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NT-proB natriuretic peptide, risk factors and asymptomatic left ventricular dysfunction: Results of the SCReening Evaluation of the Evolution of New Heart Failure Study (SCREEN-HF)
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Full Title: **NT-proB natriuretic peptide, risk factors and asymptomatic left ventricular dysfunction: Results of the SCReening Evaluation of the Evolution of New Heart Failure Study (SCREEN-HF).**

Short Title: McGrady et al. NT-proBNP and ventricular dysfunction

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ABSTRACT

Background: We assessed left ventricular dysfunction in a population at high risk for heart failure (HF), and explored associations between ventricular function, HF risk factors and NT-proB natriuretic peptide (NT-proBNP).

Methods and Results: 3,550 subjects at high risk for incident HF (≥60years plus ≥1 HF risk factor), but without pre-existing HF or left ventricular dysfunction, were recruited. Anthropomorphic data, medical history and blood for NT-proBNP were collected. Participants at highest risk (n=664) (NT-proBNP highest quintile; >30.0pmol/L) and a sample (n=51) from the lowest NT-proBNP quintile underwent echocardiography. Participants in the highest NT-proBNP quintile, compared to the lowest, were older (74 years vs. 67 years; p<0.001) and more likely to have coronary artery disease, stroke or renal impairment. In the top NT-proBNP quintile (n=664), left ventricular systolic impairment was observed in 6.6% (95% CI: 4 to 8%) of participants and was associated with male gender, coronary artery disease, hypertension and NT-proBNP. At least moderate diastolic dysfunction was observed in 24% (95% CI 20 to 27%) of participants and was associated with diabetes and NT-proBNP. In this high risk population, NT-proBNP was associated with left ventricular systolic impairment (p<0.001) and moderate to severe diastolic dysfunction (p<0.001) after adjustment for age, gender, coronary artery disease, diabetes, hypertension and obesity.

Conclusion: A high burden of ventricular dysfunction was observed in this high risk group. Combining NT-proBNP and HF risk factors may identify those with ventricular dysfunction. This would allow resources to be focused on those at greatest risk of progression to overt HF.

INTRODUCTION

Rising prevalence of heart failure (HF), with its attendant high morbidity, mortality and cost is focusing attention on earlier diagnosis and prevention [1]. Once hospital admission for HF has occurred prognosis can be poor. Indeed, recent UK data report a 40% one year mortality in the elderly despite the majority being prescribed appropriate classes of therapy [2]. Reported HF prevalence varies between 2-10%, reflecting underlying population characteristics. Prevalence rises exponentially with age [3-6], therefore, with aging populations and the increasing prevalence of some risk factors [7-10], the prevalence of HF is predicted to increase.

Left ventricular dysfunction, including asymptomatic dysfunction, is an independent predictor of mortality [11-14]. Asymptomatic dysfunction is reported in approximately equal numbers to HF cases [3, 6, 15], and the ability to detect it early and commence therapy could retard or prevent progression to overt HF. Screening strategies to achieve this have been investigated, including the use of signs and symptoms, electrocardiography, biomarkers, and echocardiography [16-22].

The most promising screening strategy includes the use of natriuretic peptides. The natriuretic peptides, NT-proB type natriuretic peptides (NT-proBNP) and B type natriuretic peptide (BNP), use is well established in HF diagnosis [23-25] and prognosis [26, 27], and they are increasingly being used in HF management [28-30]. Their role in screening strategies is encouraging [20, 21, 31], but the interpretation of natriuretic peptide levels for an individual can be limited by their interactions with other co-morbidities. Focusing screening strategies within high risk populations is one potential, but further investigation to understand the relationships between NT-proBNP, risk factors and patient characteristics is needed.

The SCReening Evaluation of the Evolution of New Heart Failure Study (SCREEN-HF) is a large prospective study in a high risk, but asymptomatic, population. We assessed the burden of left ventricular dysfunction and the associations between NT-proBNP, patient characteristics and HF risk factors.

METHODS

Study population

A cohort at high risk for the development of HF was enrolled between June 2007 and December 2009. High risk for incident HF was defined using 3 criteria: age, at least one pre-existing HF risk factor, and an elevated plasma NT-proBNP (Figure 1). Participants were 60 years or older. HF risk factors included self-reported history of coronary artery disease (myocardial infarction, angina, coronary angioplasty or coronary artery bypass grafts), stroke, valvular heart disease, atrial fibrillation, hypertension or diabetes treated for at least 2 years, and renal impairment (eGFR<60ml/min/1.73m^2). Three thousand five hundred and fifty participants were enrolled with the first two criteria (age and HF risk factor) and stratified using measured plasma NT-proBNP. Elevated plasma NT-proBNP was defined as being in the top quintile for the cohort (n=3,550). Participants were excluded if they had a pre-existing HF diagnosis or documented asymptomatic ventricular dysfunction.

