BMJ Open

Tayside Screening For Cardiac Events (TASCFORCE) study: a prospective cardiovascular risk screening study

Matthew A Lambert,[1] J Graeme Houston,[2] Roberta Littleford,[2]
Catherine A Fitton ![ORCID],[2] Allan Struthers,[2] Frank Sullivan ![ORCID],[3,4] Stephen Gandy,[5]
Jill J F Belch[2]

[1]Stroke, NHS Tayside, Dundee, UK
[2]Division of Molecular and Clinical Medicine, University of Dundee, Dundee, UK
[3]School of Medicine, University of St Andrews, St Andrews, UK
[4]North York General Hospital, Toronto, Ontario, Canada
[5]Medical Physics, NHS Tayside, Dundee, UK

Correspondence to
Jill J F Belch;
j.j.f.belch@dundee.ac.uk

ABSTRACT

Purpose Risk factor-based models struggle to accurately predict the development of cardiovascular disease (CVD) at the level of the individual. Ways of identifying people with low predicted risk who will develop CVD would allow stratified advice and support informed treatment decisions about the initiation or adjustment of preventive medication, and this is the aim of this prospective cohort study.

Participants The Tayside Screening for Cardiac Events (TASCFORCE) study recruited men and women aged≥40 years, free from known CVD, with a predicted 10-year risk of coronary heart disease<20%. If B-type natriuretic peptide (BNP) was greater than their gender median, participants were offered a whole-body contrast-enhanced MRI (WBCE-MRI) scan (cardiac imaging, whole-body angiography to determine left ventricular parameters, delayed gadolinium enhancement, atheroma burden). Blood, including DNA, was stored for future biomarker assays. Participants are being followed up using electronic record-linkage cardiovascular outcomes.

Findings to date 4423 (1740, 39.3% men) were recruited. Mean age was 52.3 years with a median BNP of 7.50 ng/L and 15.30 ng/L for men and women, respectively. 602 had a predicted 10-year risk of 10%–19.9%, with the remainder<10%. Age, female sex, ex-smoking status, lower heart rate, higher high-density lipoprotein and lower total cholesterol were independently associated with higher log10 BNP levels. Mean left ventricular mass was 129.2 g and 87.0 g in men and women, respectively.

Future plans The TASCFORCE study is investigating the ability of a screening programme, using BNP and WBCE-MRI, at the time of enrolment, to evaluate prediction of CVD in a population at low/intermediate risk. Blood stored for future biomarker analyses will allow testing/development of novel biomarkers. We believe this could be a new UK Framingham study allowing study for many years to come.

Clinical trial registration ISRCTN38976321.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study is one of the largest MRI/cardiovascular risk studies to be published. It could be a UK Framingham.

⇒ The MRI scanning is a novel element to a cardiovascular risk trial, particularly as it is whole body and contrast enhanced.

⇒ As many of the participants have also signed up to the Scottish Health Research Register (SHARE), it will be possible to link all subsequent blood tests from SHARE with our cohort details to study novel biomarkers as they are discovered.

⇒ As these were 'healthy' volunteers, it will take some time for cardiovascular events to occur,

⇒ Not all participants underwent MRI scanning due to cost, only those above the B-type natriuretic peptide cut-off; however, numbers (n=1528) are sufficient to allow evaluations, and all (n=4423) had the demographic and blood screening.

INTRODUCTION

Currently, statins and other drugs for cardiovascular disease (CVD) primary prevention are targeted at those at increased risk by using risk estimation tools, but these have poor external validity.[1] A significant number of CVD occurs in people with 'low' or 'intermediate' cardiovascular risk[2] and many in these groups have evidence of atherosclerosis.[3 4] Offering statins to a wider range of the population has been suggested.[5] However, offering statins more widely raises a number of economic and ethical questions and concerns,[6 7] so improved targeted therapy may be more acceptable. Risk factor-based models struggle to predict development of disease at an individual person level, and an alternative approach could be the detection of preclinical disease—an approach successfully employed in cancer. A similar strategy for CVD could facilitate individualised risk assessment and aid decisions about treatment.

The Tayside Screening for Cardiac Events (TASCFORCE) study is investigating the ability of a screening programme using B-type natriuretic peptide (BNP) and whole-body contrast-enhanced MRI (WBCE-MRI) incorporating cardiac imaging and whole-body angiography to detect preclinical disease and

predict future clinical CVD in a large population at low or intermediate risk. Blood stored will allow validation of future proposed biomarkers. The study is novel in using a relatively cheap biomarker (BNP) to decide who proceeds to a relatively expensive test (MRI scan).

The aim of this study is to provide baseline data on both imaging and blood biomarkers, to understand which, if any, may predict future cardiovascular events. The comprehensive collection of baseline cardiovascular risk and demographic data in combination with the blood and imaging biomarkers and robust follow-up via electronic health record linkage will allow further investigation of the development of CVD in this population, which we hope may become the Scottish 'Framingham'.

