






Association of Cardiac Biomarkers With Cardiovascular Outcomes in Patients With Psoriatic Arthritis and Psoriasis: A Longitudinal Cohort Study

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Objective. In patients with psoriatic disease (PsD), we determined whether cardiac troponin I (cTnI) and N-terminal pro–brain natriuretic peptide (NT-proBNP) were associated with carotid plaque burden and the development of cardiovascular events independent of the Framingham Risk Score (FRS).

Methods. Among 1,000 patients with PsD, carotid total plaque area (TPA) was measured in 358 participants at baseline. Cardiac troponin I and NT-proBNP were measured using automated clinical assays. The association between cardiac biomarkers and carotid atherosclerosis was assessed by multivariable regression after adjusting for cardiovascular risk factors. Improvement in the prediction of cardiovascular events beyond the FRS was tested using measures of risk discrimination and reclassification.

Results. In univariate analyses, cTnI (β coefficient 0.52 [95% confidence interval (95% CI) 0.3, 0.74], $P < 0.001$) and NT-proBNP (β coefficient 0.24 [95% CI 0.1, 0.39], $P < 0.001$) were associated with TPA. After adjusting for cardiovascular risk factors, the association remained statistically significant for cTnI (adjusted β coefficient 0.21 [95% CI 0, 0.41], $P = 0.047$) but not for NT-proBNP ($P = 0.21$). Among the 1,000 patients with PsD assessed for cardiovascular risk prediction, 64 patients had incident cardiovascular events. When comparing a base model (with the FRS alone) to expanded models (with the FRS plus cardiac biomarkers), there was no improvement in predictive performance.

Conclusion. In patients with PsD, cTnI may reflect the burden of atherosclerosis, independent of traditional cardiovascular risk factors. Cardiac troponin I and NT-proBNP are associated with incident cardiovascular events independent of the FRS, but further study of their role in cardiovascular risk stratification is warranted.

INTRODUCTION

Psoriasis and psoriatic arthritis (PsA), collectively known as psoriatic disease (PsD), are characterized by excess cardiovascular morbidity and mortality compared to the general population (1–4). While this excess risk is partly explained by high prevalence of traditional cardiovascular risk factors, chronic systemic inflammation promotes atherogenesis, thereby predisposing individuals with

PsD to an increased risk of cardiovascular events (5,6). Conventional cardiovascular risk scores, such as the Framingham Risk Score (FRS) (7), underestimate cardiovascular risk in patients with PsD and other inflammatory rheumatic diseases, because most rely only on traditional cardiovascular risk factors and fail to consider the independent risk conferred by immune disease per se (8,9).

Novel laboratory and imaging biomarkers improve cardiovascular risk prediction in the general population, and it has been

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suggested that they could be combined with conventional scoring systems to optimize cardiovascular risk stratification (10–12).

While findings from general population cohort studies indicate that high-sensitivity troponin cardiac I (cTnI) and N-terminal pro-brain natriuretic peptide (NT-proBNP) are strong predictors of cardiovascular risk, limited information exists on patients with rheumatic diseases and particularly those with PsD (13–18). Cardiac troponin concentrations are moderately elevated in the circulation because of myocardial ischemia, and the biomarker is used in the diagnosis of myocardial infarction when levels are markedly elevated. Previous studies of patients with psoriasis (19) and systemic lupus erythematosus (20,21) demonstrated associations between elevated high-sensitivity troponin concentration and atherosclerotic plaque burden. A single small study evaluated the predictive performance of high-sensitivity troponin in patients with rheumatoid arthritis (RA) (22). Similarly, NT-proBNP, which is released by cardiac myocytes in response to volume overload and ventricular wall distension and may be elevated after myocardial ischemia, hypoxia, and fibrosis, is also increased in patients with RA. NT-proBNP has also been associated with higher all-cause mortality in patients with early inflammatory arthritis and RA; however, the predictive performance of this biomarker compared to conventional cardiovascular scores has not been tested (23–25). To date, no study has investigated the ability of cTnI and NT-proBNP to improve cardiovascular risk stratification in patients with PsD.

The data highlight the potential of these cardiac biomarkers to augment existing cardiovascular scores by considering the combined direct effect of traditional cardiovascular risk factors and systemic inflammation on the heart in patients with PsD. However, it is not clear how much incremental information is gained by using these 2 cardiac biomarkers in cardiovascular risk stratification or their association with carotid atherosclerosis in patients with PsD.

In this study, we evaluated the association between cTnI and NT-proBNP and carotid atherosclerosis presence and progression. In the context of current treatment guidelines highlighting the need to identify patients with PsD who are at high cardiovascular risk, we investigated whether these cardiac biomarkers predict clinical cardiovascular events independent of traditional cardiovascular risk factors and whether they improve cardiovascular risk stratification beyond the FRS.

PATIENTS AND METHODS

Study population. We included patients from the University of Toronto PsD cohort. The cohort comprises participants with a diagnosis of psoriasis without arthritis (PsC) who have been followed up since 2006 and those with psoriatic arthritis (PsA) who have been followed up prospectively since 1978 as part of a larger study to investigate disease-related outcomes (26,27). Among PsA patients, 98% met the Classification of Psoriatic

Arthritis (CASPAR) criteria (28). PsC patients were enrolled based on a diagnosis of psoriasis without arthritis, as confirmed by a dermatologist and rheumatologist. Participants were assessed by a rheumatologist at 6–12-month intervals, and detailed information on demographic characteristics and comorbidities, including traditional cardiovascular risk factors, medications, and disease activity, were collected according to a standard protocol. All data are stored in a web-based computerized database. Inclusion criteria included having a serum sample in the cohort biobank, no history of cardiovascular events at study entry, and being followed up for at least 1 year following study entry. The study was approved by the University Health Network Ethics Board (no. 08-0630) and all patients provided informed consent.

Biomarker measurement. Annual serum samples have been collected and stored in a biobank since 2002; thus, patients entered this study at the date they provided their first serum sample. NT-proBNP (Cobas; Roche Diagnostics) and high-sensitivity cTnI (Architect Stat; Abbott Laboratories, Abbott Diagnostics) were measured in serum samples on automated clinically validated immunoassay analyzers using the manufacturers' calibrators and quality controls. The limit of detection was 5 pg/ml for NT-proBNP and 1.1 pg/ml for cTnI.

