Original Article

Prediction of Cardiovascular Disease Risk by Cardiac Biomarkers in 2 United Kingdom Cohort Studies
Does Utility Depend on Risk Thresholds For Treatment?

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Abstract—We tested the predictive ability of cardiac biomarkers N-terminal pro B-type natriuretic peptide (NT-proBNP), high-sensitivity troponin T, and midregional pro adrenomedullin for cardiovascular disease (CVD) events using the British Regional Heart Study (BRHS) of men aged 60 to 79 years, and the MIDSPAN Family Study (MFS) of men and women aged 30 to 59 years. They included 3757 and 2226 participants, respectively, and during median 13.0 and 17.3 years follow-up the primary CVD event rates were 16.6 and 5.3 per 1000 patient-years, respectively. In Cox models adjusted for basic classical risk factors, 1 SD increases in log-transformed NT-proBNP, high-sensitivity troponin T, and midregional pro adrenomedullin were generally associated with increased primary CVD risk in both the studies ($P<0.006$) except midregional pro adrenomedullin in MFS ($P=0.10$). In BRHS, QRISK2 risk factors yielded a C-index of 0.657, which was improved by 0.017 ($P=0.005$) by NT-proBNP, but not by other biomarkers. Using 28% 14-year risk as a proxy for 20% 10-year risk, NT-proBNP improved risk classification for primary CVD cases (case net reclassification index, 5.9%; 95% confidence interval, 2.8%–9.2%), but only improved classification of noncases at a 14% 14-year risk threshold (4.6%; 2.9%–6.3%). In MFS, ASSIGN risk factors yielded a C-index of 0.752 for primary CVD; none of the cardiac biomarkers improved the C-index. Improvements in risk classification were only seen using NT-proBNP and high-sensitivity troponin T among cases using the 28% 14-year risk threshold (4.7%; 1.0%–9.2% and 2.6%; 0.0%–5.8%, respectively). In conclusion, the improvement in treatment allocation gained by adding cardiac biomarkers to risk scores seems to depend on the risk threshold chosen for commencing preventative treatments. (*Hypertension.* 2016;67:00-00. DOI: 10.1161/HYPERTENSIONAHA.115.06501.) ● **Online Data Supplement**

Key Words: adrenomedullin ■ biomarkers ■ cardiovascular diseases ■ natriuretic peptides ■ risk factors ■ troponin T

Stratified medicine for estimating cardiovascular disease (CVD) risk is a major responsibility of primary care.[1] Health professionals use risk scores, such as ASSIGN, QRISK2, the Pooled Cohort Equations, and SCORE,[2–4] to stratify and treat those at higher risk with statins, antihypertensive medications, and lifestyle advice as required. The American Heart Association/American College of Cardiology task force recently altered its definition of a high-risk treatment threshold in primary prevention from 20% 10-year risk to 7.5% 10-year risk.[5] The National Institute of Health and Care Excellence in England and Wales also reduced the threshold, from 20% to 10% 10-year risk,[6] whereas other national guidelines are still under revision.

Recently, cardiac biomarkers have become a major focus of attempts to improve CVD risk scores. Use of such biomarkers is attractive because they integrate signals from different pathophysiological pathways, including cardiac, vascular, and renal health. Data from several different cohort studies indicate that high-sensitivity troponins (hs-Tn) and N-terminal pro B-type natriuretic peptide (NT-proBNP)[7–10] are strong predictors of CVD risk. A recent editorial from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial emphasises the importance of troponin data from cohort studies by suggesting that cardiac troponin values may become routinely used for risk stratification across the spectrum of ischemic heart disease.[11] More

recently, midregional pro adrenomedullin (MR-proADM) has also emerged as a biomarker of potential interest in CVD risk prediction.[12–14] ADM, a natriuretic and diuretic peptide, is produced in human cardiac tissue (as well as adrenal glands, kidney tissues, and the vasculature) in response to mechanical stretch, much like natriuretic peptides. However, it is still not clear how much incremental information is gained by the use of multiple cardiac biomarkers in risk stratification, or whether they capture only overlapping risk information. Furthermore, although there is as yet no formal meta-analysis, the vast majority of cohort studies measuring cardiac biomarkers have focused on older and clinical trial cohorts, who will have substantially more prevalent and subclinical CVD than the young primary prevention groups CVD risk scores are intended for. Finally, in the context of national guidelines recommending lower thresholds of CVD risk for intervention with drugs to lower cholesterol or blood pressure, it is particularly important to test whether any refinement of CVD risk scores using cardiac biomarkers improves the specificity of risk prediction, because specificity falls as thresholds are lowered.[15]

Given these uncertainties, we aimed to investigate the ability of these 3 cardiac biomarkers to predict CVD in 2 United Kingdom cohort studies. The 20-year follow-up British Regional Heart Study (BRHS Q20) is a cohort of older British men, and the MIDSPAN Family Study (MFS) is a British cohort of younger men and women. The hypothesis was that cardiac biomarkers would improve clinical decision making in risk prediction models, but that changing treatment thresholds would alter their utility.

Methods

British Regional Heart Study

The BRHS is a socioeconomically representative prospective study involving 7735 men, aged 40 to 59 years, of predominantly white European ethnicity (>99%), drawn from 1 general practice in each of 24 British towns, who were screened between 1978 and 1980.[16] In 1998 to 2000, all surviving men, then aged 60 to 79 years, were invited for a 20th year follow-up examination (Q20), on which the analyses presented here are based.[8] Follow-up has been achieved for 99% of the cohort. Data relating NT-proBNP to CVD in BRHS have been previously published using a different modeling approach, and without other cardiac biomarkers.[8]

In BRHS, CVD events were defined as a composite of CVD death (all of those who died with *International Classification of Diseases Ninth Revision* 401 to 459 listed on the death certificate as a primary or secondary cause) and nonfatal myocardial infarction or stroke. Evidence of nonfatal myocardial infarction or stroke was obtained by ad hoc reports from general practitioners supplemented by biennial reviews of the patients' practice records (including hospital and clinic correspondence) through to the end of the study period. A nonfatal myocardial infarction was diagnosed according to World Health Organisation criteria. Nonfatal stroke events were those that produced a neurological deficit that was present for >24 hours.[8]

MIDSPAN Family Study

The MFS took place between March and December 1996. The study recruited adult sons and daughters of couples who had participated in the original Renfrew/Paisley prospective cohort study.[17] In brief, offspring of the married couples identified within the Renfrew/Paisley cohort, aged 30 to 59 years and living locally, formed the eligible population (3202 offspring from 1767 families). In all, 1040 male and 1298 female offsprings from 1477 families took part, and all participants were white[18].

End points were identified by periodic review of the cohort using a national database: the Information Services Division National Health Service record linkage for Scotland. The Information Services Division–linked database contains information on Scotland's morbidity records for acute specialty day case and inpatient discharges from hospital (Scotland's morbidity record 01) since January 1981. Death certificates were obtained from the National Health Service Central Register where the participants were flagged. For this study, the CVD end point was any event included in the national ASSIGN risk score definition of CVD: *International Classification of Diseases Tenth Revision* codes I20-25, G45, I60-69, as well as death from CVD (I00-I99), and OPCS4 procedure codes L29.5, L31.1, K40-46, K49, and K75 (procedures comprising carotid endarterectomy, carotid angioplasty, coronary artery bypass graft, and percutaneous transluminal coronary angioplasty).

Biomarker Measurement

NT-proBNP and hsTnT were measured in plasma samples from both the studies on an automated clinically validated immunoassay analyzer (e411, Roche Diagnostics, Burgess Hill, United Kingdom) using the manufacturers' calibrators and quality control reagents. MR-proADM was measured on an automated B.R.A.H.M.S Kryptor Compact plus (Thermo Fisher Scientific Hemel Hempstead, United Kingdom). The limit of detection was 5 pg/mL for NT-proBNP, 3 pg/mL for hsTnT, and 0.05 nmol/L for MR-proADM. Quality control materials >2 levels for each biomarker ran between 4.4% and 7.7% between runs.

Statistics

From screening in 1998 to 2000 in the BRHS and 1996 in MFS, CVD events were based on follow-up to a first qualifying CVD event or censoring at a maximum 14.3 years of follow-up (median, 13.0 years) in BRHS and maximum 17.8 years of follow-up (median, 17.3 years) in MFS.