COHORT DESCRIPTION
Study design
TASCFORCE is a prospective normal volunteer cardiovascular risk screening study (ISRCTN number: ISRCTN38976321).

The study is registered at http://www.controlled-trials.com/ISRCTN38976321 on the ISRCTN registry.

Men and women aged 40 years or older living in Tayside or Fife, Scotland, who were free from CVD and had a predicted 10-year risk of coronary heart disease (CHD)<20% were recruited. Participants were excluded if they were pregnant, breast feeding, of childbearing potential not using adequate contraception, unable to give consent or had another accepted indication for statin therapy. To produce a cohort able to participate in a potential future statin intervention study those with contraindications to a statin were excluded, including known alcohol abuse or participation in a clinical trial other than observational trials or registries concurrently or within 30 days prior to screening, were excluded.

Participants were recruited from general practice (GP) surgeries, local employers, publicity campaigns, via press and radio coverage of the project, direct mailing and using human research ethics committee approved leaflets. We aimed to obtain a locally representative population, so recruitment was targeted at socioeconomic and ethnic groups often under-represented in studies. Participants were recruited between November 2007 and February 2013.

Patient and public involvement
The Souter Foundation trustees ('lay' people) were involved in the design of the study. Volunteers who were recruited to the study were involved in the design, regarding the scheduling and timing of testing, to improve convenience for participants. Many volunteers were involved in further recruitment, by passing on information via word of mouth. Results of the final analysis using linked data will be disseminated to the participants via postal address.

Screening visit and risk estimation
Following written informed consent for the study, and for data linkage for up to 20 years, the following information

was obtained: medical history, lifestyle risk factors (diet/exercise/smoking status), risk perception question, family history of premature CVD and concomitant medication. Risk perception included questions regarding family history, exercise frequency, cigarette smoking and added salt to food. Subjects were examined to obtain their height, weight, waist circumference and blood pressure (BP) and a 12-lead ECG was recorded. Plasma BNP, random lipid profile and random plasma glucose levels were determined using point of care testing equipment (Alere Triage BNP assay with Alere Triage MeterPro for BNP and Alere Cholestech LDX analyser for lipids and glucose).

Each participant's predicted CHD event rate was calculated by using the National Cholesterol Education Program Adult Treatment Panel III guidelines.[8] Participants who had a predicted risk≥20% or a BP>145/90 mm Hg were excluded but were asked for consent to be followed up. Ineligible subjects were informed of their risk factors, given a copy of their results and asked to attend their GP for formal review. All participants received counselling on modifiable risk factors by study staff aided by British Heart Foundation leaflets.

Magnetic resonance imaging
Those with a BNP greater than the median (determined after 200 participants) were invited to attend for a WBCE-MRI scan. At a prespecified review after 1000 subjects, it was observed that the median BNP was higher for women than men. The trial steering committee (comprising of the authors) decided to invite for a scan based on gender-specific median BNP and the protocol was amended accordingly. Those recruited earlier who would be eligible based on the amended gender-specific median were recalled. If the delay was greater than 3 months, they had their BNP, cholesterol and CHD risk score reassessed to ensure continued eligibility.

Combined cardiac and whole-body angiography MRI scans were performed on a 32-channel 3T Magnetom Trio scanner (Siemens, Erlangen, Germany) and used gadoteric acid contrast agent (Dotarem; Guerbet Laboratories, France). The scan protocol development and validation has been described in detail elsewhere.[9 10]

Details of the image acquisition, analysis and validation of the technique have been described and validated in earlier publications.[9–11] Cardiac magnetic resonance (CMR) images were analysed offline by four blinded observers using commercial software ('Argus', Siemens Multi-modality Work Platform, V.VB15). Electronic region of interest contours were placed around endocardial and epicardial left ventricular borders at end diastole and end systole on all CMR image slices identified to contain≥50% full-thickness myocardium. Quantitative measurement of left ventricular mass (LVM), ejection fraction, end-diastolic volume, end-systolic volume and stroke volume was derived. The presence of luminal stenosis was assessed in 30 arterial segments from the internal carotids to the distal anterior tibial arteries (the

coeliac artery was not included due to marked anatomical variation resulting in poor interobserver agreement). A categorical grading scale from 0 to 4 was applied to each arterial segment as follows: grade 0=healthy segment, grade 1=1%–50% stenosis, grade 2=51%–70% stenosis, grade 3=71%–99% stenosis and grade 4=vessel occlusion. An additional point was added for presence of aneurysm>50% of the native vessel diameter. If any arterial segment contained more than one luminal abnormality, the more severe abnormality was scored. If a segment was uninterpretable because of poor image quality, it was not allocated a numeric score. A standardised atheroma score (SAS) to express atheroma burden severity across the body as a percentage was calculated using the following equation, where n is the number of interpretable segments: $SAS=((\sum score/n) \times 1/4) \times 100$.