Carotid ultrasound assessment of atherosclerosis.

Vascular imaging studies have shown increased atherosclerotic plaques and vascular inflammation in patients with PsD (29–34). As this noninvasive assessment can serve as a surrogate measure for cardiovascular risk by identifying subclinical atherosclerosis in asymptomatic patients (35), we performed a nested cohort study that included 358 patients who underwent a baseline carotid ultrasound assessment between 2009 and 2015. Each patient underwent a second carotid ultrasound 2–3 years after the baseline assessment. A single trained physician (LE) performed all ultrasound measurements in accordance with a study protocol that has previously been described in detail (29). Scans were performed with MyLab 30 and MyLab 70 XVision scanners with a linear LA523 7–13-MHz transducer (all from Esaote). The scan included detailed B-mode images of both the right and the left common carotid arteries as well as the carotid bulb, internal carotid, and external carotid arteries. All ultrasound scans were saved as video files for later reading.

The burden of atherosclerotic plaques was measured by carotid total plaque area (TPA), as previously described by Spence (36). The plane for measurement of each plaque was chosen by reviewing the video of the scan to find the largest extent of plaque as seen in the longitudinal view. The image was then frozen, and the plaque was measured by tracing around the perimeter with a cursor on the screen. The assessor then moved on to the next plaque and repeated the process until all observed plaques in the common, external, and internal carotid arteries were measured. TPA (cm²) was recorded as the sum of

areas of all plaques in the right and left carotid arteries. The outcomes of interest were TPA at baseline and the average annual progression rate of TPA that was calculated by subtracting the baseline TPA value from the follow-up TPA value, divided by the number of years between visits. Reading of the scans was performed independently of the scanning, and readers were blinded with regard to clinical data. The intraobserver intraclass correlation coefficient for TPA was 0.94.

Incident cardiovascular events. The FRS was calculated for each patient to estimate the 10-year risk of cardiovascular disease (CVD) (7). Risk factors included in the score were age, sex, current smoking status, systolic blood pressure, treatment for hypertension, diabetes mellitus, total cholesterol, and high-density lipoprotein cholesterol (HDL-c).

The primary end point was the occurrence of the first clinical cardiovascular event. A composite outcome that included the following clinical cardiovascular events was identified within 10 years of biomarker measurement: angina pectoris, myocardial infarction, transient ischemic attack (TIA), ischemic cerebrovascular accident (CVA), revascularization procedures, and cardiovascular death. Revascularization procedures included percutaneous coronary intervention, coronary artery bypass surgery, carotid endarterectomy, and vascular surgery for peripheral artery disease.

Potential cardiovascular events were first identified by searching the cohort database and linking patients' records to provincial mortality and hospitalization databases. All Ontarians are insured under a single-payer health care system, covering all hospital services. The Canadian Institute for Health Information Discharge Abstract Database and National Ambulatory Care Reporting System contain detailed information about all inpatient hospital discharges, emergency room visits, and same-day surgeries from all hospitals in Ontario, Canada. International Classification of Diseases, Tenth Revision codes were used to identify hospitalizations due to a cardiovascular event (Supplementary Table 1, available on the *Arthritis & Rheumatology* website at <https://onlinelibrary.wiley.com/doi/10.1002/art.42079>). Underlying causes of death due to CVD were verified from the Ontario Vital Statistics Death Registry. Subsequently, complete medical records describing the cardiovascular event were obtained, where available, from patients' primary care providers and specialists. Each identified potential cardiovascular event was adjudicated by reviewing data from hospital admissions, death certificates, and medical records from relevant specialists. Uncertain cases were discussed with a cardiologist (SA for cardiac events) and neurologist (RW for neurologic events) to determine whether to consider them as cardiovascular events.

Statistical analysis. Baseline characteristics were calculated as the mean \pm SD for continuous variables or frequency for categorical variables. Cardiac biomarker concentrations and

TPA were log-transformed to better approximate the normal distribution. First, we evaluated the association between cardiac biomarkers and carotid atherosclerosis.

We performed multivariable linear regression to assess the association between cardiac biomarker concentrations and TPA at baseline in patients with PsD. Adjustment was made for the following variables: age, sex, body mass index, hypertension, diabetes mellitus, current smoking, low-density lipoprotein cholesterol, HDL-c, creatinine level, and use of lipid lowering therapy. Beta coefficients and 95% confidence intervals (95% CIs) were calculated. Next, logistic regression was used to assess the association of cardiac biomarker concentrations and carotid atherosclerosis progression, defined as an annual rate of TPA progression greater than the 75th percentile.

We then evaluated the association between cardiac biomarkers and clinical cardiovascular events. This association was analyzed separately for each biomarker using a series of cause-specific Cox regression models. Subjects entered the risk set at the date of the first available serum sample and the event occurred at the date of the first cardiovascular event within 10 years. Patients who were event-free at the date at which they were last known to be alive were censored. Non-cardiovascular death was considered as a competing event. Biomarker associations were first adjusted for age and sex, followed by the FRS. The nature of the associations were tested and illustrated using penalized splines and modeled using the median value of each biomarker as the reference (37). Plots of the scaled Schoenfeld residuals against time and a statistical test of proportionality were used to assess the assumption of multiplicative covariate effects (38). We subsequently assessed the ability of cardiac biomarkers to predict cardiovascular events using cause-specific Cox regression models adjusted for the FRS. Improvement in the clinical prediction of cardiovascular events beyond the FRS was tested using the area under the receiver operating characteristic curve (AUC), net reclassification index (NRI), and integrated discrimination index (IDI). Odds ratios (ORs), hazard ratios (HRs), and 95% CIs were calculated. Analyses were performed with R (version 3.6.2) and SAS Studio 3.8.

Data availability. All data relevant to the study are included in the article or uploaded as supplementary materials (available on the *Arthritis & Rheumatology* website at <https://onlinelibrary.wiley.com/doi/10.1002/art.42079>). Requests for additional study-related data can be sent to the corresponding author.

