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

Paul Welsh, Carole Hart, Olia Papacosta, David Preiss, Alex McConnachie, Heather Murray, Sheena Ramsay, Mark Upton, Graham Watt, Peter Whincup, Goya Wannamethee,* Naveed Sattar*

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. \((\text{Hypertension. 2016;67:309-315. DOI: 10.1161/HYPERTENSIONAHA.115.06501.}) \bullet \text{Online Data Supplement}\n
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 treat stratified medicine for estimating cardiovascular disease.\(^1\) 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 treat

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.\textsuperscript{13}–\textsuperscript{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 significantly more prevalent and subclinical CVD than the young 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. 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.\textsuperscript{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.\textsuperscript{17} 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.\textsuperscript{18}

In BRHS, CVD events were defined as a composite of CVD death (all of those who died with previous CVD, either self-reported or occurring in previous sur- vey, 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 base- line 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.

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 analy- sis, secondary CVD risk prediction was also tested in those with base-line 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.\textsuperscript{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\textsuperscript{6}), and in MFS using predictors broadly based on those included in ASSIGN (the risk score used in Scotland\textsuperscript{6}). 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.\textsuperscript{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).\textsuperscript{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

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 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.

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.\textsuperscript{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.\textsuperscript{17} 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.\textsuperscript{18}

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.\textsuperscript{3}

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.\textsuperscript{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\textsuperscript{18}.
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
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 (0.97–1.41) | 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; CVD, cardiovascular disease; MFS, MIDSPAN Family Study.

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 |
|-------------|--------------|-----------|-------------------------|
|             |              | Reference score | Classical Markers | Classical+NT-proBNP | Classical+hsTnT |
| BRHS primary CVD* | 2811 (507) | 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=0.028) | 0.675 (P=0.030) | … |
| | 2811 (507) | MR-proADM | 0.662 (P=0.11) | 0.675 (P=0.072) | 0.663 (P=0.024) |
| 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=0.025) |
| | 1890 (142) | Troponin T | 0.758 (P=0.28) | 0.765 (P=0.055) | … |
| | 1890 (142) | MR-proADM | 0.754 (P=0.065) | 0.763 (P=0.066) | 0.759 (P=0.074) |

BRHS indicates British Regional Heart Study; CVD, cardiovascular disease; MFS, MIDSPAN Family Study; MR-proADM, midregional pro adrenomedullin; and NT-proBNP, N-terminal pro B-type natriuretic peptide.

*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.
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, particularly because the specificity of cardiovascular risk prediction falls as 10-year CVD risk thresholds are lowered.

Recent mendelian randomization studies have shown that the active BNP hormone might protect against diabetes mellitus. 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 and lowering blood pressure in the context of heart failure with reduced ejection fraction. 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

### 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 | 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. BRHS indicates British Regional Heart Study; CVD, cardiovascular disease; CI, confidence interval; MFS, MIDSPAN Family Study; MR-proADM, midregional pro adrenomedullin; NRI, net reclassification index; and NT-proBNP, N-terminal pro B-type natriuretic peptide.
the 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 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 Diamicon 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.23 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 used in clinical practice to prevent CVD was influenced by personal risk estimation: the MORGAM Biomarker Project Scottish Cohort.22 The evidence of predictive ability of cardiac biomarkers in CVD prediction is 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.22

**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.

**Acknowledgments**

We thank Elaine Butler, Lynne Cherry, and Sara-Jane Duffus (University of Glasgow) for technical support.

**Sources of Funding**

The British Regional Heart Study receives support from the British Heart Foundation Program grant (RG/08/013/25942). The MIDSPAN Family Study was funded by the Wellcome Trust and the National Health Service Cardiovascular Research and Development Program. None of the funding bodies were involved in the study design or the collection, analysis, and interpretation of data for this article or in the writing of the report. Dr Welsh is supported by British Heart Foundation fellowship FS/12/62/29889, which funded biomarker work.

**Disclosures**

P. Welsh and N. Sattar hold a separate research grant from the Chief Scientist Office (Scottish Government Health and Social Care Directorates) relating to the use of cardiac biomarkers in cardiovascular disease risk prediction. The other authors report no conflicts.