Of those invited, 1528 (74.8%) completed or partially completed an MRI scan. Overall, 34 were not safe to scan due to metal in situ, 373 did not agree to proceed to have a scan and 12 failed to attend. Overall, 101 participants abandoned their scan mainly due to claustrophobia (n=83), with others abandoned due to large body habitus, problems with intravenous access or other technical issues. Overall, 32 participants (2.1% participants scanned) had an incidental finding on their MRI scan (myocardial infarction (MI) detected by delayed enhancement, structural cardiac abnormality, benign masses, malignant masses, peripheral vascular abnormality, anatomical variation). These subjects were removed from the key study group.

Baseline characteristics

Participant flow is summarised in the Consolidated Standards of Reporting Trials diagram (figure 1); 5015 people (n=2066, 41.2% men) were screened. In total, 438 failed screening due to either hypertension (n=291, 137 (47.1%) men), a predicted 10-year CHD risk≥20% (n=146, 142 (97.3%) men) or marked dyslipidaemia (n=1, women). The enrolled population was determined to be at low or intermediate risk of CVD (online supplemental table 1). We have a specific ethnic group of South Asian people (n=20) deliberately enrolled to attempt to cater for ethnic diversity. These subjects were recruited with the help of a local Mosque. The remainder are white British. These two ethnic groups are dominant in Tayside and the relative proportions enrolled reflects the distribution in the population. Further, we have documented the Scottish Index of Multiple Deprivation (SIMD) for all subjects that is, the area of deprivation in which they lived at time of enrolment. As the Scottish population is not very mobile, we believe this can be used in our 10-year analyses. We also have other risk factors, which relate to socioeconomic status such as obesity (body mass index (BMI), waist circumference), cigarette smoking and sex. These social determinants will all be evaluated in our 10-year analysis. A total of 4423 (1740, 39.3% men) participants were eligible for the study.
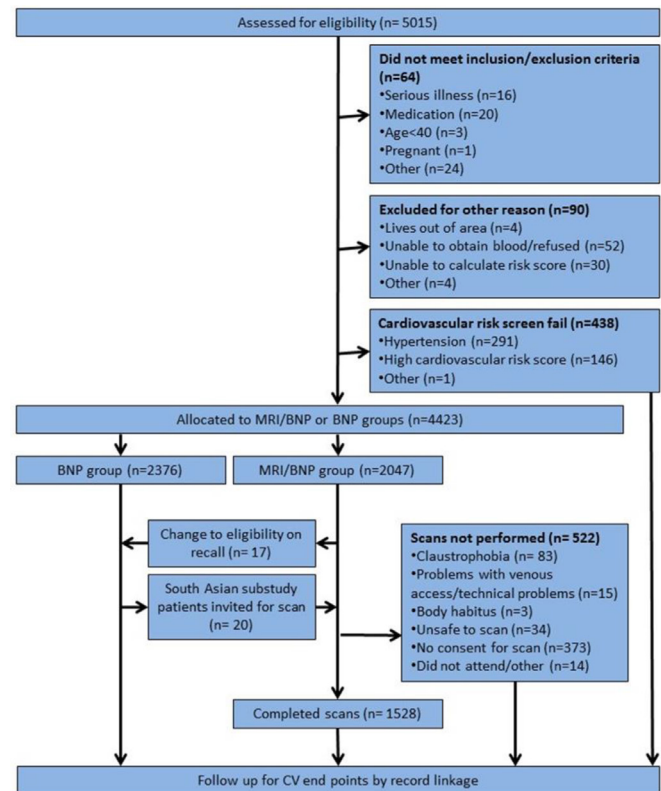

Figure 1 Consolidated Standards of Reporting Trials diagram showing Tayside Screening For Cardiac Events study recruitment. BNP, B-type natriuretic peptide; CV, cardiovascular.

Median (IQR) BNP levels for men and women were 7.50 (8.90) and 15.30 (17.63) ng/L, respectively. The cutoff BNP values for being offered an MRI scan were 8.2 and 16.4 ng/L, respectively; all South Asian participants were invited for MRI irrespective of BNP level. The characteristics of those invited for an MRI scan (MRI/BNP group) and those not invited (BNP group) are summarised in table 1.

Follow-up

Electronic anonymised data linkage by the health informatics centre at the University of Dundee will provide follow-up data on hospital admissions (including diagnoses and procedures) and GP prescriptions at regular intervals for up to 20 years (10, 15 and 20 years planned). This uses data from the Scottish Office's Information Services Division which collects data on all hospital and GP encounters including prescriptions, diagnoses and procedures and from the General Registrar's office which collects data on all deaths in Scotland. Endpoints of interest are myocardial infarction, hospitalisation for angina, requirement for any endovascular procedure, stroke, critical limb ischaemia, amputation, sudden death, cardiac and all-cause mortality. Underlying cause of death recorded on death certificates is supplemented by information from hospital records, including postmortem examinations, if performed.