RESULTS

Cardiac biomarkers and carotid atherosclerosis.

Characteristics of the study participants are shown in Table 1. An ultrasound assessment was performed in 358 patients with PsD. The mean \pm SD duration of follow-up was 3.69 ± 1.9 years.

Table 1. Baseline characteristics of the study population with psoriatic disease*

Variable	Carotid ultrasound assessment (n = 358)	Incident cardiovascular events (n = 1,000)
PsA, no. (%)	251 (70.1)	648 (64.8)
PsC, no. (%)	107 (29.9)	352 (35.2)
Age, years	53.8 ± 11	49 ± 12.8
Female sex, no. (%)	164 (45.8)	446 (44.6)
Psoriasis disease duration, years	23.9 ± 14.5	20 ± 14.1
PsA disease duration, years	15.1 ± 11.3	11.8 ± 10.3
Caucasian ethnicity, no. (%)	313 (87.4)	834 (83.4)
Current smoker, no. (%)	40 (11.2)	164 (16.4)
PASI score	3 ± 4.1	4.1 ± 6.3
Tender joint count†	3 ± 5.6	3.8 ± 7.3
Swollen joint count†	0.9 ± 1.9	1.5 ± 3.3
Current daily use of NSAIDs, no. (%)	135 (37.7)	265 (26.5)
Current use of DMARDs, no. (%)	137 (38.3)	362 (36.2)
Current use of biologics, no. (%)	162 (45.3)	214 (21.4)
Total cholesterol, mmol/liter	5.1 ± 1	4.2 ± 0.9
LDL-c, mmol/liter	3.0 ± 0.9	1.6 ± 0.5
HDL-c, mmol/liter	1.4 ± 0.4	1.2 ± 0.3
BMI, kg/m ²	28.4 ± 5.8	28.7 ± 5.9
Diabetes mellitus, no. (%)	19 (5.3)	77 (7.7)
Hypertension, no. (%)‡	96 (26.8)	274 (27.4)
Use of lipid-lowering medications, %	93	100
cTnl, ng/liter	3.3 ± 2.5	4.4 ± 5.1
NT-proBNP, pg/ml	73.2 ± 111	63.3 ± 115.9
Total plaque area, cm ²	0.17 ± 0.3	-
Framingham Risk Score, no. (%)		
Low-risk (<10%)	-	720 (72.0)
Medium-risk (10–19%)	-	187 (18.7)
High-risk (≥20%)	-	93 (9.3)

* Except where indicated otherwise, values are the mean ± SD. PsC = psoriasis without arthritis; PASI = Psoriasis Area Severity Index; NSAIDs = nonsteroidal antiinflammatory drugs; DMARDs = disease-modifying antirheumatic drugs; LDL-c = low-density lipoprotein cholesterol; HDL-c = high-density lipoprotein cholesterol; BMI = body mass index; cTnl = cardiac troponin I; NT-proBNP = N-terminal pro-brain natriuretic peptide.

† Only in patients with psoriatic arthritis (PsA).

‡ Systolic blood pressure >140 mm Hg or use of antihypertensive medications.

Table 2. Association of levels of cardiac biomarkers (cTnl and NT-proBNP) with carotid total plaque area in patients with PsD, using linear regression*

	Univariable analysis, β (95% CI)	P	Multivariable analysis, cTnl, β (95% CI)	P	Multivariable analysis, NT-proBNP, β (95% CI)	P
Female sex	-0.32 (-0.65, 0.02)	0.06	-0.14 (-0.47, 0.18)	0.39	-0.32 (-0.66, 0.01)	0.06
Age	0.07 (0.06, 0.09)	<0.001	0.06 (0.04, 0.07)	<0.001	0.06 (0.04, 0.07)	<0.001
BMI	0.04 (0.01, 0.06)	0.02	0.01 (-0.01, 0.04)	0.36	0.02 (0, 0.05)	0.18
Hypertension	0.77 (0.4, 1.14)	<0.001	0.09 (-0.26, 0.45)	0.60	0.06 (-0.3, 0.42)	0.75
Diabetes mellitus	0.74 (0, 1.48)	0.05	0.31 (-0.34, 0.95)	0.35	0.33 (-0.32, 0.98)	0.32
Current smoker	0.15 (-0.38, 0.69)	0.58	0.44 (-0.01, 0.89)	0.06	0.28 (-0.17, 0.73)	0.22
LDL-c	0.18 (0, 0.37)	0.05	0.26 (0.1, 0.42)	0.001	0.26 (0.1, 0.42)	0.002
HDL-c	0.07 (-0.36, 0.51)	0.74	0.01 (-0.39, 0.41)	0.96	0.02 (-0.39, 0.42)	0.92
Use of lipid-lowering therapy	1.10 (0.73, 1.46)	<0.001	0.73 (0.39, 1.07)	<0.001	0.67 (0.32, 1.01)	<0.001
Creatinine	1.48 (0.37, 2.58)	0.01	0.43 (-0.59, 1.45)	0.41	0.44 (-0.61, 1.48)	0.42
cTnl	0.52 (0.3, 0.74)	<0.001	0.21 (0, 0.41)	0.047	-	-
NT-proBNP	0.24 (0.1, 0.39)	0.002	-	-	0.09 (-0.05, 0.23)	0.21

* PsD = psoriatic disease; 95% CI = 95% confidence interval (see Table 1 for other definitions).

Using linear regression models, the association between cardiac biomarker levels and TPA at baseline was examined (Table 2). In univariate analyses, cTnI (β coefficient 0.52 [95% CI 0.3, 0.74]) and NT-proBNP (β coefficient 0.24 [95% CI 0.1, 0.39]) were associated with TPA. After adjusting for cardiovascular risk factors, lipid-lowering therapy, and creatinine level, the association remained statistically significant for cTnI (adjusted β coefficient 0.21 [95% CI 0, 0.41]) but not for NT-proBNP. We then evaluated the association between cardiac biomarker levels and atherosclerosis progression in patients with PsD using logistic regression models. Of the 358 participants, 89 had atherosclerosis progression. In the univariate analysis, cTnI was associated with atherosclerosis progression (OR 1.52 [95% CI 1.04, 2.23]) but not with NT-proBNP (OR 1.08 [95% CI 0.87, 1.34]) (Supplementary Table 2, available on the *Arthritis & Rheumatology* website at <https://onlinelibrary.wiley.com/doi/10.1002/art.42079>). In the multivariable analysis, current smoking, creatinine level, and baseline TPA predicted atherosclerosis progression. However, there was no association with either cTnI or NT-proBNP. No interaction was found between each of the biomarkers and sex.