In both the studies, analyses were conducted for primary CVD events (defined as events occurring in the cohort after excluding those with previous CVD, either self-reported or occurring in previous surveys, and those taking statin medication at baseline) as well as all CVD events (ie, without the above exclusions). As a post hoc analysis, secondary CVD risk prediction was also tested in those with baseline CVD in the BRHS, but not in MFS because of lower power. All available data were used in all models, leading to models with more risk factors having fewer observations because of missing covariates.

Standard crude analyses and Cox proportional hazard models were used. C-indices were derived using the somersd package (STATA) used for survival data.[19] C-indices were calculated in BRHS using predictors broadly based on those included in QRISK2 (the risk score used by National Institute of Health and Care Excellence for the United Kingdom[6]), and in MFS using predictors broadly based on those included in ASSIGN (the risk score used in Scotland[4]). Increased concordance was tested on addition of combinations of cardiac biomarkers. Improved prediction was also tested using the net reclassification index for survival data using the nricens package (R) with 5000 bootstraps.[20] To improve comparability of the cohorts while maximizing study power for this metric, follow-up times for both the studies were censored at 14 years (representing the maximum available whole year of follow-up time of BRHS). The categorical net reclassification index was calculated using binary risk thresholds for clinical treatments of 14% 14-year risk and 28% 14-year risk (which were taken to ≈10% 10-year risk and 20% 10-year risk frequently cited in clinical guidelines).[6] All analyses were performed in STATA (version 13.1) and R (version 3.1.1).

Results

Baseline Data

In BRHS, 3757 of 4252 male participants had complete baseline data for all 3 cardiac biomarkers (88.3%). At baseline across thirds of all 3 cardiac biomarkers, there was a trend for higher levels to be associated with higher risk demographic

and cardiometabolic characteristics, with the exception that NT-proBNP and hsTnT were inversely associated with total cholesterol. A CVD event occurred in 788 participants, and the event rate was 21.0 per 1000 patient-years in the full cohort and 16.6 per 1000 patient-years in those without baseline CVD or statin prescription. Those who experienced an incident CVD event generally had more adverse classical CVD risk factor characteristics (see online-only Data Supplement).

In MFS, 2226 of 2338 participants had complete baseline data for all 3 cardiac biomarkers and consented to long-term follow-up (95.2%). Higher levels of NT-proBNP were associated with adverse risk factor characteristics (older age, chronic kidney disease, and higher baseline CVD prevalence) but also many protective characteristics (female sex, lower body mass index, enhanced lipid profile, and lower glucose/diabetes mellitus). In contrast, higher levels of hsTnT and MR-proADM were more consistently associated with adverse risk characteristics. In MFS, 195 experienced a CVD event, and the event rate was 5.8 per 1000 patient-years in the full cohort with biomarker measurements and 5.3 per 1000 patient-years in those without baseline CVD or statin prescription. Those who experienced an incident CVD event generally had a more adverse classical CVD risk factor characteristics (see online-only Data Supplement).

Associations of Cardiac Biomarkers With CVD Risk

Across thirds of the biomarker distribution, elevated levels of all 3 cardiac biomarkers were associated with decreased event-free survival during the follow-up time (Figure). In BRHS, 1 SD increases in all 3 cardiac biomarkers because continuous variables were associated with increased risk of all CVD in extensively adjusted models (Table 1). Of the 3 cardiac biomarkers, NT-proBNP was the most strongly associated with risk. After cross adjusting for all 3 cardiac biomarkers (through inclusion in the same model; Table 1 model 3), both NT-proBNP and hsTnT remained associated with CVD risk, but the association of MR-proADM with all CVD outcomes was attenuated to the null. These results were consistent when the model was restricted to those without previous CVD or statin prescription, although the strength of the associations was somewhat attenuated to the null in all models.

In MFS, both NT-proBNP and hsTnT were positively associated with risk of all CVD and primary CVD (Table 1). NT-proBNP and hsTnT were more weakly associated with all CVD outcomes than in BRHS, but there was little difference in the strength of hazard ratios between the 2 cohorts for primary CVD, although confidence intervals were wider in MFS reflecting lower power. Cross adjustment for all 3 cardiac biomarkers in the same model attenuated results to the null, although both NT-proBNP and hsTnT retained a weak association with both all CVD and primary CVD (Table 1).

Prediction of CVD in Risk Score Models

In BRHS participants without baseline CVD or previous statin prescription, a risk score based on factors included in QRISK2 yielded a C-index of 0.657 (Table 2). The c-index improved by 0.017 (*P*=0.005), 0.005 (*P*=0.28), and 0.005 (*P*=0.11) on addition of NT-proBNP, hsTnT, and MR-proADM, respectively. There was no evidence that combinations of biomarkers improved discrimination beyond the improvement gained from the addition of NT-proBNP. Data were essentially unchanged when ASSIGN score risk factors were used as the baseline predictor model in BRHS, therefore, demonstrating consistency of the results by different modeling approaches. In an exploratory post hoc analysis testing risk prediction of secondary CVD, hsTnT particularly strongly improved the discrimination of secondary CVD events (see online-only Data Supplement). Investigating risk category reclassification in primary CVD using binary models, NT-proBNP improved risk classification of 5.9% (95% confidence interval, 2.8%– 9.2%) among cases (but not noncases) at a conservative 28% 14-year threshold. In contrast, NT-proBNP improved classification among noncases (4.6%; 2.9%–6.3%; but not cases) at a more radical 14% 14-year threshold (Table 3). Similar trends were observed for hsTnT. There was no evidence that MR-proADM improved risk classification in any model.

In MFS participants without baseline CVD or previous statin prescription, a risk score based on risk factors included in ASSIGN (the risk score generally used in Scotland) yielded a C-index of 0.752 (Table 2). There was no evidence that individual or combined biomarkers improved discrimination. NT-proBNP improved risk classification only among cases at a 28% 14-year risk threshold by 4.7% (95% confidence interval, 1.0%–9.2%), but not at a 14% 14-year risk threshold. NT-proBNP did not improve the classification of noncases in any model (Table 3). hsTnT slightly improved risk classification only among cases at the 28% 14-year threshold. MR-proADM did not improve risk classification in any model.

Discussion

In these 2 British cohort studies with a 23-year mean age difference and substantially different primary CVD event rates, the cardiac biomarker NT-proBNP only improved discrimination of CVD in the older BRHS cohort. Importantly, there was evidence that NT-proBNP and hsTnT improved classification of cases at a 28% 14-year risk threshold (theoretically resulting in more correct decisions to commence preventative treatment), but only improved classification of noncases at a 14% 14-year risk threshold (resulting in more correct decisions to not treat). As such, these biomarkers improved the sensitivity of risk prediction at the higher threshold, but improved specificity at the lower threshold. In contrast, MR-proADM was consistently a poor risk predictor of CVD. These data suggest that the clinical use (and health economics) of measuring these biomarkers in CVD risk stratification will depend on the risk threshold chosen for commencing preventative treatments, as well as characteristics of the screening population. These data are important to highlight in the context of ongoing changes to national guidelines for CVD risk scoring,[5,6] particularly because the specificity of cardiovascular risk prediction falls as 10-year CVD risk thresholds are lowered.[15]