**References**

1. Yu T, Vollenweider D, Varadhan R, Li T, Boyd C, Puhan MA. Support of personalized medicine through risk-stratified treatment recommenda-
tions—an environmental scan of clinical practice guidelines. *BMC Med*. 2013;11:7. doi: 10.1186/1741-7015-11-7.

2. Hippius-Cox J, Coupland C, Robson J, Brindle P. Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovas-
cular disease: cohort study using QResearch database. *BMJ*. 2010;341:c6624.

3. Perk J, De Backer G, Gohlke H, et al; Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice; European Association for Cardiovascular Prevention and Rehabilitation. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Atherosclerosis*. 2012;223:1–68. doi: 10.1016/j.atherosclerosis.2012.05.007.

4. Woodward M, Brindle P, Tunstall-Pedoe H; SIGN Group on Risk Estimation. Adding social deprivation and family history to cardiovascu-
lar risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHIEC). *Heart*. 2007;93:172–176. doi: 10.1136/ "ht.2006.108167.

5. Stone NJ, Robinson JG, Lichtenstein AH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25 pt B):2889–2934. doi: 10.1016/j.jacc.2013.11.002.

6. National Institute for Health and Care Excellence. Lipid Modification: Cardiovascular Risk Assessment and the Modification of Blood Lipids for the Primary and Secondary Prevention of Cardiovascular Disease. 2014. http://www.nice.org.uk/guidance/cg181/chapter/1-recommendations. Accessed November 11, 2015.

7. Welsh P, Doolin O, Willett P, Packard C, Macfarlane P, Cobbie S, Gudanovic V, Di Angelantonio E, Ford I, Sattar N. N-terminal pro-B-type natriuretic peptide and the prediction of primary cardiovascular events: results from 15-year follow-up of WOSCOPS. *Eur Heart J*. 2013;34:443–450. doi: 10.1093/eurheartj/ehts239.

8. Wannamethee SG, Welsh P, Lowe GD, Gudanovic V, Di Angelantonio E, Lannon L, Rumley A, Whincup PH, Sattar 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. doi: 10.1016/j.jacc.2011.02.041.

9. Zeller T, Tunstall-Pedoe H, Saarela O, Ojeda F, Schnabl RB, Tuovinen T, Woodward M, Struthers A, Hughes M, Kee F, Solomaa V, Kaukasmaa K, Blankenberg S; MORGAM Investigators. High population prevalence of cardiac troponin I measured by a high-sensitivity assay and cardiovascular risk estimation: the MORGAM Biomarker Project Scottish Cohort. *Eur Heart J*. 2014;35:271–281. doi: 10.1093/eurheartj/eht406.

10. Hillis GS, Welsh P, Chalmers J, Perkovic V, Chow CK, Li Q, Jun M, Neal B, Zoungas S, Poulter N, Mancia G, Williams B, Sattar N, Woodward M. The relative and combined ability of high-sensitivity cardiac troponin T and N-terminal pro-B-type natriuretic peptide to predict
cardiovascular events and death in patients with type 2 diabetes. *Diabetes Care*. 2014;37:295–303. doi: 10.2337/dc13-1165.

11. Melloni C, Roe MT. Cardiac troponin and risk stratification in ischemic heart disease. *N Engl J Med*. 2015;373:672–674. doi: 10.1056/NEJMoa1506298.

12. Sabatine MS, Morrow DA, de Lemos JA, Onland T, Sloan S, Jarolim P, Solomon SD, Pfeffer MA, Braunwald E. Evaluation of multiple biomarkers of cardiovascular stress for risk prediction and guiding medical therapy in patients with stable coronary disease. *Circulation*. 2012;125:233–240. doi: 10.1161/CIRCULATIONAHA.111.063842.

13. Schnabel RB, Schulz A, Messow CM, et al. Multiple marker approach to risk stratification in patients with stable coronary artery disease. *Eur Heart J*. 2010;31:3024–3031. doi: 10.1093/eurheartj/ehq322.