Cardiac biomarkers and incident cardiovascular events. One thousand participants (PsA [n = 648], PsC [n = 352]) who were evaluated from 2002 to 2019 were included in this analysis. During a mean follow-up of 7.1 years (7,099 person-years), 64 patients developed an incident cardiovascular event (angina [n = 10], myocardial infarction [n = 20], TIA [n = 7], CVA [n = 11], revascularization [n = 11], cardiovascular death [n = 5]), resulting in an incidence rate of 0.9 events per 100 person-years (95% CI 0.7, 1.0).

First, we evaluated associations between cardiac biomarker levels and incident cardiovascular events. In a model

adjusted for the FRS, both cTnI (HR 3.02 [95% CI 1.12, 8.16]) and NT-proBNP (HR 2.02 [95% CI 1.28, 3.18]) were associated with cardiovascular events per 1 SD increase (Figure 1). The association was stronger in men compared to women. For cTnI, the HR in men was 3.71 (95% CI 1.10, 12.5) compared to women (HR 2.72 [95% CI 0.48, 15.5]). For NT-proBNP, the HR in men was 1.91 (95% CI 1.09, 3.36) compared to women (HR 2.11 [95% CI 0.85, 5.27]). However, the interactions between sex and either biomarker were not statistically significant.

Including both cardiac biomarkers and the FRS in a single model, NT-proBNP (HR 1.91 [95% CI 1.23, 2.97]) retained statistical significance, but cTnI only showed a trend toward an association (HR 2.60 [95% CI 0.98, 6.87]). To better understand the relationship between cardiac biomarkers and cardiovascular events, a nonlinear cardiac biomarker effect was incorporated in the Cox regression model, and this nonlinear effect was modeled using penalized splines. Figure 2 shows the splines-based HR curves using the median concentration level of each biomarker as the reference. In general, a nonlinear relationship was observed for both biomarkers and cardiovascular events. For both unadjusted and adjusted models, cTnI showed a gradual rise in cardiovascular risk up to 10 ng/liter, and then a rapid rise in increasing risk at higher levels of cTnI. NT-proBNP showed almost no increase in cardiovascular risk up to a level of 100 pg/ml and a rapid incline following this level, with almost a doubling of the HR from 100 pg/ml to 200 pg/ml (2.5 to 4.9, respectively).

Finally, we evaluated whether cardiac biomarkers could improve the performance of FRS by improving classification of patients to cardiovascular risk categories. The FRS demonstrated moderate performance (AUC 73.8) in predicting cardiovascular

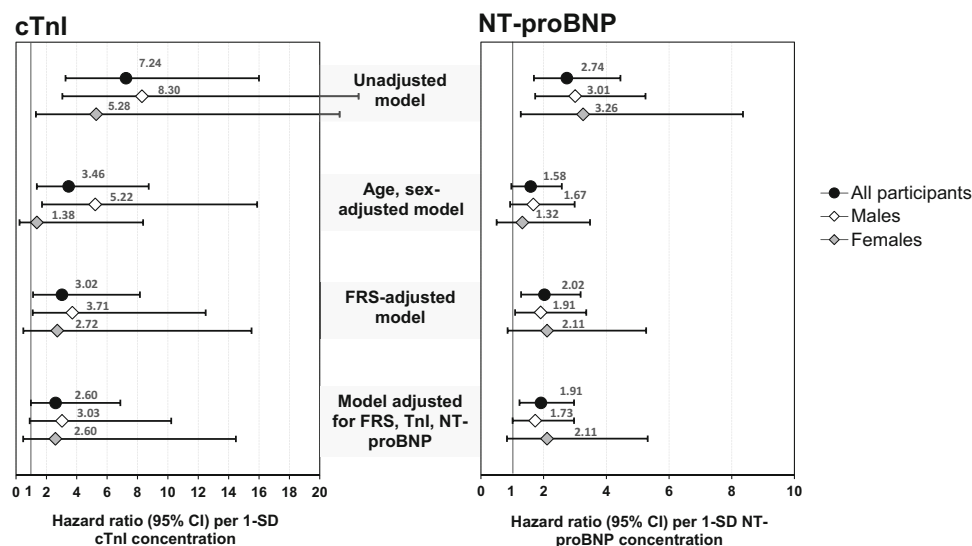


Figure 1. Hazard ratios of cardiac biomarker measures with incident cardiovascular events (n = 1,000; 64 events). Error bars show 95% confidence intervals (95% CIs). cTnI = cardiac troponin I; FRS = Framingham Risk Score; NT-proBNP = N-terminal pro-brain natriuretic peptide.