Recent mendelian randomization studies have shown that the active BNP hormone might protect against diabetes mellitus.[21] Data from the Prospective Comparison of ARNi With ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial of the LCZ696 drug suggest that a neprilysin inhibitor, which prevents degradation of circulating natriuretic hormones is efficacious in improving outcomes
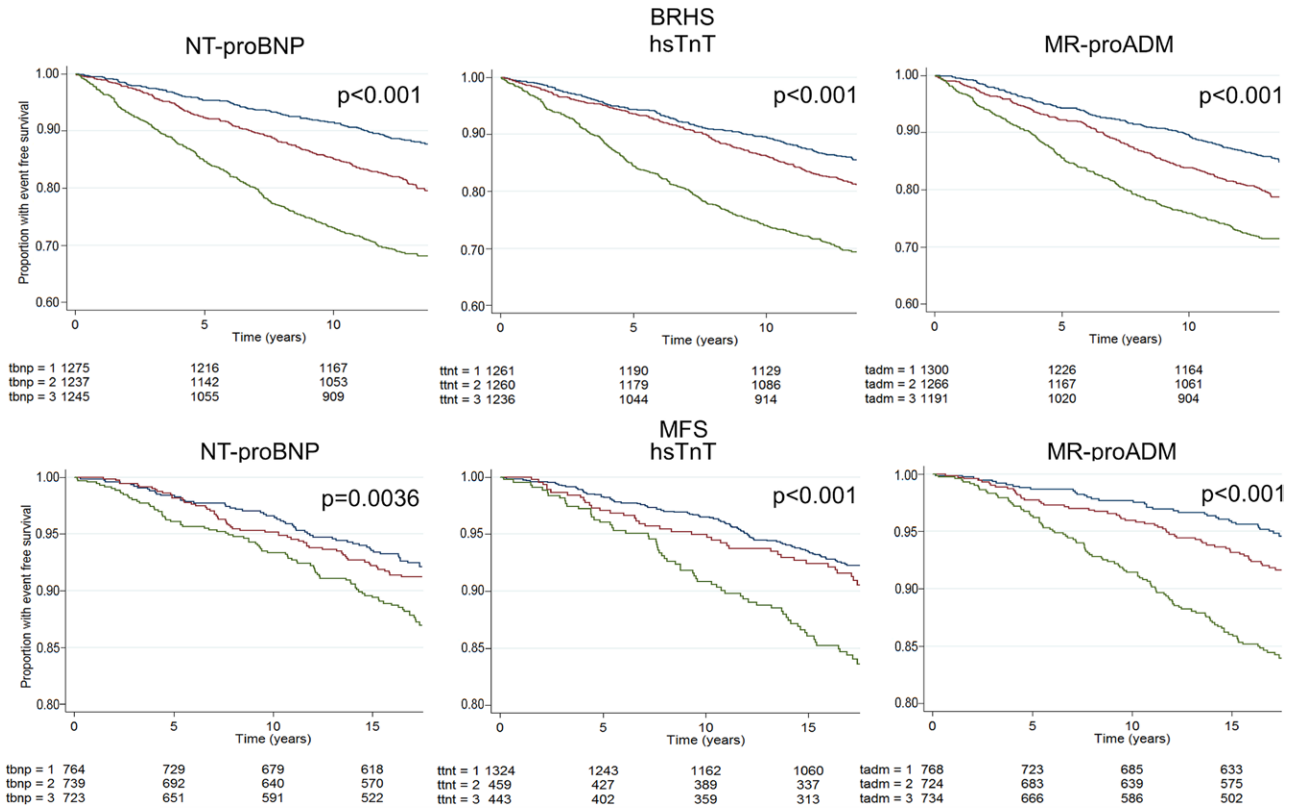
Figure. Kaplan–Meier curves showing cardiovascular disease event-free survival by thirds of all 3 cardiac biomarkers in both British Regional Heart Study (BRHS) and MIDSPAN Family Study (MFS). Blue line represents the lowest tertile (t1), red line intermediate (t2), and green top tertile (t3). Cut points ranges for thirds are defined in the online-only Data Supplement. *P* values are for log-rank tests. hsTnT indicates high-sensitivity troponin T; MR-proADM, midregional pro adrenomedullin; and NT-proBNP, N-terminal pro B-type natriuretic peptide.

and lowering blood pressure in the context of heart failure with reduced ejection fraction.[22] As such, it is important to bear in mind that natriuretic peptides are physiologically protective hormones, and slightly elevated NT-proBNP in young people may not always be reflective of pathology. However, in older people with more comorbidity, elevated levels of natriuretic peptides become a more consistent biomarker of pathophysiological processes. In contrast to NT-proBNP, elevated troponin T seems to be a more consistent marker of characteristics that increase the risk of CVD in both the studies. Therefore characteristics of the

Table 1.   Associations of Cardiac Biomarkers (Per SD Increase on Log Scale) With CVD During Maximum Follow-Up Time

Study/Events	Variable	Model 1			Model 2			Model 3		
		n (n Events)	HR (95% CI)	P Value	n (n Events)	HR (95% CI)	P Value	n (n Events)	HR (95% CI)	P Value
BRHS all CVD events	NT-proBNP	3538 (736)	1.49 (1.38–1.62)	<0.001	3319 (681)	1.46 (1.34–1.59)	<0.001	3319 (681)	1.38 (1.26–1.51)	<0.001
	hsTnT		1.37 (1.27–1.47)	<0.001		1.34 (1.24–1.45)	<0.001		1.24 (1.14–1.34)	<0.001
	MR-proADM		1.17 (1.07–1.28)	<0.001		1.16 (1.05–1.28)	0.003		0.98 (0.90–1.08)	0.70
BRHS primary* CVD	NT-proBNP	2884 (514)	1.41 (1.28–1.56)	<0.001	2715 (475)	1.35 (1.21–1.50)	<0.001	2715 (475)	1.30 (1.16–1.46)	<0.001
	hsTnT		1.26 (1.15–1.38)	<0.001		1.23 (1.11–1.35)	<0.001		1.16 (1.05–1.29)	0.004
	MR-proADM		1.17 (1.05–1.32)	0.006		1.12 (0.99–1.26)	0.07		0.99 (0.88–1.11)	0.89
MFS all CVD	NT-proBNP	1907 (154)	1.35 (1.15–1.60)	<0.001	1746 (145)	1.27 (1.06–1.51)	0.008	1746 (145)	1.18 (0.99–1.42)	0.07
	hsTnT		1.21 (1.09–1.33)	<0.001		1.18 (1.06–1.31)	0.002		1.15 (1.02–1.29)	0.02
	MR-proADM		1.23 (1.02–1.48)	0.027		1.17 (0.97–1.43)	0.11		1.11 (0.91–1.35)	0.30
MFS primary* CVD events	NT-proBNP	1878 (141)	1.43 (1.18–1.72)	<0.001	1721 (135)	1.33 (1.09–1.62)	0.005	1721 (135)	1.24 (1.01–1.52)	0.04
	hsTnT		1.22 (1.11–1.34)	<0.001		1.20 (1.08–1.33)	<0.001		1.17 (1.05–1.30)	0.005
	MR-proADM		1.17 (0.97–1.42)	0.10		1.16 (0.95–1.41)	0.15		1.09 (0.89–1.33)	0.39

Model 1: adjusting for: age, sex, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, index of multiple deprivation (fifths), smoking (yes, no, and ex-smoker), diabetes mellitus, family history, chronic kidney disease, treated blood pressure, rheumatoid arthritis, previous CVD. Model 2: additionally for: glucose, physical activity, forced expiratory volume in 1 s, alcohol use, and C-reactive protein. Model 3: additionally cross adjusted for N-terminal pro B-type natriuretic peptide (NT-proBNP), high-sensitivity troponin T (hsTnT), midregional pro adrenomedullin (MR-proADM); as relevant. BRHS indicates British Regional Heart Study; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; and MFS, MIDSPAN Family Study.

*Primary CVD excluding baseline CVD and baseline statin use.

Table 2.   C-Index for the Prediction of Primary CVD (Among Those Not Taking Statin Medication at Baseline) by Cardiac Biomarkers in Addition to Risk Factors Based on Classical Risk Scores (QRISK2 and ASSIGN) During Maximum Follow-Up

| Study Model | n (n Events) | Biomarker | C-Index Comparator Model | | |
			Classical Markers	Classical+NT-proBNP	Classical+hsTnT
BRHS primary CVD*	2811 (507)	Reference score	0.657	0.674	0.662
	2811 (507)	NT-proBNP	0.674 (*P*=0.005)	…	0.675 (*P*=0.007)
	2811 (507)	Troponin T	0.662 (*P*=0.28)	0.675 (*P*=0.80)	…
	2811 (507)	MR-proADM	0.662 (*P*=0.11)	0.675 (*P*=0.72)	0.663 (*P*=0.24)
MFS primary CVD†	1890 (142)	Reference score	0.752	0.763	0.758
	1890 (142)	NT-proBNP	0.763 (*P*=0.17)	…	0.765 (*P*=0.25)
	1890 (142)	Troponin T	0.758 (*P*=0.28)	0.765 (*P*=0.55)	…
	1890 (142)	MR-proADM	0.754 (*P*=0.65)	0.763 (*P*=0.66)	0.759 (*P*=0.74)

Abbreviations as in Table 1.