3

Table 1 Baseline characteristics of participants

		BNP group (n=2376)	MRI/BNP group (n=2047)	Difference between BNP and MRI/BNP groups*
Median (IQR) age (years)		49.5 (10.6)	53.4 (12.5)	p<0.001
No (%) men		937 (39.4)	803 (39.3)	p=0.94
No (%) current smokers		351 (14.8)	221 (10.8)	p<0.001
No (%) former smokers		663 (27.9)	563 (27.5)	p=0.81
No (%) never smokers		1361 (57.3)	1256 (61.4)	p=0.004
Mean (SD) systolic BP (mm Hg)		122.1 (11.74)	122.9 (11.97)	p=0.027
Mean (SD) diastolic BP (mm Hg)		73.6 (9.40)	73.1 (9.23)	p=0.06
Median (IQR) heart rate (beats per min)		67.0 (14)	63.0 (12)	p<0.001
Mean (SD) total cholesterol (mmol/L)		5.47 (1.02)	5.48 (0.99)	p=0.79
Mean (SD) high-density lipoprotein (mmol/L)		1.34 (0.44)	1.43 (0.42)	p<0.001
Mean (SD) low-density lipoprotein (mmol/L)		3.41 (0.92)	3.40 (0.42)	p=0.84
Median (IQR) triglycerides (mmol/L)		1.38 (1.18)	1.29 (1.02)	p<0.001
Median (IQR) body mass index (kg/m^2)		26.7 (5.80)	26.2 (5.35)	p<0.001
Median (IQR) weight (kg)		75.0 (21.23)	74.1 (19.95)	p=0.08
Mean (SD) height (cm)		167.10 (9.09)	167.67 (9.29)	p=0.041
Mean (SD) waist circumference (cm)		88.0 (13.56)	86.9 (12.95)	p=0.006
Median (IQR) 10-year CHD event risk estimation (%)		2.0 (5.0)	2.0 (5.0)	p<0.001
No (%) with 10-year CHD risk 10%–19.9%		286 (12.0)	316 (15.4)	p=0.001
No (%) with family history of cardiovascular disease		561 (23.6)	514 (25.1)	p=0.25
Scottish Index of Multiple Deprivation decile, number (%)	1	132 (5.6)	85 (4.2)	p=0.054
	2	145 (6.1)	106 (5.2)	
	3	208 (8.8)	149 (7.3)	
	4	134 (5.6)	116 (5.7)	
	5	143 (6.0)	126 (6.2)	
	6	218 (9.2)	206 (10.1)	
	7	349 (14.7)	334 (16.3)	
	8	442 (18.6)	401 (19.6)	
	9	428 (18.0)	371 (18.1)	
	10	169 (7.1)	150 (7.3)	
	N/A	8 (0.3)	3 (0.1)	–

*Comparisons for variables with normal distributions are independent samples t-tests and for skewed distribution the Mann-Whitney-Wilcoxon test.
BNP, B-type natriuretic peptide; BP, blood pressure; CHD, coronary artery disease.

Statistical analysis

Analysis was performed using R (V.3.1) and SPSS (V.21). Continuous variables were expressed as mean and SD for those with a normal distribution or median and IQR for those with a skewed distribution, and categorical variables were expressed as numbers and percentages. When comparing characteristics between participant groups independent samples t-tests were used for variables with a normal distribution and Wilcoxon Mann-Whitney tests were used for those with a skewed distribution. To reduce skewness, BNP levels were log10 transformed before regression analyses. Multivariable linear regression analysis was used to determine independent predictors of log10 BNP level. The following variables were initially included in the model: age, sex, smoking status, systolic BP, diastolic BP, heart rate, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein cholesterol, triglycerides, glucose, BMI, waist circumference, family history of CVD and SIMD decile. Analysis of correlations used Pearson correlation coefficients for variables with a normal distribution and Spearman rank correlation for those with a skewed distribution.

Table 2 Predictors of log10 BNP: multivariable regression analysis

	Unstandardised coefficient (95% CIs)	P value
Age (years)	0.010 (0.009 to 0.011)	<0.001
Male sex	−0.211 (−0.230 to 0.192)	<0.001
Ex-smoker	−0.026 (−0.045 to 0.006)	0.01
Heart rate (bpm)	−0.006 (−0.007 to 0.005)	<0.001
Total cholesterol (mmol/L)	−0.020 (−0.028 to 0.011)	<0.001
High-density lipoprotein (mmol/L)	0.055 (0.033 to 0.076)	<0.001

FINDINGS TO DATE

Increasing age, female sex, ex-smoking status (but not current smoking status), lower heart rate, higher HDL and lower total cholesterol were significantly associated with higher log10 BNP levels (table 2).