14. Melander O, Newton-Cheh C, Almgren P, Hedblad B, Berglund G, Engström G, Persson M, Smith JG, Magnusson M, Christenson R, Struck J, Morgenthaler NG, Bergmann A, Pencina MJ, Wang TJ. Novel and conventional biomarkers for prediction of incident cardiovascular events in the community. *JAMA*. 2009;302:49–57. doi: 10.1001/jama.2009.943.

15. Brindle PM, McConnachie A, Upton MN, Hart CL, Davey Smith G, Watt GC. The accuracy of the Framingham risk-score in different socioeconomic groups: a prospective study. *Br J Gen Pract*. 2005;55:838–845.

16. Shaper AG, Pocock SJ, Walker M, Cohen NM, Wale CJ, Thomson AG. British Regional Heart Study: cardiovascular risk factors in middle-aged men in 24 towns. *BMJ (Clin Res Ed).* 1981;283:179–186.

17. Upton MN, McConnachie A, McSharry C, Hart CL, Smith GD, Gillis CR, Watt GC. Intergenerational 20 year trends in the prevalence of asthma and hay fever in adults: the Midspan family study surveys of parents and offspring. *BMJ*. 2000;321:88–92.

18. Welsh P, Doolin O, McConnachie A, Boulton E, McNeil G, Macdonald H, Hardcastle A, Hart C, Upton M, Watt G, Sattar N. Circulating 25OHD, dietary vitamin D, PTH, and calcium associations with incident cardiovascular disease and mortality: the MIDSPAN Family Study. *J Clin Endocrinol Metab*. 2012;97:4578–4587. doi: 10.1210/jc.2012-2272.

19. Newson RB. Comparing the predictive powers of survival models using Harrell’s C or Somers’ D. *Stat J*. 2010;10:339–358.

20. Uno H, Tian L, Cai T, Kohane IS, Wei LJ. A unified inference procedure for a class of measures to assess improvement in risk prediction systems with survival data. *Stat Med*. 2013;32:2430–2442. doi: 10.1002/sim.5647.

21. Pfister R, Sharp S, Ruben R, Welsh P, Barroso I, Salomaa V, Meirhaeghe A, Khaw KT, Sattar N, Langenberg C, Wareham NJ. Mendelian randomization study of B-type natriuretic peptide and type 2 diabetes: evidence of causal association from population studies. *PLoS Med*. 2011;8:e1001112. doi: 10.1371/journal.pmed.1001112.

22. McMurray JJ, Packer M, Desai AS, Gog J, Leffkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993–1004. doi: 10.1056/NEJMoa1409077.

23. Daniels LB, Clopton P, deFilippi CR, Sanchez O, Bahrami H, Lima JAC, Tracy RP, Siscovick D, Bertoni AG, Greenland P, Cushman M, Maisel AS, Craciuc MH. Serial measurement of N-terminal pro-B-type natriuretic peptide and cardiac troponin T for cardiovascular disease risk assessment in the Multi-Ethnic Study of Atherosclerosis (MESA). *Am Heart J*. 2015;170:1170–1183.

---

# 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 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 2 United Kingdom Cohort Studies: Does Utility Depend on Risk Thresholds For Treatment?
Paul Welsh, Carole Hart, Olia Papacosta, David Preiss, Alex McConnachie, Heather Murray, Sheena Ramsay, Mark Upton, Graham Watt, Peter Whincup, Goya Wannamethee and Naveed Sattar

Hypertension. 2016;67:309-315; originally published online December 14, 2015; doi: 10.1161/HYPERTENSIONAHA.115.06501

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/67/2/309
Free via Open Access

Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2015/12/14/HYPERTENSIONAHA.115.06501.DC1.html

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/
ONLINE SUPPLEMENT

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

Paul Welsh¹, Carole Hart², Olia Papacosta³, David Preiss¹, Alex McConnachie⁴, Heather Murray⁴, Sheena Ramsay³, Mark Upton⁵, Graham Watt², Peter Whincup³, Goya Wannamethee⁵*, Naveed Sattar¹*
*Joint senior authors