*Includes QRISK2-based variables (sex and ethnicity omitted)—age, index of multiple deprivation (fifths), systolic blood pressure, smoking (yes, no, and ex-smoker), diabetes mellitus, family history, chronic kidney disease (estimated glomerular filtration rate<60), atrial fibrillation, blood pressure treatment, rheumatoid arthritis, total:HDL cholesterol ratio, body mass index.

†Includes ASSIGN-based style variables—age, sex, index of multiple deprivation (continuous), family history, diabetes mellitus, rheumatoid arthritis, cigarettes smoked, systolic blood pressure, total cholesterol, HDL-cholesterol.

risk screening population may have some bearing on how cardiac biomarkers perform as risk predictors.

The evidence of predictive ability of cardiac biomarkers in BRHS probably reflects (1) greater statistical power, (2) a greater burden of underlying subclinical disease in the older BRHS participants, and (3) a lower C-index in BRHS using classical risk factors compared with MFS. Cohorts that have hereto tested the use of cardiac biomarkers in CVD prediction

Table 3.   Cardiac Biomarker 14-Year NRIs for Primary CVD Prediction in Those Not Taking Statins at Baseline

| Study Model | Biomarker | n (n Events) | Group | NRI (95% CI) | |
				Risk Categories 0% to 28%, >28%	Risk Categories 0% to 14%, >14%
BRHS primary CVD	NT-proBNP	2811 (507)	Cases	5.9% (2.8% to 9.2%)	−0.9% (−4.2% to 2.3%)
			Non-cases	−1.0% (−2.2% to 0.1%)	4.6% (2.9% to 6.3%)
			Overall	4.9% (1.4% to 8.3%)	3.7% (0.0% to 6.8%)
	Troponin T	2811 (507)	Cases	4.0% (1.8% to 6.5%)	−2.0% (−4.6 to 0.8%)
			Non-cases	−0.4% (−1.3% to 0.6%)	2.1% (0.7% to 3.6%)
			Overall	3.7% (1.1% to 6.3%)	0.2% (−2.9% to 3.3%)
	MR-proADM	2811 (507)	Cases	0.2% (−1.8% to 2.2%)	1.1% (−1.0% to 3.1%)
			Non-cases	−0.6% (−1.3% to 0.0%)	1.1% (0.1% to 2.2%)
			Overall	−0.4% (−2.5% to 1.7%)	2.2% (−0.2% to 4.5%)
	All 3 biomarkers	2811 (507)	Cases	5.3% (2.0% to 8.6%)	−1.4% (−4.4% to 1.7%)
			Non-cases	−1.3% (−2.5% to −0.1%)	6.3% (4.5% to 7.9%)
			Overall	4.0% (0.4% to 7.5%)	4.9% (1.1% to 8.5%)
MFS primary CVD	NT-proBNP	1890 (107)	Cases	4.7% (1.0% to 9.2%)	−1.7% (−8.2% to 4.4%)
			Non-cases	−0.6% (−1.1% to −0.1%)	−0.4% (−1.4% to 0.5%)
			Overall	4.2% (0.5% to 8.6%)	−2.2% (−8.6% to 4.2%)
	Troponin T	1890 (107)	Cases	2.6% (0.0% to 5.8%)	−0.1% (−6.6% to 6.3%)
			Non-cases	−0.5% (−0.8% to −0.1%)	0.0% (−0.7% to 0.8%)
			Overall	2.1% (−0.4% to 5.4%)	−0.1% (−6.6% to 6.3%)
	MR-proADM	1890 (107)	Cases	−1.7% (−4.4% to 0.0%)	3.9% (−0.9% to 9.2%)
			Non-cases	−0.2% (−0.5% to 0.1%)	−0.4% (−1.0% to 0.3%)
			Overall	−1.9% (−4.6% to −0.1%)	3.5% (−1.3% to 8.8%)
	All 3 biomarkers	1890 (107)	Cases	6.2% (1.6% to 11.3%)	1.2% (−5.6% to 8.3%)
			Non-cases	−0.3% (−0.8% to 0.1%)	−0.1% (−1.1% to 0.8%)
			Overall	5.9% (1.6% to 11.3%)	1.1% (−5.9% to 8.3%)

Risk score prediction variables as per Table 2. Models approximate clinical thresholds for high risk at 10% 10-year risk (using 14% 14-year risk), and 20% 10-year risk (using 28% 14-year risk) across the 2 cohort. Abbreviations as in Table 1.

have primarily comprised older participants at relatively high CVD risk, so the apparently low incremental discrimination gained from measuring cardiac biomarkers in the younger MFS is interesting. Indeed, our recent data from the Action in Diabetes and Vascular Disease: PreterAx and Diamicron MR Controlled Evaluation (ADVANCE) trial of patients with long-standing type 2 diabetes mellitus (a high-risk group) suggested that both NT-proBNP and hsTnT were much stronger predictors than was seen in the studies reported here.[10] Recent data from Multi-Ethnic Study of Atherosclerosis (MESA) suggests that ethnicity is unlikely to importantly modify the predictive ability of cardiac biomarkers.[23] Therefore, generalizability of cardiac biomarkers in CVD prediction is an ongoing area of interest. Large ongoing cohort studies, including Generation Scotland, as well as future meta-analyses will address these issues.

Strengths and weaknesses of the study require consideration. These are 2 large well-phenotyped prospective United Kingdom–based population studies, although small event numbers in MFS limited our power to observe small improvements in discrimination and risk classification. Differences between the studies include not only age but also geographic location, sex composition, and definitions of CVD. The differences in age at baseline allow a contrasting investigation of risk prediction, although BRHS only included male participants. Measurement of multiple cardiac biomarkers in the studies allowed assessment of the use of combinations of biomarkers. NT-proBNP and hsTnT are already routinely measured by automated methods in many routine biochemistry laboratories, and thus clinical translation potential is high. Risk prediction models are based on self-calibration in the cohorts, rather than using published risk scores. This was a decision made to prevent overestimation of the clinical use of the cardiac biomarkers. The improvements we see for discrimination using NT-proBNP are generally consistent with those seen for troponin I and BNP in a recent study in the Scottish Heart and Health Extended Cohort.[9]

Perspectives

The ability of NT-proBNP and hsTnT to correctly influence clinical treatment decisions to prevent CVD was influenced by the risk threshold chosen for commencing preventative treatments, which is important in given recent changes to treatment thresholds in the guidelines. Meta-analysis and cost-effectiveness modeling are required to assess the use of cardiac biomarkers to aid risk prediction in a range of clinical settings.

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Novelty and Significance

What Is New?

- N-terminal pro B-type natriuretic peptide improved discrimination of future cardiovascular disease in the British Regional Heart Study (BRHS) cohort but not in the MIDSPAN Family Study cohort. In a model approximating the clinical 20% 10-year cardiovascular disease risk treatment threshold, inclusion of N-terminal pro B-type natriuretic peptide and high-sensitivity troponin T in risk scores improved treatment decisions among cases in both the studies. In contrast, in a model approximating the 10% 10-year treatment threshold, inclusion of cardiac biomarkers in the risk score in BRHS resulted in improved treatment decisions among noncases only.

What Is Relevant?

- The ability of cardiac biomarkers to improve treatment decisions was influenced by the risk threshold chosen for commencing preventative treatments. This is important against a background where guidelines are changing treatment thresholds in clinical practice toward interventions being indicated at lower risk.

Summary

Cardiac biomarkers still hold promise for cardiovascular disease risk prediction, but the changing landscape of the clinical risk prediction guidelines to identify high-risk patients may limit the ability of cardiac biomarkers to improve risk score sensitivity.

PREDICTION OF CARDIOVASCULAR DISEASE RISK BY CARDIAC BIOMARKERS IN TWO UK COHORT STUDIES: DOES UTILITY DEPEND ON RISK THRESHOLDS FOR TREATMENT?