The left ventricular characteristics are shown in table 3. A total of 10 patients (0.67%) displayed late gadolinium enhancement (LGE), indicating the presence of an unidentified myocardial infarct (UMI).[12]

Three cases (0.2%) were consistent with UMI, and seven were considered non-specific and located in the mid-myocardium (n=4), epicardium (n=1) or right ventricular insertion points (n=2). Spearman rank correlations of left ventricular measurements with predicted CHD risk score are shown in table 4.

For WB-MRA 2468 segment locations (5%) demonstrated stenoses, of which 1649 (3.5%) showed stenosis<50% and 484 (1.0%) showed stenosis≥50%.[13] The median, 80th percentile and 90th percentiles of

Table 3 Left ventricular characteristics by gender

	Men		Women		
	Mean	SD	Mean	SD	P value*
LVM (g)	129.2	24.4	87.0	16.7	<0.001
LVEDV (mL)	155.0	27.7	119.6	21.1	<0.001
LVESV (mL)	50.2	14.8	37.1	12.0	<0.001
LVM/LVEDV (g/mL)	0.85	0.16	0.74	0.13	<0.001
Ejection fraction (%)	67.9	6.2	69.3	6.6	<0.001
Stroke volume (mL)	104.8	19.0	82.5	14.2	<0.001
Cardiac output (L/min)	6.46	1.20	5.47	1.13	<0.001
LVM/height	73.2	13.1	53.5	9.8	<0.001
LVM/height$^{1.7}$	49.3	8.7	38.1	7.0	<0.001
LVM/height$^{2.7}$	28.0	5.0	23.5	4.4	<0.001
LVM/BSA	64.3	10.6	49.5	8.0	<0.001

*Comparison between men and women using independent samples t-test.
BSA, body surface area; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVM, left ventricular mass.

SASs were 0.00, 1.67 and 3.33, respectively, for men and 0.83, 2.50 and 4.17, respectively, for women. There was no significant difference between SASs for men and women (p=0.08). The predicted CHD scores for those with a SAS above and below 80th centile and with and without the presence of any stenosis are shown in table 5.

The TASCFORCE study assesses the ability of a novel screening programme combining 'traditional' clinical cardiovascular risk estimation with BNP and WBCE-MRI to predict future cardiovascular events. No other studies have investigated screening using this combination of blood and imaging biomarkers of preclinical disease as a potential method to predict future CVD in people free from and at 'low' or 'intermediate' predicted risk of future disease. The cohort is large and well characterised in terms of cardiovascular risk factors, with an Index of Multiple Deprivation similar to the community from which it was drawn. Of those recruited, 602 have a predicted 10-year risk of 10%–19.9% (classified as intermediate risk); a group that is often debated as to what approach should be taken in terms of primary prevention.

During recruitment, a significant number of people had a previously unknown predicted risk≥20% over 10 years. A total of 97% were men, and from areas with increased deprivation compared with those who were lower risk and entered the main study. These findings also highlight the problem of currently undetected cardiovascular risk, particularly among men and those from areas of deprivation, illustrating the need for improved identification and engagement of those at risk. This could bring greater public health benefits than giving statins to more people at lower risk.

As expected, the BNP levels in the TASCFORCE population were within a 'normal' clinical range and were significantly higher in women compared with men, justifying our use of gender-specific medians for invitation for MRI scan.[12 13] Age was independently associated with BNP levels. This is well recognised,[14–16] although the exact mechanism for the association remains unclear. Age related alterations in production, secretion, biological effect or degradation of BNP may be responsible.[17 18] The effect of age is independent of renal function, atrial volume, left ventricular dimension and LV mass.[14] Increasing levels with age may suggest that age-specific reference ranges of BNP should be used. However, because age is an important risk factor for CVD, BNP may be reflecting this increased risk. Thus, correcting for age when using BNP as a screening tool is inadvisable.