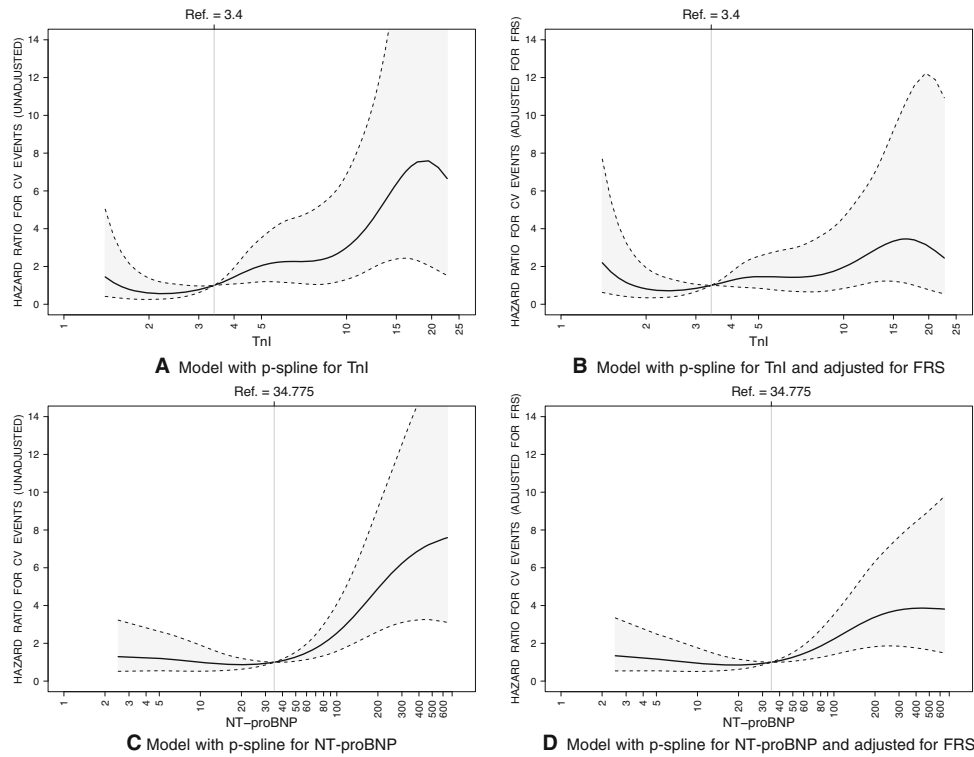


Figure 2. Splines-based hazard ratio (HR) curves to illustrate the association of cTnI and NT-proBNP with cardiovascular events, unadjusted and adjusted for the FRS. The reference (HR = 1) is the median value of each biomarker. Both penalized splines are on a log scale. Shaded areas show the lower and upper bounds of the 95% CI. CV = cardiovascular (see Figure 1 for other definitions).

risk in patients with PsD (Figure 3). When comparing a base model (with the FRS alone) to expanded models (with the FRS plus cardiac biomarkers), there was no significant improvement in predictive accuracy. The addition of cTnI, NT-proBNP, or both cTnI and NT-proBNP to the FRS did not demonstrate

improvements in any measure of risk discrimination or reclassification, including AUC, NRI, and IDI (Table 3).

DISCUSSION

In this study, we demonstrate several important findings: 1) cTnI was independently associated with the burden of atherosclerosis as measured by carotid ultrasound; 2) elevated cTnI and NT-proBNP levels were associated with a higher risk of developing future cardiovascular events independent of traditional cardiovascular risk factors, and the associations were stronger in men compared to women; and 3) the addition of cTnI or NT-proBNP did not improve the performance of the FRS for predicting cardiovascular events in patients with PsD. These findings suggest that increased atherosclerotic plaque burden is associated with subclinical cardiac injury, which is associated with elevated concentrations of cardiac biomarkers. This, in turn, may ultimately lead to clinical cardiovascular events, as observed by the strong link between cardiac biomarkers and clinical cardiovascular events. To our knowledge, this is the largest prospective study to assess the association of cardiac biomarkers with subclinical atherosclerosis, and the first study to evaluate the clinical utility of cardiac biomarkers for cardiovascular risk stratification in patients with PsD, suggesting that this noninvasive assessment offers clinical translation potential.

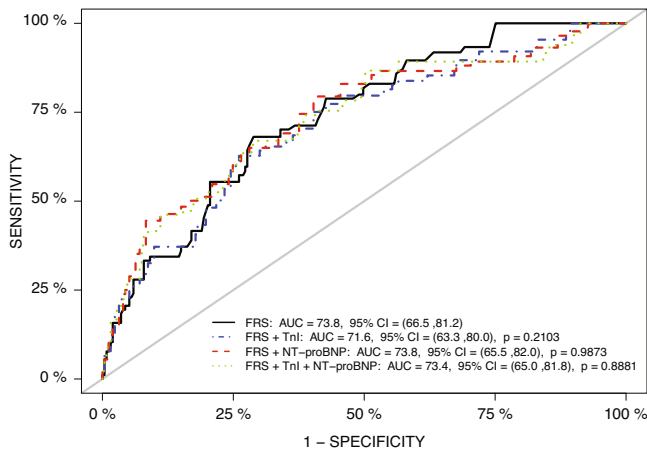


Figure 3. Comparison of the predictive performance of the base model (FRS alone) and expanded models for prediction of cardiovascular events in patients with psoriatic disease. AUC = area under the receiver operating characteristic curve (see Figure 1 for other definitions).

Table 3. Summary of predictive and reclassification indices for cardiovascular events using the FRS (base model) with and without cardiac biomarkers as model covariates, based on cause-specific Cox regression models*

	AUC			NRI			IDI		
	Estimate	95% CI	<i>P</i>	Estimate	95% CI	<i>P</i>	Estimate	95% CI	<i>P</i>
Base model	73.8	66.5, 81.2	–	–	–	–	–	–	–
Model 1 vs. base model	71.6	63.3, 80.0	0.21	0.081	–0.198, 0.20	0.67	0.005	–0.005, 0.035	0.37
Model 2 vs. base model	73.8	65.5, 82.0	0.99	0.20	–0.02, 0.38	0.06	0.017	–0.002, 0.058	0.10
Model 3 vs. base model	73.4	65.0, 81.8	0.89	0.27	0.002, 0.42	0.047	0.021	0, 0.068	0.053

* Base model = Framingham Risk Score (FRS) alone; model 1 = FRS and cTnI; model 2 = FRS and NT-proBNP; model 3 = FRS, cTnI, and NT-proBNP. AUC = area under the receiver operator characteristic curve; 95% CI = 95% confidence interval; NRI = net reclassification improvement; IDI = integrated discrimination index (see Table 1 for other definitions).