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Supplementary methods
BRHS
All men completed a mailed questionnaire providing information on their lifestyle and medical history, had a physical examination and provided a fasting blood sample. The samples were frozen and stored at -20°C on the day of collection and transferred for storage at -70°C until analysis. Baseline CVD, DM and rheumatoid arthritis, as well as family history of CVD, statin use, blood pressure medication use, and CKD were binary variables (1). Baseline CVD and diabetes was defined as either self-reported CVD (comprising MI or stroke)/diabetes or incident CVD/diabetes events occurring during follow-up in previous surveys. CKD was defined as an eGFR <60 ml/min/1.73 m2. Baseline RA was defined as taking any presumed rheumatoid arthritis treatment drug: BNF 10.1.2.1, 10.1.2.2, 10.1.3, and 10.1.5 although non-steroidal anti-inflammatory drugs (BNF 10.1.1) were not included due to indication for other conditions. Atrial fibrillation (AF) was diagnosed from ECG data at the study visit. Smoking was analysed as a categorical variable (never-smoker, ex-smoker, current-smoker). Alcohol use was from self-reported questionnaire data: never, occasional/light drinking (<1drink per week- 15 units of alcohol per week), or moderate/heavy classified as 16+ units per week or those who were unclassified. Physical activity from self-reported data: never, occasional/light, or moderate/vigorous. The Index of Multiple Deprivation (IMD) for England, Scotland and Wales was applied to the BRHS based on postcode of residence. IMD is a composite measure of deprivation available for small geographical areas ('lower super output' areas with an average of 1500 people). Fifths (quintiles) of IMD (qIMD) were defined according to national distribution of deprivation indices and applied to the BRHS. Family history of CVD was defined as self-report of mother or father dying of a "heart trouble" before the age of 60 (QRISK2 focuses on angina and MI before the age of 60, and not stroke).

All men provided written informed consent to the investigations, which were carried out in accordance with the Declaration of Helsinki, and approval was gained from relevant local ethics committees.

MFS
Where possible, covariate data was included in the same form as BRHS data (2–6). All information on physical activity, smoking, occupation, diet, socioeconomic status, and alcohol consumption were based on self-reported answers from standard questionnaires (5,6). Blood samples obtained were spun down, plasma separated, aliquoted, and stored at −80 C for subsequent analysis. Baseline CVD (MI/stroke) was defined as self-reported disease in the questionnaire. Baseline DM was defined as self-reported diabetes or fasting plasma glucose >7mmol/L. Baseline RA was self-reported and coded to ICD9 code 714.0. Smoking was analysed as a categorical variable (never-smoker, ex-smoker, current-smoker), but also was included as a continuous variable in some ASSIGN models according to number of cigarettes smoked per day. Alcohol use was from self-reported questionnaire data: never, occasional/light drinking (<1drink per week- 15 units of alcohol per week), or moderate/heavy classified as 16+ units per week or those who were unclassified. Physical activity from self-reported data of usual physical activities: never ("not at all physically active"), occasional/light ("not very physically active"), or moderate/vigorous ("fairly or very physically active"). The Scottish Index of Multiple Deprivation (SIMD) is a postcode based measure of deprivation developed specifically for Scotland, and used in the national CVD risk score (7). MFS participant deprivation was recorded using the earliest available (2004)

SIMD data (8). Family history of CVD of CVD was defined as parental death from MI or stroke before the age of 60 or where discharge records show parents were admitted to hospital for CVD (ICD9 390-459) before the age of 60.

All participants provided written informed consent to the investigations, which were carried out in accordance with the Declaration of Helsinki, and approval was gained from local ethics committees and the Scottish Privacy Advisory Committee (PAC) for electronic record linkage.

Statistical analysis
Analyses were restricted to those with complete data for the three cardiac biomarkers at baseline, otherwise all available data were used. Subjects who went on to experience CVD events were compared to those who did not using medians and interquartile ranges (IQR) to summarize non-normally distributed data, means and standard deviation for normally distributed data, and frequencies and percentages for categorical data. Time-to-event curves were calculated for the three biomarkers across thirds of the distribution (using the lower limit of sensitivity as the bottom tertile for hsTnT) by the Kaplan–Meier method.

Normal distributions were approximated by taking logarithms of positively skewed cardiac biomarker variables for survival analyses. The associations of these markers with CVD risk were summarized using hazard ratios (HRs) derived from Cox proportional hazards models (proportional hazard assumptions were met in all cases), using continuous models (HR per 1 standard deviation [sd] increase) for circulating cardiac biomarkers. Adjustment models were fitted using the same markers in both studies for the Cox models as detailed in table legends; these generally had more risk factors than risk prediction models used clinically. In MFS overdispersion caused by familial clustering was tested using a model that allowed for frailty; this had no significant impact on data for any cardiac biomarker, and so models without a frailty component are presented.

QRISK 2 risk score variables include: Age, sex (all BRHS participants are male) , ethnicity (>99% of BRHS participant or of White European ethnicity), postcode based deprivation index, smoking status, diabetes status, angina or heart attack in a 1st degree relative, CKD, AF, BP treatment, rheumatoid arthritis, total Chol/HDl ratio, SBP, BMI. (Available at http://www.qrisk.org/)

ASSIGN risk score variables include: Age, sex, postcode based deprivation index, Family history of CHD or stroke, diabetes status, rheumatoid arthritis, cigarettes smoked per day, SBP, total cholesterol, HDL cholesterol. (Available at http://assign-score.com/estimate-the-risk/)

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Supplementary tables

S1 Characteristics across thirds of NT-proBNP in BRHS
S2 Characteristics across thirds of hsTnT in BRHS
S3 Characteristics across thirds of MR-proADM in BRHS
S4 Characteristics across thirds of NT-proBNP in MFS
S5 Characteristics across thirds of hsTnT in MFS
S6 Characteristics across thirds of MR-proADM in MFS
S7 Demographics, biochemistries and cardiac biomarkers by case status in both cohort studies
S8 Sensitivity analysis using ASSIGN risk score variables in both cohorts. C-index for the prediction of primary CVD (in those not taking statin medication at baseline) by cardiac biomarkers in addition to risk factors based on ASSIGN over maximum follow-up. Data for MFS identical to table 3 in main paper (included for comparison to BRHS)
S9 C-index for the prediction of secondary CVD using cardiac biomarkers in addition to risk factors based on classical risk scores (QRISK2 and ASSIGN) over maximum follow-up time

S1 Characteristics across thirds of NT-proBNP in BRHS

Variable	T1 (n=1275) ≤59pg/ml	T2 (n=1237) 60-142pg/ml	T3 (n=1245) ≥143pg/ml	p-value
Age	66.2 (4.6)	68.7 (5.3)	71.2 (5.4)	<0.001
Smoking				<0.001
-Never	428 (33.7%)	346 (28.1%)	317 (25.5%)	
-Ex	700 (55.0%)	732 (59.4%)	760 (61.1%)	
-Current	145 (11.4%)	155 (12.6%)	167 (13.4%)	
BMI	26.9 (3.5)	26.9 (3.6)	26.8 (3.92)	0.61
IMD score	19.6 (14.4)	19.8 (14.4)	21.4 (15.3)	0.002
SBP	144.2 (20.6)	149.2 (23.4)	153.4 (26.9)	<0.001
DBP	85.1 (9.9)	85.0 (10.9)	85.0 (12.6)	0.95
TC	6.19 (1.07)	6.01 (1.05)	5.80 (1.07)	<0.001
HDL	1.32 (0.33)	1.32 (0.34)	1.32 (0.36)	0.97
Glucose	6.01 (1.95)	5.99 (1.78)	6.09 (2.00)	0.37
EGFR	74.9 (11.1)	73.3 (13.0)	68.8 (13.5)	<0.001
CKD (EGFR<60)	110 (8.6%)	162 (13.1%)	295 (23.7%)	<0.001
Physical activity				<0.001
-Inactive	96 (7.8%)	110 (9.2%)	196 (16.4%)	
-Occasional/light	488 (39.7%)	498 (41.9%)	540 (45.0%)	
-Moderate/vigorous	646 (52.5%)	582 (48.9%)	463 (38.6%)	
Alcohol use				0.19
-None	117 (9.3%)	108 (8.9%)	141 (11.5%)	
-Occasional/light	897 (71.5%)	864 (70.8%)	842 (68.9%)	
-Moderate/heavy	241 (19.2%)	248 (20.3%)	240 (19.6%)	
Baseline CVD	79 (6.3%)	159 (13.1%)	358 (29.3%)	<0.001
Baseline DM	85 (6.7%)	78 (6.3%)	110 (8.8%)	0.031
Family history	62 (5.0%)	60 (5.0%)	86 (7.2%)	0.028
Statin use	47 (3.7%)	69 (5.6%)	130 (10.4%)	<0.001
BP med	228 (18.1%)	386 (31.6%)	592 (48.3%)	<0.001
CRP (mg/L)	1.24 (0.66, 2.71)	1.56 (0.82, 3.39)	2.07 (1.00, 4.55)	<0.001
hsTnT (pg/ml)	10.1 (7.7, 13.5)	11.4 (8.8, 15.3)	14.6 (10.9, 19.8)	<0.001
MR-proADM (nmol/L)	0.52 (0.46, 0.59)	0.57 (0.49, 0.65)	0.65 (0.56, 0.77)	<0.001