1 BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, UK
2 Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK
3 Department of Primary Care and Population Health, University College London, London, UK
4 Robertson Centre for Biostatistics, University of Glasgow, Glasgow, UK
5 Helmsley Medical Centre, Helmsley, York, UK

Short Title: CARDIAC BIOMARKERS & CARDIOVASCULAR RISK PREDICTION

Correspondence to:
Paul Welsh, BHF Glasgow Cardiovascular Research Centre, 126 University Place, Glasgow G12 8TA
Tel: +441413302569 Fax: +441413306955
Email: paul.welsh@glasgow.ac.uk
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 (<1 drink 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 >7 mmol/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 (<1 drink 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/](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/](http://assign-score.com/estimate-the-risk/))

**References**
1. Walker M. The British Regional Heart Study 1975-2004. *Int J Epidemiol.* 2004;33:1185–1192.
2. Hart CL, MacKinnon PL, Watt GCM, Upton MN, McConnachie A, Hole DJ, Davey Smith G, Gillis CR, Hawthorne VM. The Midspan studies. *Int J Epidemiol.* 2005;34:28–34.
3. Upton MN, McConnachie A, McSharry C, Hart CL, Smith GD, Gillis CR, Watt GC. Intergenerational 20 year trends in the prevalence of asthma and hay fever in adults: the Midspan family study surveys of parents and offspring. *BMJ.* 2000;321:88–92.
4. Welsh P, Doolin O, McConnachie A, Boulton E, McNeil G, Macdonald H, Hardcastle A, Hart C, Upton M, Watt G, Sattar N. Circulating 25OHD, dietary vitamin D, PTH, and calcium associations with incident cardiovascular disease and mortality: the MIDSPAN Family Study. *J Clin Endocrinol Metab.* 2012;97:4578–4587.

5. Hart CL, Davey Smith G, Upton MN, Watt GCM. Alcohol consumption behaviours and social mobility in men and women of the Midspan Family study. *Alcohol Alcohol.* 2009;44:332–336.

6. Abu-Rmeileh NME, Hart CL, McConnachie A, Upton MN, Lean MEJ, Watt GCM. Contribution of Midparental BMI and other determinants of obesity in adult offspring. *Obesity (Silver Spring).* 2008;16:1388–1393.

7. Woodward M, Brindle P, Tunstall-Pedoe H. Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). *Heart.* 2007;93:172–176.