In general, studies of troponin and NT-proBNP in PsD are limited (19,39,40). Ultrasound findings in our study suggest that elevated cTnI level is associated with early vascular changes in the carotid artery and may identify patients at increased risk of future myocardial injury beyond traditional cardiovascular risk factors. Although mechanisms behind elevated cardiac biomarker levels in PsD are unclear, potential pathways include cardiomyocyte injury from inflammatory cytokines and systemic inflammation driving endothelial dysfunction or indirectly causing cardiac strain (41,42). The inflammatory hypothesis of CVD in psoriatic patients has stemmed from the observation of elevated levels of C-reactive protein (CRP) and proinflammatory cytokines, as well as studies targeting reductions in inflammatory burden among patients with inflammatory rheumatic diseases. In a prospective cohort study of patients with PsD, treatment with tumour necrosis factor inhibitors (TNFi) led to improvement in vascular inflammation, while reduced progression of carotid plaques was reported in men (43). In patients with active RA, treatment with TNFi decreased circulating levels of NT-proBNP, suggesting a potential cardiovascular risk benefit (44). Biomarkers driven by immune disease arguably might not serve to enhance prediction because they are confounded by the impact of the underlying immune disease. In our study, we assessed the role of conventional vascular biomarkers to reduce this risk.

Overall, the ability of cTnI to predict both burden and progression of carotid plaque may reflect the presence of atherosclerotic disease and/or subclinical cardiac myocyte damage, which may progress to clinical cardiovascular events. Natriuretic peptides such as NT-proBNP have a physiologically protective role, but elevated levels tend to reflect pathology in older individuals with more comorbidities (15). Therefore, in contrast to NT-proBNP, elevated cTnI level seems to be a superior marker of atherosclerotic cardiovascular risk. The utility of cTnI alone or in conjunction with carotid ultrasound to improve cardiovascular risk stratification in patients with PsD warrants further assessment. We acknowledge that we have carried out an association analysis between the cardiac biomarkers and the outcomes of interest. Causal analysis could be of interest to some, and we note that the effects of some of the

baseline variables could be affected by collider bias (45) if these baseline variables have causal effects on any intermediate biomarkers. In such cases, a more formal mediation analysis involving inverse probability weighting could be undertaken. This would require a clear specification of the causal estimates of interest.

We examined the association of cardiac biomarkers with incident cardiovascular events. One-SD increases in cTnI and NT-proBNP were strongly associated with incident cardiovascular events in the FRS-adjusted models. Interestingly, after adjusting for both cardiac biomarkers and the FRS through inclusion in the same model, NT-proBNP, but not cTnI, remained associated with cardiovascular events. These findings are consistent with those of a large European population-based cohort study, which found that both biomarkers, when included in a multimarker model, were associated with increased primary cardiovascular risk independent of traditional cardiovascular risk factors (15). Variable characteristics of the screening population, such as those of the University of Toronto PsD cohort, may influence the performance of cardiac biomarkers as risk predictors. However, a recent study of the same PsD cohort found that the burden of systemic inflammation and level of disease activity were independent risk factors of heart failure events (46).

Our study did not find an added benefit of cardiac biomarkers with regard to cardiovascular risk stratification. The addition of each biomarker individually or in combination to the FRS did not improve measures of risk discrimination or reclassification. Proving the added benefit of biomarkers to conventional scoring methods such as the FRS is challenging due to the relatively small number of events and variability in sample populations and treatment effects. The lack of improvement in performance is consistent with other studies of inflammatory rheumatic diseases that attempted to add cardiac biomarkers to the FRS to improve risk stratification (47). While the FRS was moderately predictive of subsequent cardiovascular events in our study, the addition of each biomarker resulted in similar or inferior performance. In studies of the general population, the clinical utility of cTnI and NT-proBNP in cardiovascular risk stratification also remains unclear. In a large prospective study of British women, NT-proBNP did not improve risk prediction beyond

traditional cardiovascular risk factors (48). However, in another study of older British men, inclusion of NT-proBNP in an FRS-based model yielded significant improvement in risk discrimination, and its performance was superior to an FRS-based model with CRP (49). Other approaches have included the development of multimarker scores with troponin and NT-proBNP, in combination with other emerging biomarkers of cardiovascular stress, albeit with mixed results (50). Current guidelines for the general population do not suggest using cardiac biomarkers for cardiovascular risk stratification for primary prevention in asymptomatic patients, as they are only used to assess symptoms suspected to be of cardiac origin.

Our study has notable strengths. This is the first study to investigate cTnI and NT-proBNP and their relationship with noninvasive measures of carotid atherosclerosis and clinical cardiovascular events in a large longitudinal cohort of patients with PsD. Serum samples were collected during a time when lipid-lowering therapies and disease-modifying antirheumatic drugs were widely available; therefore, the benefit of modern preventive treatments is likely reflected in the reported cardiovascular risk estimates. Further, the use of high-sensitivity assays allowed measurement of biomarker concentrations below conventional levels of detection, revealing a spectrum of low and high levels of circulating cTnI and NT-proBNP. The limitations of this study include the relatively small number of cardiovascular events, which prevented in-depth analyses of subgroups of interest (e.g., by disease group). Our study did not include a comparator group of patients without PsD, so we could not determine whether the levels of cardiac biomarkers are higher in patients with PsD. We were unable to include CRP in the analysis as we did not have measurements for all patients in the study.

In conclusion, this study established the association between elevated cardiac biomarkers, atherosclerosis, and clinical cardiovascular events in patients with PsD. Cardiac troponin I may be as effective as established measures of carotid plaque burden for identifying subclinical atherosclerosis long before cardiovascular events occur. Both cTnI and NT-proBNP are associated with incident cardiovascular events independent of traditional cardiovascular risk factors and may reflect the excess risk in patients with PsD. However, the lack of improvement in prediction metrics beyond the FRS does not support the routine use of these cardiac biomarkers for cardiovascular risk stratification in asymptomatic patients with PsD. These data encourage additional research evaluating the utility of cTnI and NT-proBNP in cardiovascular risk stratification in this patient population.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Eder had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Eder.

Acquisition of data. Colaco, Chandran, Gladman, Eder.

Analysis and interpretation of data. Colaco, Lee, Akhtari, Winer, Welsh, Sattar, McInnes, Harvey, Cook, Piguet, Eder.