Data are means (standard deviations), medians (interquartile ranges), or n (%)
BMI, body mass index; BP med, blood pressure medication; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus eGFR, estimated glomerular filtration rate; HDL-c, high density lipoprotein cholesterol; IMD, index multiple deprivation; RA, rheumatoid arthritis; SBP, systolic blood pressure; TC, total cholesterol

S2 Characteristics across thirds of hsTnT in BRHS

Variable	T1 (n=1261) ≤9.8pg/ml	T2 (n=1260) 9.9-14.2pg/ml	T3 (n=1236) ≥14.3pg/ml	p-value
Age	66.2 (4.6)	68.9 (5.3)	71.0 (5.5)	<0.001
Smoking				<0.001
-Never	415 (33.0%)	363 (28.9%)	313 (25.4%)	
-Ex	672 (53.5%)	727 (57.8%)	793 (64.2%)	
-Current	170 (13.5%)	168 (13.4%)	129 (10.5%)	
BMI	26.4 (3.3)	26.9 (3.6)	27.3 (4.0)	<0.001
IMD score	19.3 (14.4)	20.2 (14.6)	21.3 (15.2)	0.004
SBP	145.2 (22.6)	148.9 (23.0)	152.6 (25.9)	<0.001
DBP	85.0 (10.5)	84.9 (10.9)	85.3 (12.0)	0.66
TC	6.06 (1.05)	6.00 (1.07)	5.95 (1.12)	0.023
HDL	1.33 (0.34)	1.32 (0.34)	1.32 (0.35)	0.55
Glucose	5.81 (1.24)	5.99 (1.92)	6.30 (2.38)	<0.001
EGFR	75.8 (11.6)	72.4 (11.1)	68.8 (14.5)	<0.001
CKD (EGFR<60)	100 (8.0%)	166 (13.2%)	301 (24.4%)	<0.001
Physical activity				<0.001
-Inactive	100 (8.2%)	123 (10.2%)	179 (15.1%)	
-Occasional/light	522 (42.8%)	480 (39.7%)	524 (44.1%)	
-Moderate/vigorous	599 (49.1%)	607 (50.2%)	485 (40.8%)	
Alcohol use				0.08
-None	104 (8.3%)	136 (11.0%)	126 (10.4%)	
-Occasional/light	886 (71.1%)	881 (71.1%)	836 (69.0%)	
-Moderate/heavy	257 (20.6%)	222 (17.9%)	250 (20.6%)	
Baseline CVD	129 (10.4%)	200 (16.2%)	267 (22.1%)	<0.001
Baseline DM	59 (4.7%)	81 (6.4%)	133 (10.8%)	<0.001
Family history	70 (5.7%)	60 (4.9%)	78 (6.5%)	0.23
Statin use	78 (6.2%)	77 (6.1%)	91 (7.4%)	0.37
BP med use	321 (25.8%)	396 (31.9%)	489 (40.0%)	<0.001
CRP (mg/L)	1.30 (0.70, 2.70)	1.60 (0.84, 3.47)	2.07 (0.99, 4.60)	<0.001
NT-proBNP (pg/ml)	64 (35, 114)	92 (49, 184)	150 (70, 419)	<0.001
MR-proADM (nmol/L)	0.53 (0.47, 0.61)	0.57 (0.49, 0.65)	0.63 (0.54, 0.77)	<0.001

Data are means (standard deviations), medians (interquartile ranges), or n (%)
BMI, body mass index; BP med, blood pressure medication; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus eGFR, estimated glomerular filtration rate; HDL-c, high density lipoprotein cholesterol; IMD, index multiple deprivation; RA, rheumatoid arthritis; SBP, systolic blood pressure; TC, total cholesterol

S3 Characteristics across thirds of MR-proADM in BRHS

Variable	T1 (n=1300) ≤0.52nmol/L	T2 (n=1266) 0.53-0.62nmol/L	T3 (n=1191) ≥0.63nmol/L	p-value
Age	66.4 (4.8)	68.6 (5.3)	71.2 (5.4)	<0.001
Smoking				<0.001
-Never	491 (37.9%)	342 (27.0%)	258 (21.7%)	
-Ex	669 (51.6%)	759 (60.0%)	764 (64.3%)	
-Current	136 (10.5%)	164 (13.0%)	167 (14.1%)	
BMI	25.9 (3.1)	26.9 (3.4)	27.9 (4.2)	<0.001
IMD score	18.7 (13.5)	19.7 (14.7)	22.6 (15.8)	<0.001
SBP	145.8 (21.9)	149.9 (24.0)	151.2 (25.9)	<0.001
DBP	84.9 (10.2)	85.2 (11.1)	85.0 (12.2)	0.80
TC	6.02 (1.06)	6.04 (1.06)	5.95 (1.11)	0.09
HDL	1.37 (0.35)	1.31 (0.33)	1.28 (0.34)	<0.001
Glucose	5.88 (1.53)	6.03 (2.07)	6.21 (2.09)	<0.001
EGFR	77.3 (11.5)	73.8 (11.1)	65.5 (12.9)	<0.001
CKD (EGFR<60)	72 (5.6%)	111 (8.8%)	384 (32.3%)	<0.001
Physical activity				<0.001
-Inactive	89 (7.1%)	110 (9.0%)	203 (17.9%)	
-Occasional/light	479 (38.0%)	514 (42.1%)	533 (46.9%)	
-Moderate/vigorous	693 (55.0%)	596 (48.9%)	402 (35.3%)	
Alcohol use				<0.001
-None	111 (8.7%)	112 (9.0%)	143 (12.3%)	
-Occasional/light	950 (74.2%)	884 (70.7%)	769 (66.0%)	
-Moderate/heavy	220 (17.2%)	254 (20.3%)	255 (21.9%)	
Baseline CVD	121 (9.5%)	191 (15.4%)	284 (24.4%)	<0.001
Baseline DM	79 (6.1%)	80 (6.3%)	114 (9.6%)	0.001
Family history	64 (5.0%)	71 (5.7%)	73 (6.4%)	0.36
Statin use	75 (5.8%)	80 (6.3%)	91 (7.6%)	0.16
BP med use	254 (19.9%)	388 (31.0%)	564 (47.9%)	<0.001
CRP (mg/L)	1.08 (0.57, 2.30)	1.49 (0.85, 3.19)	2.58 (1.30, 5.40)	<0.001
hsTnT (pg/ml)	10.2 (7.9, 13.7)	11.3 (8.7, 15.0)	14.9 (10.8, 20.5)	<0.001
NT-proBNP (pg/ml)	59 (31, 105)	88 (49, 175)	178 (86, 436)	<0.001

Data are means (standard deviations), medians (interquartile ranges), or n (%)
BMI, body mass index; BP med, blood pressure medication; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus eGFR, estimated glomerular filtration rate; HDL-c, high density lipoprotein cholesterol; IMD, index multiple deprivation; RA, rheumatoid arthritis; SBP, systolic blood pressure; TC, total cholesterol