8. The Scottish Government. Scottish Index of Multiple Deprivation. Scottish Government. Available from: [http://www.gov.scot/Publications/2005/01/20458/49127](http://www.gov.scot/Publications/2005/01/20458/49127). Accessed November 11, 2015.
**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) | T2 (n=1237) | T3 (n=1245) | p-value  |
|-------------------------|-------------|-------------|-------------|----------|
| **Age**                 |             |             |             |          |
| -Never                  | 66.2 (4.6)  | 68.7 (5.3)  | 71.2 (5.4)  | <0.001   |
| -Ex                     | 700 (55.0%) | 732 (59.4%) | 760 (61.1%) | <0.001   |
| -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**                 | 6.19 (1.07) | 6.01 (1.05) | 5.80 (1.07) | <0.001   |
| **TC**                  | 6.01 (1.95) | 5.99 (1.78) | 6.09 (2.00) | 0.37     |
| **HDL**                 | 74.9 (11.1) | 73.3 (13.0) | 68.8 (13.5) | <0.001   |
| **Glucose**             | 110 (8.6%)  | 162 (13.1%) | 295 (23.7%) | <0.001   |
| **EGFR**                | 96 (7.8%)   | 110 (9.2%)  | 196 (16.4%) | <0.001   |
| **Physical activity**   |             |             |             |          |
| -Inactive               | 488 (39.7%) | 498 (41.9%) | 540 (45.0%) |          |
| -Occasional/light       | 646 (52.5%) | 582 (48.9%) | 463 (38.6%) |          |
| **Moderate/vigorous**   |             |             |             |          |
| -None                   | 117 (9.3%)  | 108 (8.9%)  | 141 (11.5%) |          |
| -Occasional/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**                 | 1.24        | 1.56        | 2.07        |          |
| (mg/L)                  | (0.66, 2.71) | (0.82, 3.39) | (1.00, 4.55) | <0.001   |
| **hsTnT**               | 10.1        | 11.4        | 14.6        |          |
| (pg/ml)                 | (7.7, 13.5) | (8.8, 15.3) | (10.9, 19.8) | <0.001   |
| **MR-proADM**           | 0.52        | 0.57        | 0.65        |          |
| (nmol/L)                | (0.46, 0.59) | (0.49, 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) | T2 (n=1260) | T3 (n=1236) | p-value |
|---------------------------|-------------|-------------|-------------|---------|
| Age                       | 66.2 (4.6)  | 68.9 (5.3)  | 71.0 (5.5)  | <0.001  |
| Smoking                   |             |             |             |         |
| -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               |             |             |             |         |
| -None                     | 104 (8.3%)  | 136 (11.0%) | 126 (10.4%) |         |
| -Occasional/heavy         | 886 (71.1%) | 881 (71.1%) | 836 (69.0%) |         |
| 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                       | 1.30        | 1.60        | 2.07        |         |
| (mg/L)                    | (0.70, 2.70)| (0.84, 3.47)| (0.99, 4.60)| <0.001  |
| NT-proBNP                 | 64          | 92          | 150         |         |
| (pg/ml)                   | (35, 114)   | (49, 184)   | (70, 419)   | <0.001  |
| MR-proADM                 | 0.53        | 0.57        | 0.63        |         |
| (nmol/L)                  | (0.47, 0.61)| (0.49, 0.65)| (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; IMD, index multiple deprivation; RA, rheumatoid arthritis; SBP, systolic blood pressure; TC, total cholesterol
| Variable                        | T1 (n=1300) | T2 (n=1266) | T3 (n=1191) | 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%) |          |
| **Moderate/vigorous**          |             |             |             |          |
| -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**                        | 1.08        | 1.49        | 2.58        |          |
| (mg/L)                         | (0.57, 2.30)| (0.85, 3.19)| (1.30, 5.40)| <0.001   |
| **hsTnT**                      | 10.2        | 11.3        | 14.9        |          |
| (pg/ml)                        | (7.9, 13.7) | (8.7, 15.0) | (10.8, 20.5)| <0.001   |
| **NT-proBNP**                  | 59          | 88          | 178         |          |
| (pg/ml)                        | (31, 105)   | (49, 175)   | (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
### Characteristics across thirds of NT-proBNP in MFS

| Variable          | T1 (n=764) | T2 (n=739) | T3 (n=723) | p-value |
|-------------------|------------|------------|------------|---------|
| **Age**           | 44.3 (5.7) | 45.4 (6.1) | 47.2 (6.2) | <0.001  |
| **Sex**           | 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       | 0.81       | 1.06       |          |
| **hsTnT (pg/ml)** | (0.33-1.96)| (0.34-1.98)|(0.46-2.51)| <0.001   |
| **MR-proADM (nmol/L)** | 0.29 | 0.29 | 0.30 |          |

