities of any events. Additional data appear in eTable 6 and eTables 10-13 in Supplement 1. The analyses stratified by age appear in eTable 16 in Supplement 1.

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Sensitivity analyses also were performed that included information on cholesterol-lowering medication, which was available in 71.2% of the study population (eTable 19 in Supplement 1). These findings were consistent with the primary study findings.

Discussion

In this individual-level analysis, the value of the most commonly used biomarkers for cardiovascular risk prediction in the general population was investigated using harmonized, multinational population data (from 28 cohorts in 12 countries and 4 continents).

There were 4 salient findings. First, all investigated biomarkers were predictors not only of incident atherosclerotic cardiovascular disease events, but also of all-cause mortality, heart failure, myocardial infarction, and ischemic stroke. Even though prior studies from the general population focused on the association of biomarkers with fatal or nonfatal atherosclerotic cardiovascular disease in general, most did not consider other important outcomes.[7,8,22,23] Previous analyses examining incident heart failure or ischemic stroke were limited by (1) small numbers of events, (2) the availability of aggregate data only, or (3) shorter duration of follow-up.[7] Interestingly, there was a stronger association of all the investigated biomarkers with all-cause mortality, and particularly with heart failure, compared with fatal and nonfatal atherosclerotic cardiovascular disease events.

In the current dataset, all-cause mortality was the most frequently reported outcome (25 346 events), highlighting the potential competing risk of death for any regression analyses. Thus, the consideration of competing risk by using Fine and Gray regression analyses may be a possible explanation for opposite results compared with prior studies[10,22,24] and strengthens the findings from the current analysis. The strong predictive value for heart failure outcomes is particularly notable given the increase in options available for preventing incident heart failure (such as intensive blood pressure control and treatment with sodium-glucose cotransporter 2 inhibitors).[25] Importantly, the magnitude of change in the C statistic for the outcomes of all-cause mortality and heart failure reported in the current study is similar to other studies that investigated the addition of coronary calcium scoring to classic cardiovascular risk factors to predict atherosclerotic cardiovascular disease.[26]

The second significant finding was that the combination of the biomarkers high-sensitivity cardiac troponin I, NT-proBNP, and high-sensitivity CRP into 1 model provided the largest incremental predictive value and that all 3 biomarkers were independent predictors. These 3 biomarkers represent 3 different pathophysiological pathways, had the highest availability in the cohorts examined, are routinely available, and were also identified as the strongest predictors in earlier analyses of multiple biomarkers.[27] Most prior studies focused on 1 specific cardiovascular biomarker and did not attempt to combine several markers into 1 model.[28] The combination of high-sensitivity cardiac troponin I, NT-proBNP, and high-sensitivity CRP in the current study resulted in the biggest improvements in the C statistic for most outcomes investigated.

Interestingly, the multivariable model showed the highest HRs for NT-proBNP for all outcomes except for incident myocardial infarction for which high-sensitivity CRP showed the strongest association. This ranking of biomarkers is comparable with prior analyses from the FINRISK and Belfast PRIME cohorts,[27] for which the highest HRs for atherosclerotic cardiovascular disease events were observed for NT-proBNP; however, no high-sensitivity troponin assay was available for comparison at that time.

The third important finding is a sustained association of improved risk prediction when biomarkers were added to conventional risk factors over a time horizon of more than 10 years. The long follow-up (median duration of nearly 12 years) enabled the assessment of the C statistic over a long time frame, and the incremental value of the biomarkers was apparent even beyond 10 years. This observation highlights the potential value of biomarkers for incorporation in primary prevention strategies, which ideally should address long-term effects. Prior post hoc analyses from the JUPITER, WOSCOPS, and SPRINT large clinical trials[29-31] investigated the role of biomarkers, especially cardiac troponin and NT-proBNP for decision-making in preventive care. Data from the JUPITER trial[29] showed that those individuals with higher concentrations of high-sensitivity cardiac troponin I or BNP were at higher risk for atherosclerotic cardiovascular disease events and may have a higher absolute risk reduction with statin treatment.

In the WOSCOPS trial,[30] longitudinal measurements were available for high-sensitivity cardiac troponin I and showed an association with atherosclerotic cardiovascular disease events and also their decrease 1 year after statin treatment. Recently, post hoc analyses from the SPRINT trial revealed that individuals with elevated concentrations of high-sensitivity cardiac troponin I and NT-proBNP had a substantially increased risk of all-cause mortality and heart failure, but also had the highest absolute risk reduction with treatment compared with individuals with normal concentrations of the biomarkers.[31]

The fourth novel finding is the greater incremental value of biomarkers in older individuals (aged ≥65 years) compared with younger individuals (aged <65 years). Prior studies showed that with increasing age, the effect of conventional risk factors is attenuated.[3,32,33] In the current study, the conventional risk factor model had a C statistic of 0.632 in older individuals vs 0.812 in younger individuals. This resulted in the development of risk prediction models specifically for older people.[3,34]

However, there remains substantial residual risk when predicting incident atherosclerotic cardiovascular disease events, highlighting the need for other clinically relevant risk markers. In this context, the current study findings support the relevance of cardiovascular biomarkers, especially in older individuals. This observation was primarily driven by the increasing predictive value of NT-proBNP in older people, whereas the predictive value of high-sensitivity CRP decreased. Importantly, these findings were not limited to atherosclerotic cardiovascular disease events, but were also observed for all of the secondary outcomes, especially all-cause mortality and heart failure.

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Limitations

This analysis has limitations. First, this study used 5 established biomarkers that are widely available in routine clinical practice; however, the absolute measurements for high-sensitivity cardiac troponin T and BNP were limited. Second, most individuals were recruited from high-income cohorts in Europe and North America, which limits the worldwide generalizability of the findings.

Third, there were a limited number of Black participants. Non-Black participants systematically have higher concentrations of high-sensitivity CRP and higher absolute risks. Fourth, important questions remain before cardiovascular biomarkers may be considered for implementation into clinical practice. These questions include the need for cost-effectiveness analyses and the identification of a target population.

Conclusions

Cardiovascular biomarkers were strongly associated with fatal and nonfatal cardiovascular events and mortality. The addition of biomarkers to established risk factors led to only a small improvement in risk prediction metrics for atherosclerotic cardiovascular disease, but was more favorable for heart failure and mortality.

ARTICLE INFORMATION

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Concept and design: Neumann, Weimann, Ferrario, Lewis, Sans, Tonkin, Blankenberg.
Acquisition, analysis, or interpretation of data: Neumann, Twerenbold, Weimann, Ballantyne, Benjamin, Costanzo, de Lemos, deFilippi, Di Castelnuovo, Donfrancesco, Dörr, Eggers, Engstrom, Felix, Gansevoort, Giampaoli, Giedraitis, Hedberg, Iacoviello, Jørgensen, Kee, Koenig, Kuulasmaa, Lewis, Lorenz, Lyngbakken, Magnussen, Melander, Nauck, Niiranen, Nilsson, Olsen, Omland, Oskarsson, Palmieri, Thorand, Prince, Qaderi, Vasan, Salomaa, Sans, Smith, Söderberg, Peters, Tonkin, Tunstall-Pedoe, Veronesi, T. Watanabe, M. Watanabe, Zeiher, Zeller, Ojeda.
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