S4 Characteristics across thirds of NT-proBNP in MFS

Variable	T1 (n=764) ≤26pg/ml	T2 (n=739) 27-49pg/ml	T3 (n=723) ≥50pg/ml	p-value
Age	44.3 (5.7)	45.4 (6.1)	47.2 (6.2)	<0.001
Sex male	520 (68.1%)	293 (39.7%)	181 (25.0%)	<0.001
Smoking				0.008
-Never	383 (50.1%)	342 (46.3%)	322 (44.5%)	
-Ex	157 (20.6%)	194 (26.3%)	207 (28.7%)	
-Current	224 (29.3%)	203 (27.5%)	194 (26.8%)	
BMI	26.6 (4.1)	25.8 (4.5)	26.1 (5.1)	0.001
IMD score	17.4 (13.6)	18.9 (14.5)	19.8 (14.7)	0.005
SBP	127.8 (14.0)	126.1 (15.6)	127.1 (18.0)	0.13
DBP	76.2 (10.6)	74.3 (10.7)	73.1 (12.3)	<0.001
TC	5.38 (0.93)	5.18 (0.93)	5.22 (1.01)	<0.001
HDL	1.34 (0.32)	1.44 (0.37)	1.47 (0.38)	<0.001
Glucose	5.58 (1.98)	5.25 (1.33)	5.23 (1.30)	<0.001
eGFR	103.0 (64.2)	101.7 (25.5)	99.6 (27.1)	0.30
CKD (EGFR<60)	4 (0.5%)	4 (0.6%)	15 (2.1%)	0.004
Physical activity				0.01
-Inactive	65 (8.6%)	39 (5.3%)	50 (6.9%)	
-Occasional/light	308 (40.4%)	276 (37.4%)	250 (34.6%)	
-Moderate/vigorous	390 (51.1%)	424 (57.4%)	423 (58.5%)	
Alcohol use				<0.001
-None	111 (14.5%)	128 (17.3%)	148 (20.5%)	
-Occasional/light	364 (47.6%)	407 (55.1%)	414 (57.3%)	
-Moderate/heavy	289 (37.8%)	204 (27.6%)	161 (22.3%)	
Baseline CVD	3 (0.4%)	3 (0.4%)	19 (2.6%)	<0.001
Baseline DM	44 (5.8%)	27 (3.7%)	32 (4.4%)	0.14
Family history	43 (5.7%)	44 (6.0%)	43 (6.0%)	0.95
Statin use	5 (0.7%)	3 (0.4%)	6 (0.8%)	0.59
BP med use	34 (4.5%)	55 (7.4%)	118 (16.3%)	<0.001
CRP (mg/L)	0.78 (0.33-1.96)	0.81 (0.34-1.98)	1.06 (0.46-2.51)	<0.001
hsTnT (pg/ml)	3.0 (3.0-4.0)	3.0 (3.0-4.0)	3.0 (3.0-4.4)	0.15
MR-proADM (nmol/L)	0.29 (0.23-0.35)	0.29 (0.23-0.35)	0.30 (0.24-0.39)	<0.001

Data are means (standard deviations), medians (interquartile ranges), or n (%)
BMI, body mass index; BP med, blood pressure medication; CKD, chronic kidney disease;
CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM,
diabetes mellitus eGFR, estimated glomerular filtration rate; HDL-c, high density
lipoprotein cholesterol; IMD, index multiple deprivation; RA, rheumatoid arthritis; SBP,
systolic blood pressure; TC, total cholesterol

S5 Characteristics across thirds of hsTnT in MFS

Variable	T1 (n=1324) <3pg/ml	T2 (n=459) 3.0-4.6pg/ml	T3 (n=443) ≥4.7pg/ml	p-value
Age	44.8 (6.0)	46.1 (6.2)	47.4 (6.2)	<0.001
Sex male	437 (33.0%)	274 (59.7%)	283 (63.9%)	<0.001
Smoking				<0.001
-Never	611 (46.2%)	218 (47.5%)	218 (49.2%)	
-Ex	389 (29.4%)	96 (20.9%)	73 (16.5%)	
-Current	324 (24.5%)	145 (31.6%)	152 (34.3%)	
BMI	25.7 (4.3)	26.6 (4.5)	27.2 (5.0)	<0.001
IMD score	18.7 (14.4)	18.0 (14.0)	19.3 (14.4)	0.40
SBP	124.8 (14.8)	129.5 (16.0)	131.2 (17.7)	<0.001
DBP	72.9 (10.5)	76.4 (11.0)	77.6 (12.6)	<0.001
TC	5.20 (0.94)	5.31 (0.99)	5.41 (0.97)	<0.001
HDL	1.44 (0.37)	1.40 (0.38)	1.37 (0.32)	0.002
Glucose	5.26 (1.36)	5.37 (1.42)	5.62 (2.23)	<0.001
eGFR	102.9 (52.2)	101.2 (25.8)	97.4 (23.8)	0.07
CKD (EGFR<60)	10 (0.8%)	3 (0.7%)	10 (2.3%)	0.018
Physical activity				0.31
-Inactive	86 (6.5%)	42 (9.2%)	26 (5.9%)	
-Occasional/light	500 (37.8%)	167 (36.5%)	167 (37.7%)	
-Moderate/vigorous	738 (55.7%)	249 (54.4%)	250 (56.4%)	
Alcohol use				<0.001
-None	230 (17.4%)	81 (17.7%)	76 (17.2%)	
-Occasional/light	763 (57.6%)	222 (48.4%)	200 (45.2%)	
-Moderate/heavy	331 (25.0%)	156 (34.0%)	167 (37.7%)	
Baseline CVD	13 (1.0%)	3 (0.7%)	9 (2.0%)	0.11
Baseline DM	52 (4.0%)	25 (5.5%)	26 (5.9%)	0.15
Family history	80 (6.0%)	25 (5.5%)	25 (5.6%)	0.88
Statin use	6 (0.5%)	3 (0.7%)	5 (1.1%)	0.30
BP med use	102 (7.7%)	49 (10.7%)	56 (12.7%)	0.004
CRP (mg/L)	0.84 (0.35-2.06)	0.82 (0.38-1.90)	1.06 (0.43-2.36)	0.0074
NT-proBNP (pg/ml)	35 (21-56)	35 (21-54)	40 (24-68)	0.0027
MR-proADM (nmol/L)	0.28 (0.22-0.34)	0.32 (0.25-0.38)	0.32 (0.26-0.40)	<0.001

Data are means (standard deviations), medians (interquartile ranges), or n (%)
BMI, body mass index; BP med, blood pressure medication; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus eGFR, estimated glomerular filtration rate; HDL-c, high density lipoprotein cholesterol; IMD, index multiple deprivation; RA, rheumatoid arthritis; SBP, systolic blood pressure; TC, total cholesterol

S6 Characteristics across thirds of MR-proADM in MFS

Variable	T1 (n=768) ≤0.25nmol/L	T2 (n=724) 0.26-0.33nmol/L	T3 (n=734) ≥0.34nmol/L	p-value
Age	44.2 (5.8)	45.4 (6.0)	47.3 (6.2)	<0.001
Sex male	261 (34.0%)	338 (46.7%)	395 (53.8%)	<0.001
Smoking				<0.001
-Never	417 (54.3%)	346 (47.8%)	284 (38.7%)	
-Ex	142 (18.5%)	184 (25.4%)	232 (31.6%)	
-Current	209 (27.2%)	194 (26.8%)	218 (29.7%)	
BMI	24.8 (3.6)	26.0 (4.4)	27.8 (5.1)	<0.001
IMD score	17.0 (13.3)	18.0 (14.4)	21.2 (14.9)	<0.001
SBP	123.6 (14.8)	126.3 (15.6)	131.3 (16.3)	<0.001
DBP	72.2 (10.7)	74.3 (11.0)	77.3 (11.5)	<0.001
TC	5.10 (0.93)	5.27 (0.93)	5.42 (1.00)	<0.001
HDL	1.47 (0.37)	1.40 (0.35)	1.37 (0.37)	<0.001
Glucose	5.18 (1.10)	5.28 (1.50)	5.61 (2.01)	<0.001
EGFR	104.1 (25.0)	103.0 (67.2)	97.1 (23.7)	0.0037
CKD (EGFR<60)	5 (0.7%)	5 (0.7%)	13 (1.8%)	0.054
Physical activity				0.16
-Inactive	50 (6.5%)	45 (6.2%)	59 (8.1%)	
-Occasional/light	267 (34.8%)	287 (39.6%)	280 (38.2%)	
-Moderate/vigorous	451 (58.7%)	392 (54.1%)	394 (53.8%)	
Alcohol use				<0.001
-None	123 (16.0%)	129 (17.8%)	135 (18.4%)	
-Occasional/light	477 (62.1%)	377 (52.1%)	331 (45.1%)	
-Moderate/heavy	168 (21.9%)	218 (30.1%)	268 (36.5%)	
Baseline CVD	6 (0.8%)	7 (1.0%)	12 (1.6%)	0.26
Baseline DM	21 (2.7%)	25 (3.5%)	57 (7.8%)	<0.001
Family history	49 (6.4%)	43 (5.9%)	38 (5.2%)	0.60
Statin use	3 (0.4%)	3 (0.4%)	8 (1.1%)	0.16
BP med use	42 (5.5%)	61 (8.4%)	104 (14.2%)	<0.001
CRP (mg/L)	0.71 (0.29-1.69)	0.75 (0.34-1.63)	1.32 (0.58-3.03)	<0.001
hsTnT (pg/ml)	3.0 (3.0-3.3)	3.0 (3.0-4.0)	3.1 (3.0-4.8)	<0.001
NT-proBNP (pg/ml)	35 (21-54)	34 (20-54)	39 (24-67)	<0.001