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) | T2 (n=459) | T3 (n=443) | p-value |
|---------------------------|-------------|------------|------------|---------|
|                           | <3pg/ml     | 3.0-4.6pg/ml | ≥4.7pg/ml   |         |
| 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 -Never             | 611 (46.2%) | 218 (47.5%) | 218 (49.2%) |         |
|                           | -Ex         | 389 (29.4%) | 96 (20.9%)  |         |
|                           | -Current    | 324 (24.5%) | 145 (31.6%) |         |
| 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 -Inactive| 86 (6.5%)   | 42 (9.2%)   | 26 (5.9%)   |         |
|                           | -Occasional/light | 500 (37.8%) | 167 (36.5%) |         |
|                           | -Moderate/vigorous| 738 (55.7%) | 249 (54.4%) |         |
| Alcohol use -None          | 230 (17.4%) | 81 (17.7%)  | 76 (17.2%)  | <0.001  |
|                           | -Occasional/light | 763 (57.6%) | 222 (48.4%) |         |
|                           | -Moderate/heavy | 331 (25.0%) | 156 (34.0%) |         |
| 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        | 0.82        | 1.06        |         |
| NT-proBNP (pg/ml)         | 35          | 35          | 40          |         |
| (pg/ml)                   | (21-56)     | (21-54)     | (24-68)     | 0.0027  |
| MR-proADM (nmol/L)        | 0.28        | 0.32        | 0.32        |         |
|                           | (0.22-0.34) | (0.25-0.38) | (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
### 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%)            |         |
| Smoking                    | 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 (0.37)             | 5.28 (0.35)                 | 5.61 (0.21)            | <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               |                         |                             |                        |         |
| -None                     | 123 (16.0%)             | 129 (17.8%)                 | 135 (18.4%)            | <0.001  |
| -Occasional/heavy         | 477 (62.1%)             | 377 (52.1%)                 | 331 (45.1%)            |         |
| 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                       | 0.71                    | 0.75                        | 1.32                   |         |
| (mg/L)                    | (0.29-1.69)             | (0.34-1.63)                 | (0.58-3.03)            | <0.001  |
| hsTnT (pg/ml)             | 3.0                     | 3.0                         | 3.1                    |         |
| NT-proBNP                 | 35                      | 34                          | 39                     |         |
| (pg/ml)                   | (21-54)                 | (20-54)                     | (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
| Variable          | BRHS No incident CVD (n=2969) | BRHS Incident CVD (n=788) | p-value | MFS No incident CVD (n=2031) | MFS 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           | -Never                      | 892 (30.1%)              | 0.006   | 980 (48.4%)                | 65 (33.3%)               | <0.001  |
|                   | -Ex                         | 1725 (58.2%)             |         | 485 (23.9%)                | 73 (37.4%)               |         |
|                   | -Current                    | 349 (11.8%)              |         | 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 | Inactive                    | 281 (9.8%)               |         | 134 (6.6%)                 | 20 (10.3%)               |         |
|                   | Occasional/light            | 1201 (41.8%)             |         | 775 (38.2%)                | 59 (30.3%)               |         |
|                   | Moderate/vigorous           | 1389 (48.4%)             |         | 1121 (55.2%)               | 116 (59.5%)              |         |
| Alcohol use       | -None                       | 273 (9.3%)               | 0.08    | 345 (17.0%)                | 42 (21.5%)               |         |
|                   | -Occasional/light           | 2073 (70.8%)             |         | 1100 (54.2%)               | 85 (43.6%)               |         |
|                   | -Moderate/heavy             | 581 (19.9%)              |         | 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                        | 2.00                     | <0.001  | 0.84                       | 1.34                     | <0.001  |
| NT-proBNP (pg/ml) | (0.78, 3.27)                | (1.00, 4.35)             | <0.001  | (0.36-2.00)                | (0.60-3.04)              |         |
| (pg/ml)           | 82                          | 148                      |         | 35                         | 41                       | 0.002   |
| (pg/ml)           | (43, 169)                   | (72, 392)                | <0.001  | (21-56)                    | (23-73)                  |         |
| hsTnT             | 11.3                        | 14.1                     | <0.001  | 3.0                        | 3.1                      | <0.001  |
| (pg/ml)           | (8.6, 15.4)                 | (10.2, 19.6)             | <0.001  | (3.0-4.0)                  | (3.0-5.5)                | <0.001  |
| MR-proADM (nmol/L)| 0.56                        | 0.61                     | <0.001  | 0.29                       | 0.34                     | <0.001  |
|                   | (0.49, 0.65)                | (0.53, 0.73)             |         | (0.23-0.35)                | (0.28-0.42)              |         |

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
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       | 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
### 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     |                   | 0.660 |
|                      | 554 (204)    | NT-proBNP      | 0.639     |                   | 0.665 |
|                      |              |                 | (p=0.036) |                   | (p=0.17) |
|                      | 554 (204)    | Troponin T     | 0.660     | 0.665              | -     |
|                      |              |                 | (p=0.008) | (p=0.079)          |       |
|                      | 554 (204)    | MR-proADM      | 0.612     | 0.640              | 0.661 |
|                      |              |                 | (p=0.82)  | (p=0.59)           | (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.