REFERENCES

- Polachek A, Touma Z, Anderson M, Eder L. Risk of cardiovascular morbidity in patients with psoriatic arthritis: a meta-analysis of observational studies. *Arthritis Care Res (Hoboken)* 2017;69:67–74.
- Miller IM, Ellervik C, Yazdanyar S, Jemec GB. Meta-analysis of psoriasis, cardiovascular disease, and associated risk factors. *J Am Acad Dermatol* 2013;69:1014–24.
- Eder L, Wu Y, Chandran V, Cook R, Gladman DD. Incidence and predictors for cardiovascular events in patients with psoriatic arthritis. *Ann Rheum Dis* 2016;75:1680–6.
- Colaco K, Widdifield J, Luo J, Rosen CF, Alhusayen R, Paterson JM, et al. Trends in mortality and cause-specific mortality among patients with psoriasis and psoriatic arthritis in Ontario, Canada. *J Am Acad Dermatol* 2021;84:1302–9.
- Gistera A, Hansson GK. The immunology of atherosclerosis. *Nat Rev Nephrol* 2017;13:368–80.
- Szentpetery A, Haroon M, FitzGerald O. Cardiovascular comorbidities in psoriatic disease. *Rheumatol Ther* 2020;7:5–17.
- D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;117:743–53.
- Colaco K, Ocampo V, Ayala AP, Harvey P, Gladman DD, Piguet V, et al. Predictive utility of cardiovascular risk prediction algorithms in inflammatory rheumatic diseases: a systematic review. *J Rheumatol* 2020;47:928–38.
- Eder L, Chandran V, Gladman DD. The Framingham Risk Score underestimates the extent of subclinical atherosclerosis in patients with psoriatic disease. *Ann Rheum Dis* 2014;73:1990–6.
- Vasan RS. Biomarkers of cardiovascular disease: molecular basis and practical considerations. *Circulation* 2006;113:2335–62.
- Sillescu H, Sartori S, Sandholt B, Baber U, Mehran R, Fuster V. Carotid plaque thickness and carotid plaque burden predict future cardiovascular events in asymptomatic adult Americans. *Eur Heart J Cardiovasc Imaging* 2018;19:1042–50.
- Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation* 2007;115:459–67.
- Willeit P, Welsh P, Evans JD, Tschiderer L, Boachie C, Jukema JW, et al. High-sensitivity cardiac troponin concentration and risk of first-ever cardiovascular outcomes in 154,052 participants. *J Am Coll Cardiol* 2017;70:558–68.
- Everett BM, Zeller T, Glynn RJ, Ridker PM, Blankenberg S. High-sensitivity cardiac troponin I and B-type natriuretic Peptide as predictors of vascular events in primary prevention: impact of statin therapy. *Circulation* 2015;131:1851–60.
- Welsh P, Hart C, Papacosta O, Preiss D, McConnachie A, Murray H, et al. Prediction of cardiovascular disease risk by cardiac biomarkers in 2 United Kingdom cohort studies: does utility depend on risk thresholds for treatment? *Hypertension* 2016;67:309–15.
- Di Angelantonio E, Chowdhury R, Sarwar N, Ray KK, Gobin R, Saleheen D, et al. B-type natriuretic peptides and cardiovascular risk: systematic review and meta-analysis of 40 prospective studies. *Circulation* 2009;120:2177–87.
- Blankenberg S, Salomaa V, Makarova N, Ojeda F, Wild P, Lackner KJ, et al. Troponin I and cardiovascular risk prediction in the general population: the BiomarCaRE consortium. *Eur Heart J* 2016;37:2428–37.

18. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Omland T, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med* 2004;350:655–63.
19. Zhou W, Abdelrahman KM, Dey AK, Reddy A, Uceda DE, Lateef SS, et al. Association among noncalcified coronary burden, fractional flow reserve, and myocardial injury in psoriasis. *J Am Heart Assoc* 2020;9:e017417.
20. Divard G, Abbas R, Chenevier-Gobeaux C, Chanson N, Escoubet B, Chauveheid MP, et al. High-sensitivity cardiac troponin T is a biomarker for atherosclerosis in systemic lupus erythematosus patients: a cross-sectional controlled study. *Arthritis Res Ther* 2017;19:132.
21. Winau L, Baydes RH, Braner A, Drott U, Burkhardt H, Sangle S, et al. High-sensitive troponin is associated with subclinical imaging bio-signature of inflammatory cardiovascular involvement in systemic lupus erythematosus. *Ann Rheum Dis* 2018;77:1590–8.
22. Karpouzas GA, Estis J, Rezaeian P, Todd J, Budoff MJ. High-sensitivity cardiac troponin I is a biomarker for occult coronary plaque burden and cardiovascular events in patients with rheumatoid arthritis. *Rheumatology (Oxford)* 2018;57:1080–8.
23. Provan S, Angel K, Semb AG, Atar D, Kvien TK. NT-proBNP predicts mortality in patients with rheumatoid arthritis: results from 10-year follow-up of the EURIDISS study. *Ann Rheum Dis* 2010;69:1946–50.
24. Mirjafari H, Welsh P, Verstappen SM, Wilson P, Marshall T, Edlin H, et al. N-terminal pro-brain-type natriuretic peptide (NT-pro-BNP) and mortality risk in early inflammatory polyarthritis: results from the Norfolk Arthritis Registry (NOAR). *Ann Rheum Dis* 2014;73:684–90.
25. Breunig M, Kleinert S, Lehmann S, Kneitz C, Feuchtenberger M, Tony HP, et al. Simple screening tools predict death and cardiovascular events in patients with rheumatic disease. *Scand J Rheumatol* 2018;47:102–9.
26. Gladman DD, Shuckett R, Russell ML, Thorne JC, Schachter RK. Psoriatic arthritis (PSA)—an analysis of 220 patients. *Q J Med* 1987;62:127–41.
27. Eder L, Chandran V, Shen H, Cook RJ, Shanmugarajah S, Rosen CF, et al. Incidence of arthritis in a prospective cohort of psoriasis patients. *Arthritis Care Res (Hoboken)* 2011;63:619–22.
28. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006;54:2665–73.
29. Eder L, Jayakar J, Shanmugarajah S, Thavaneswaran A, Pereira D, Chandran V, et al. The burden of carotid artery plaques is higher in patients with psoriatic arthritis compared with those with psoriasis alone. *Ann Rheum Dis* 2013;72:715–20.
30. Eder L, Thavaneswaran A, Chandran V, Cook R, Gladman DD. Increased burden of inflammation over time is associated with the extent of atherosclerotic plaques in patients with psoriatic arthritis. *Ann Rheum Dis* 2015;74:1830–5.
31. Mehta NN, Yu Y, Saboury B, Foroughi N, Krishnamoorthy P, Raper A, et al. Systemic and vascular inflammation in patients with moderate to severe psoriasis as measured by [18F]-fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET/CT): a pilot study. *Arch Dermatol* 2011;147:1031–9.
32. Shen J, Wong KT, Cheng IT, Shang Q, Li EK, Wong P, et al. Increased prevalence of coronary plaque in patients with psoriatic arthritis without prior diagnosis of coronary artery disease. *Ann Rheum Dis* 2017;76:1237–44.
33. Sobchak C, Akhtari S, Harvey P, Gladman D, Chandran V, Cook R, et al. Value of carotid ultrasound in cardiovascular risk stratification in patients with psoriatic disease. *Arthritis Rheumatol* 2019;71:1651–9.
34. Lam SH, Cheng IT, Li EK, Wong P, Lee J, Yip RM, et al. DAPSA, carotid plaque and cardiovascular events in psoriatic arthritis: a longitudinal study. *Ann Rheum Dis* 2020;79:1320–6.
35. Johnsen SH, Mathiesen EB, Joakimsen O, Stensland E, Wilsgaard T, Lochen ML, et al. Carotid atherosclerosis is a stronger predictor of myocardial infarction in women than in men: a 6-year follow-up study of 6226 persons: the Tromso Study. *Stroke* 2007;38:2873–80.
36. Spence JD. Technology insight: ultrasound measurement of carotid plaque—patient management, genetic research, and therapy evaluation. *Nat Clin Pract Neurol* 2006;2:611–9.
37. Meira-Machado L, Cadarso-Suarez C, Gude F, Araujo A. smoothHR: an R package for pointwise nonparametric estimation of hazard ratio curves of continuous predictors. *Comput Math Methods Med* 2013;2013:745742.
38. Therneau TM, Grambsch PM. Chapter 6. In: *Modeling survival data: extending the Cox Model*. New York: Springer-Verlag New York; 2000. p. 127–52.
39. Pietrzak A, Bartosinska J, Blaszczyk R, Chodorowska G, Brzozowski W, Hercogova J, et al. Increased serum level of N-terminal Pro-B-type natriuretic peptide as a possible biomarker of cardiovascular risk in psoriatic patients. *J Eur Acad Dermatol Venereol* 2015;29:1010–4.
40. Furer V, Shenhar-Tsarfaty S, Berliner S, Arad U, Paran D, Mailis I, et al. Prevalence of high-sensitivity cardiac troponin T in real-life cohorts of psoriatic arthritis and general population: a cross-sectional study. *Rheumatol Int* 2020;40:437–44.
41. Welsh P, Tuckwell K, McInnes IB, Sattar N. Effect of IL-6 receptor blockade on high-sensitivity troponin T and NT-proBNP in rheumatoid arthritis. *Atherosclerosis* 2016;254:167–71.
42. Bradham WS, Bian A, Oeser A, Gebretsadik T, Shintani A, Solus J, et al. High-sensitivity cardiac troponin-I is elevated in patients with rheumatoid arthritis, independent of cardiovascular risk factors and inflammation. *PLoS One*. 2012;7:e38930.
43. Eder L, Joshi AA, Dey AK, Cook R, Siegel EL, Gladman DD, et al. Association of tumor necrosis factor inhibitor treatment with reduced indices of subclinical atherosclerosis in patients with psoriatic disease. *Arthritis Rheumatol* 2018;70:408–16.
44. Peters MJ, Welsh P, McInnes IB, Wolbink G, Dijkmans BA, Sattar N, et al. Tumour necrosis factor α blockade reduces circulating N-terminal pro-brain natriuretic peptide levels in patients with active rheumatoid arthritis: results from a prospective cohort study. *Ann Rheum Dis* 2010;69:1281–5.
45. Westreich D, Greenland S. The table 2 fallacy: presenting and interpreting confounder and modifier coefficients. *Am J Epidemiol* 2013;177:292–8.
46. Koppikar S, Colaco K, Harvey P, Akhtari S, Chandran V, Gladman DD, et al. Incidence of and risk factors for heart failure in patients with psoriatic disease—a cohort study. *Arthritis Care Res (Hoboken)* 2021. DOI: 0.1002/acr.24578. E-pub ahead of print.
47. Finckh A, Courvoisier DS, Pagano S, Bas S, Chevallier-Ruggeri P, Hochstrasser D, et al. Evaluation of cardiovascular risk in patients with rheumatoid arthritis: do cardiovascular biomarkers offer added predictive ability over established clinical risk scores? *Arthritis Care Res (Hoboken)* 2012;64:817–25.
48. Sattar N, Welsh P, Sarwar N, Danesh J, Di Angelantonio E, Gudnason V, et al. NT-proBNP is associated with coronary heart disease risk in healthy older women but fails to enhance prediction beyond established risk factors: results from the British Women’s Heart and Health Study. *Atherosclerosis* 2010;209:295–9.
49. Wannamethee SG, Welsh P, Lowe GD, Gudnason V, Di Angelantonio E, Lennon L, et al. N-terminal pro-brain natriuretic peptide is a more useful predictor of cardiovascular disease risk than C-reactive protein in older men with and without pre-existing cardiovascular disease. *J Am Coll Cardiol* 2011;58:56–64.
50. Wang TJ, Wollert KC, Larson MG, Coglianese E, McCabe EL, Cheng S, et al. Prognostic utility of novel biomarkers of cardiovascular stress: the Framingham Heart Study. *Circulation* 2012;126:1596–604.