MRI is a safe, relatively non-invasive imaging modality, free from ionising radiation making it more acceptable for use as a screening tool compared with coronary artery calcification scoring using CT. By combining cardiac imaging with whole-body angiography, it is conceivable that the sensitivity to detect subclinical disease may be improved as more target organs are imaged. The images also provide a reference for normal values within a low/intermediate risk population. The MRI protocol was kept simple, with the main constituents being WBCE-MRI

Table 4 Correlations of left ventricular measures with predicted 10-year coronary heart disease risk

	LVM	LVM/height (g/m)	LVM/height$^{1.7}$ (g/m$^{1.7}$)	LVM/height$^{2.7}$ (g/m$^{2.7}$)	LVMI/BSA (g/m^2)	LVM/LVEDV (g/mL)
Men	−0.07 (0.12)	−0.04 (0.31)	−0.02 (0.67)	−0.01 (0.73)	−0.05 (0.24)	0.17 (<0.001)
Women	0.08 (0.018)	0.11 (0.001)	0.13 (<0.001)	0.16 (<0.001)	0.10 (0.002)	0.30 (<0.001)

Correlations are Spearman rank correlations (ρ and (p) values are given) with predicted 10-year coronary heart disease risk using the Adult Treatment Panel III algorithm.
BSA, body surface area; LVEDV, left ventricular end diastolic volume; LVM, left ventricular mass; LVMI, Left Ventricular Mass Index.

together with CMR for quantification of LV structure and function—all completed within 45 min. The CMR acquisition was undertaken at the midpoint of the protocol (commencing after the first gadolinum contrast injection) to optimise the protocol in terms of time usage and to enable an assessment of LGE at this stage. The acquisition of other measures such as T1, extracellular volume, T2 mapping or myocardial strain would have been desirable, but the study was limited by the time available and the technological capabilities of the scanner.

The mean LVM values in our cohort are similar to those reported by other studies that have used steady state free precision imaging sequence MRI to determine LVM in a healthy population without CVD and free from hypertension, high cholesterol or treatment.[19] Mean LVM was also higher in men than women similar to other studies. Increased LVM-to-volume ratio (a marker of left ventricular remodelling) was more strongly correlated with predicted CHD risk than LVM or LVM index in both men and women. This measure has been shown to be independently associated with incident CHD[20] and stroke,[20 21] and suggests this may be a better measure of risk than LVM or LVM index which may not be able to differentiate between physiologically increased LVM due to, for example, exercise.

The majority of participants had no evidence of atheroma; however, a higher SAS was associated with a higher predicted CHD risk. A WBCE-MRI angiography derived atheroma score similar to ours was associated

with traditional cardiovascular risk factors,[22] and with the combined end point of cardiac death, MI, stroke or coronary revascularisation when adjusted for multiple risk factors in a study of 70 year olds, some of whom had a history of CVD.[23] The score improved discrimination and reclassification when added to the Framingham risk score. In our study, the median SAS of 0.83% for women indicates that at least half the female group did have detectable arterial narrowing. This median approached statistical significance (p=0.08) relative to the equivalent for males, although we do not believe this has clinical implications since the overwhelming number of segments assessed (over 40 000, 94.7%) were classified as normal.

We report a sex differential regarding LVM and 10-year CHD risk, where LVM and indexed LVM were not correlated among men, but significantly correlated among women. Three large observational studies (n=1715–4988) reported raised LVM and Left Ventricular Mass Index (LVMI), which was associated with higher incident CVD events, but did not report any sex difference.[24–26] Our finding that the LVM and LVMI was significantly associated with predicted 10-year CHD risk in women, but not in men, appears novel.

Healthcare in Scotland is delivered within the public sector National Health Service, and all healthcare contacts, diagnoses and procedures are systematically recorded. Further, all prescribing information from GPs is available in an anonymised form. Follow-up is via electronic health record linkage, which will reduce the

Table 5 Predicted CHD risk in those with standardised atheroma scores (SAS) above and below 80th percentile and in those with and without any stenosis

	Males			Females		
	≤80th centile SAS (n=464)	>80th centile SAS (n=113)	p value*	≤80th centile SAS (n=786)	>80th centile SAS (n=150)	p value*
Median (IQR) predicted CHD risk score (%/10 years)	6 (6)	10 (5)	<0.001	1 (2)	2 (3)	<0.001
	No stenosis (n=308)	Any stenosis (n=269)	p value*	No stenosis (n=457)	Any stenosis (n=479)	p value*
Median (IQR) predicted CHD risk score (%/10 years)	6 (6)	8 (7)	**<0.001**	1 (2)	1 (2)	**<0.001**

*Mann-Whitney test used to compare groups. SAS, standardised atheroma score. 80th centile 1.67 for men and 2.50 for women.
CHD, coronary heart disease; SAS, standardised atheroma score.

number lost to follow-up as direct contact is not required. This will allow analysis of whether the combination of BNP with cardiac MRI markers are able to improve prediction of future CVD. Stored serum, plasma and DNA will allow future novel biomarkers to be discovered or validated.

There is potential bias in the imaged population as those imaged are at the upper end of the BNP range. The MRI results therefore may not represent the low-risk population and will prevent comparison of imaging biomarkers between those with high and low BNP levels. However, clinical outcomes between the two groups will be analysed to determine if lower BNP levels can exclude future events.

Given the cost of MRI, the economic viability of this programme will need to be assessed. This will be done through a comprehensive follow-up, which will involve collecting data on hospital admissions and prescriptions, facilitating future economic evaluations of this screening programme.