Data are means (standard deviations), medians (interquartile ranges), or n (%)
BMI, body mass index; BP med, blood pressure medication; CKD, chronic kidney disease;
CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM,
diabetes mellitus eGFR, estimated glomerular filtration rate; HDL-c, high density lipoprotein
cholesterol; IMD, index multiple deprivation; RA, rheumatoid arthritis; SBP, systolic blood
pressure; TC, total cholesterol

S7 Demographics, biochemistries and cardiac biomarkers by case status in both cohort studies

Variable	BRHS			MFS		
	No incident CVD (n=2969)	Incident CVD (n=788)	p-value	No incident CVD (n=2031)	Incident CVD (n=195)	p-value
Age (years)	68.2 (5.4)	70.5 (5.5)	<0.001	45.3 (6.1)	49.0 (5.7)	<0.001
Sex male	3128 (100%)	628 (100%)	-	874 (43.0%)	120 (61.5%)	<0.001
Smoking			0.006			<0.001
-Never	892 (30.1%)	199 (25.4%)		980 (48.4%)	65 (33.3%)	
-Ex	1725 (58.2%)	467 (59.6%)		485 (23.9%)	73 (37.4%)	
-Current	349 (11.8%)	118 (16.7%)		564 (27.8%)	57 (29.2%)	
BMI (kg/m^2)	26.9 (3.7)	27.0 (3.7)	0.56	26.1 (4.5)	26.9 (5.0)	0.017
IMD score*	20.0 (14.6)	21.4 (15.3)	0.014	18.4 (14.1)	22.2 (15.4)	<0.001
SBP (mmHg)	147.7 (23.3)	153.3 (26.1)	<0.001	126.3 (15.5)	134.6 (17.7)	<0.001
DBP (mmHg)	84.9 (10.9)	85.6 (12.3)	0.12	74.1 (11.1)	79.2 (11.6)	<0.001
Total-c (mmol/L)	6.00 (1.08)	6.00 (1.08)	0.94	5.23 (0.95)	5.59 (1.00)	<0.001
HDL-c (mmol/L)	1.33 (0.34)	1.28 (0.33)	<0.001	1.43 (0.36)	1.30 (0.34)	<0.001
Glucose (mmol/L)	5.95 (1.70)	6.34 (2.53)	<0.001	5.30 (1.37)	5.97 (2.95)	<0.001
eGFR	73.1 (12.6)	70.0 (13.4)	<0.001	101.6 (44.7)	100.4 (23.5)	0.71
CKD (eGFR<60)	404 (13.6%)	163 (20.7%)	<0.001	22 (1.1%)	1 (0.5%)	0.45
Physical activity			<0.001			0.03
-Inactive	281 (9.8%)	121 (16.2%)		134 (6.6%)	20 (10.3%)	
-Occasional/light	1201 (41.8%)	325 (43.5%)		775 (38.2%)	59 (30.3%)	
-Moderate/vigorous	1389 (48.4%)	302 (40.4%)		1121 (55.2%)	116 (59.5%)	
Alcohol use			0.08			0.014
-None	273 (9.3%)	93 (12.1%)		345 (17.0%)	42 (21.5%)	
-Occasional/light	2073 (70.8%)	530 (68.7%)		1100 (54.2%)	85 (43.6%)	
-Moderate/heavy	581 (19.9%)	148 (19.2%)		586 (28.9%)	68 (34.9%)	
Baseline CVD	378 (13.0%)	218 (28.0%)	<0.001	10 (0.5%)	15 (7.7%)	<0.001
Baseline DM	187 (6.3%)	86 (10.9%)	<0.001	83 (4.1%)	20 (10.4%)	<0.001
Baseline RA	7 (0.2%)	3 (0.4%)	0.48	6 (0.3%)	1 (0.5%)	0.61
Family history CVD	150 (5.5%)	48 (6.3%)	0.41	115 (5.7%)	15 (7.7%)	0.25
Statin use	172 (5.8%)	74 (9.4%)	<0.001	10 (0.5%)	4 (2.1%)	0.009
BP med use	867 (29.6%)	339 (43.6%)	<0.001	167 (8.2%)	40 (20.5%)	<0.001
CRP (mg/L)	1.50 (0.78, 3.27)	2.00 (1.00, 4.35)	<0.001	0.84 (0.36-2.00)	1.34 (0.60-3.04)	<0.001
NT-proBNP (pg/ml)	82 (43, 169)	148 (72, 392)	<0.001	35 (21-56)	41 (23-73)	0.002
hsTnT (pg/ml)	11.3 (8.6, 15.4)	14.1 (10.2, 19.6)	<0.001	3.0 (3.0-4.0)	3.1 (3.0-5.5)	<0.001
MR-proADM (nmol/L)	0.56 (0.49, 0.65)	0.61 (0.53, 0.73)	<0.001	0.29 (0.23-0.35)	0.34 (0.28-0.42)	<0.001

Data are means (standard deviations), medians (interquartile ranges), or n (%)

BMI, body mass index; BP med, blood pressure medication; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus eGFR, estimated glomerular filtration rate; HDL-c, high density lipoprotein cholesterol; IMD, index multiple deprivation; RA, rheumatoid arthritis; SBP, systolic blood pressure; TC, total cholesterol

* Higher score indicates more deprived

S8 Sensitivity analysis using ASSIGN risk score variables in both cohorts. C-index for the prediction of primary CVD (in those not taking statin medication at baseline) by cardiac biomarkers in addition to risk factors based on ASSIGN over maximum follow-up. Data for MFS identical to table 3 in main paper (included for comparison to BRHS).

Study model	N (n events)	Biomarker	C-index comparator model		
			Classical markers	**Classical + NT-proBNP**	**Classical + hsTnT**
BRHS primary CVD	2936 (523)	Reference score	0.650	0.667	0.654
	2936 (523)	NT-proBNP	0.667 (p=0.007)	-	0.667 (p=0.01)
	2936 (523)	Troponin T	0.654 (p=0.33)	0.667 (p=0.97)	-
	2936 (523)	MR-proADM	0.655 (p=0.06)	0.667 (p=0.72)	0.655 (p=0.29)
MFS primary CVD	1890 (142)	Reference score	0.752	0.763	0.758
	1890 (142)	NT-proBNP	0.763 (p=0.17)	-	0.765 (p=0.25)
	1890 (142)	Troponin T	0.758 (p=0.28)	0.765 (p=0.55)	-
	1890 (142)	MR-proADM	0.754 (p=0.65)	0.763 (p=0.66)	0.759 (p=0.74)

Classical risk factors include ASSIGN-based style variables – age, sex, IMD (continuous), family history, diabetes, RA, cigs smoked, SBP, total cholesterol, HDL-cholesterol

S9 C-index for the prediction of secondary CVD using cardiac biomarkers in addition to risk factors based on classical risk scores (QRISK2 and ASSIGN) over maximum follow-up time

Study model	N (n events)	Biomarker	C-index comparator model		
			Classical markers	**Classical + NT-proBNP**	**Classical + hsTnT**
BRHS secondary CVD*	554 (204)	Reference score	0.613	0.639	0.660
	554 (204)	NT-proBNP	0.639 (p=0.036)	-	0.665 (p=0.17)
	554 (204)	Troponin T	0.660 (p=0.008)	0.665 (p=0.079)	-
	554 (204)	MR-proADM	0.612 (p=0.82)	0.640 (p=0.59)	0.661 (p=0.48)

* Includes QRISK 2-based variables (sex and ethnicity omitted) – age, IMD (fifths), SBP, smoking (yes, no, ex), diabetes, family history, CKD (EGFR<60), AF, BP treatment, RA, total:HDL cholesterol ratio, BMI.

Hypertension

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Prediction of Cardiovascular Disease Risk by Cardiac Biomarkers in 2 United Kingdom Cohort Studies: Does Utility Depend on Risk Thresholds For Treatment?

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