In conclusion, the TASCFORCE study is investigating the ability of a novel screening programme incorporating BNP and WBCE-MRI to predict future cardiovascular events in a population at low or intermediate predicted risk of CHD. The comprehensive collection of baseline cardiovascular risk and demographic data in combination with blood and imaging biomarkers, and robust follow-up via electronic record linkage, will allow further investigation of the development of CVD in this population, which we hope may become the Scottish 'Framingham'.

COLLABORATION

All data and materials are available stored in the University of Dundee, patient identifiable data is stored in the University of Dundee and NHS Tayside Health Informatics Centre, a Safe Haven. The datasets generated and/or analysed during the current study are not publicly available due to ongoing 10-year analyses but are available from the corresponding author on reasonable request.

and Medical School, Dundee, UK, in accordance with the Good Clinical Practice Declaration of Helsinki. The volunteers gave written informed consent to participate in this study.

ORCID iDs
Catherine A Fitton http://orcid.org/0000-0001-6403-1314
Frank Sullivan http://orcid.org/0000-0002-6623-4964

REFERENCES

1 Brindle P, Beswick A, Fahey T, *et al*. Accuracy and impact of risk assessment in the primary prevention of cardiovascular disease: a systematic review. *Heart* 2006;92:1752–9.
2 Brindle PM, McConnachie A, Upton MN, *et al*. The accuracy of the Framingham risk-score in different socioeconomic groups: a prospective study. *Br J Gen Pract* 2005;55:838–45.
3 Michos ED, Vasamreddy CR, Becker DM, *et al*. Women with a low Framingham risk score and a family history of premature coronary heart disease have a high prevalence of subclinical coronary atherosclerosis. *Am Heart J* 2005;150:1276–81.
4 Eleid MF, Lester SJ, Wiedenbeck TL, *et al*. Carotid ultrasound identifies high risk subclinical atherosclerosis in adults with low Framingham risk scores. *J Am Soc Echocardiogr* 2010;23:802–8.
5 Ebrahim S, Taylor FC, Brindle P. Statins for the primary prevention of cardiovascular disease. *BMJ* 2014;348:g280.
6 Smeeth L, Hemingway H. Improving vascular health: are pills the answer? *BMJ* 2012;344:e3802.
7 Ebrahim S, Casas JP. Statins for all by the age of 50 years? *Lancet* 2012;380:545–7.
8 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA* 2001;285:2486–97.
9 Gandy SJ, Lambert M, Belch JJF, *et al*. Technical assessment of whole body angiography and cardiac function within a single MRI examination. *Clin Radiol* 2015;70:595–603.
10 Gandy SJ, Lambert M, Belch J, *et al*. 3T MRI investigation of cardiac left ventricular structure and function in a UK population: the Tayside screening for the prevention of cardiac events (TASCFORCE) study. *J Magn Reson Imaging* 2016;44:1186–96.
11 Cerqueira MD, Weissman NJ, Dilsizian V, *et al*. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the cardiac imaging Committee of the Council on clinical cardiology of the American heart association. *Circulation* 2002;105:539–42.
12 Blankenberg S, Zeller T, Saarela O, *et al*. Contribution of 30 biomarkers to 10-year cardiovascular risk estimation in 2 population cohorts: the MONICA, risk, genetics, archiving, and monograph (MORGAM) biomarker project. *Circulation* 2010;121:2388–97.
13 Nakamura M, Tanaka F, Takahashi T, *et al*. Sex-Specific threshold levels of plasma B-type natriuretic peptide for prediction of cardiovascular event risk in a Japanese population initially free of cardiovascular disease. *Am J Cardiol* 2011;108:1564–9.

14 Redfield MM, Rodeheffer RJ, Jacobsen SJ, *et al*. Plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol* 2002;40:976–82.

15 Wang TJ, Larson MG, Levy D, *et al*. Impact of age and sex on plasma natriuretic peptide levels in healthy adults. *Am J Cardiol* 2002;90:254–8.

16 Costello-Boerrigter LC, Boerrigter G, Redfield MM, *et al*. Amino-Terminal pro-B-type natriuretic peptide and B-type natriuretic peptide in the general community: determinants and detection of left ventricular dysfunction. *J Am Coll Cardiol* 2006;47:345–53.

17 Kawai K, Hata K, Tanaka K, *et al*. Attenuation of biologic compensatory action of cardiac natriuretic peptide system with aging. *Am J Cardiol* 2004;93:719–23.

18 Giannessi D, Andreassi MG, Del Ry S, *et al*. Possibility of age regulation of the natriuretic peptide C-receptor in human platelets. *J Endocrinol Invest* 2001;24:8–16.

19 Kawel-Boehm N, Maceira A, Valsangiacomo-Buechel ER, *et al*. Normal values for cardiovascular magnetic resonance in adults and children. *J Cardiovasc Magn Reson* 2015;17:29.

20 Bluemke DA, Kronmal RA, Lima JAC, *et al*. The relationship of left ventricular mass and geometry to incident cardiovascular events: the MESA (multi-ethnic study of atherosclerosis) study. *J Am Coll Cardiol* 2008;52:2148–55.

21 Jain A, McClelland RL, Polak JF, *et al*. Cardiovascular imaging for assessing cardiovascular risk in asymptomatic men versus women: the multi-ethnic study of atherosclerosis (MESA). *Circ Cardiovasc Imaging* 2011;4:8–15.

22 Hansen T, Ahlström H, Wikström J, *et al*. A total atherosclerotic score for whole-body MRA and its relation to traditional cardiovascular risk factors. *Eur Radiol* 2008;18:1174–80.

23 Lundberg C, Johansson L, Barbier CE, *et al*. Total atherosclerotic burden by whole body magnetic resonance angiography predicts major adverse cardiovascular events. *Atherosclerosis* 2013;228:148–52.

24 Gupta S, Berry JD, Ayers CR, *et al*. Left ventricular hypertrophy, aortic wall thickness, and lifetime predicted risk of cardiovascular disease:the Dallas Heart Study. *JACC Cardiovasc Imaging* 2010;3:605–13.

25 Tsao CW, Gona PN, Salton CJ, *et al*. Left ventricular structure and risk of cardiovascular events: a Framingham heart study cardiac magnetic resonance study. *J Am Heart Assoc* 2015;4:e002188.

26 Kawel-Boehm N, Kronmal R, Eng J, *et al*. Left ventricular mass at MRI and long-term risk of cardiovascular events: the multi-ethnic study of atherosclerosis (MESA). *Radiology* 2019;293:107–14.

Supplemental Table 1. Characteristics of subjects excluded due to presence of increased CHD risk or hypertension.

		Hypertensive (BP> 145/90 mmHg) (n=291)	10-year CHD risk >20% (n=146)
Median (IQR) age (years)		58.2 (12.24)	58.7 (15.23)
No (%) men		138 (47.4)	142 (97.3)
No (%) current smokers		34 (11.7)	85 (58.2)
No (%) former smokers		65 (22.3)	24 (16.4)
No (%) never smokers		151 (51.9) *[N/A41]*	37 (25.3)
Mean (SD) systolic BP (mmHg)		156.5 (9.75)	132.2 (10.91)
Mean (SD) diastolic BP (mmHg)		88.9 (9.68)	77.3 (9.46)
Medan (IQR) heart rate (beats per min)		72.0 (16) *[N/A215]*	68.0 (14) *[N/A11]*
Mean (SD) total cholesterol (mmol/L)		5.69 (1.03) *[N/A55]*	6.07 (1.02)
Mean (SD) high density lipoprotein (mmol/l)		1.42 (0.48) *[N/A58]*	0.89 (0.24)
Mean (SD) low density lipoprotein (mmol/l)		3.34 (0.92) *[N/A71]*	3.93 (0.93) *[N/A17]*
Median (IQR) triglycerides (mmol/l)		1.82 (1.38) *[N/A55]*	2.50 (1.93)
Median (IQR) Body mass index (kg/m^2)		27.5 (5.5) *[N/A202]*	28.3 (4.7) *[N/A6]*
Median (IQR) weight (kg)		82.0 (18.60) *[N/A202]*	83.6 (17.30) *[N/A6]*
Mean (SD) height (cm)		168.5 (8.16) *[N/A202]*	173.4 (7.51) *[N/A6]*
Mean (SD) waist circumference (cm)		91.1 (13.35) *[N/A216]*	97.0 (12.93) *[N/A10]*
Median (IQR) 10-year CHD event risk (%)		5.0 (9.0) *[N/A72]*	20.0 (5.0)
No (%) with family history of cardiovascular disease		49 (16.8) *[N/A96]*	35 (23.2) *[N/A9]*
Scottish Index of Multiple Deprivation decile, number (%)	1	12 (4.1)	8 (5.5)
	2	19 (6.5)	11 (7.5)
	3	29 (10.0)	20 (13.7)
	4	19 (6.5)	10 (6.8)
	5	14 (4.8)	10 (6.8)
	6	21 (7.2)	14 (9.6)
	7	45 (15.5)	22 (15.1)
	8	51 (17.5)	22 (15.1)
	9	61 (21.0)	24 (16.4)
	10	18 (6.2)	4 (2.7)
	N/A	*2 (0.7)*	*1 (0.7)*

BP, blood pressure, CHD, coronary heart disease, IQR, inter-quartile range, SD, standard deviation. Full data were not collected for all screen failed participants: the number of participants with missing data is indicated in italics.