Participants responded to a letter of invitation from their health fund provider by returning a brief HF risk factor questionnaire to the study center. If inclusion criteria were confirmed by a trained researcher during telephone interview, then the subject was invited to participate by attendance at the study centre.

Following informed written consent, at the baseline visit, participants completed a researcher-administered structured questionnaire of past medical history, medications, and HF symptoms. Anthropomorphic measures were taken, by a trained observer, according to WHO cardiovascular survey methods [32], and including height and weight (Soehnle scales, Germany), which was used to calculate body mass index (BMI kg/m^2). Blood pressure (BP) was taken on the right arm after the participant had been seated for 5 minutes (digital blood pressure monitor A&D Medical, Kensington, Victoria), and was estimated as the mean of two measurements. Blood was collected and processed at a single, commercially-accredited pathology provider, for urea, electrolytes and creatinine, full blood count, and NT-proBNP using electrochemiluminescence immunoassay (Roche Modular E170 analyzer, Basel, Switzerland).

Plasma NT-proBNP level was used to stratify participants, and those at highest risk of incident HF (i.e. with NT-proBNP in the top quintile (n=710), were invited for a second study visit. At this visit participants undertook a clinical assessment, including BP measurement (IntelliSense: Omron HEM-907, Japan) and comprehensive echocardiogram. A small sample (n=51 consecutive participants) from the lowest NT-proBNP quintile were also invited for this second study visit.

Echocardiography

Echocardiography was undertaken according to a standardised protocol using a GE Vingmed Vivid I portable ultrasound machine (GE Medical Systems, Milwaukee, WI) with the participant in the semi-recumbent left lateral position. A single experienced cardiologist (MM) obtained scans which were digitally recorded. Measurements were then made offline by the cardiologist (blinded to all clinical details) using GE EchoPAC software, version 6.0,

(GE Medical Systems, Milwaukee, WI). Measurements were averaged from three cardiac cycles (five if an arrhythmia was present) as recommended by the American Society of Echocardiography [33]. Left ventricular ejection fraction was quantified using Simpson's rule (biplane or four chamber) if 80% of the endocardium was visible or visual estimation if not. Valves were assessed using Doppler and 2D echocardiography. Pulse wave Doppler of the mitral valve (at leaflet tips) and pulmonary vein inflows along with tissue Doppler imaging of the lateral mitral annulus were used to evaluate diastolic function [34].

Left ventricular dysfunction threshold was defined by two standard deviations below the population mean as follows: normal function (ejection fraction ≥45%), mild dysfunction (ejection fraction 44.9-40%) or moderate to severe dysfunction (ejection fraction <40%). Diastolic function was categorized from Doppler evaluation and graded into four categories (Table 1). A minimum of two Doppler criteria was required for diagnosis of moderate or severe diastolic dysfunction; if only one were present then function was characterized as indeterminate. Subjects in atrial fibrillation or with significant mitral valve disease or a prosthetic mitral valve were excluded from diastolic dysfunction analysis. Valvular heart disease was defined as at least moderate mitral or aortic, stenosis or regurgitation [35-37].

Ejection fraction could be measured by Simpson's rule in 89% of participants (biplane in 83%, single plane in 6%) and it was estimated for the remaining 11%. Visual estimation of ejection fractions was used significantly more frequently in participants with BMI≥30kg/m^2 (17% versus 8%; p=0.001), but not with increasing age (p=0.4). A second echocardiography laboratory (GH, JM) blindly reported 10% of randomly selected echocardiograms for reproducibility. Inter-observer reproducibility of key measures was good, and as follows (concordance correlation coefficient [95% CI]): Doppler of the mitral valve inflow, E wave

0.94 [0.91 to 0.97], deceleration time 0.73 [0.65 to 0.82], A wave 0.92 [0.87 to 0.96]; and tissue Doppler of the lateral mitral valve annulus 0.88[0.83 to 0.93].

Ethics

SCREEN-HF complies with the Declaration of Helsinki and was approved by The Alfred Hospital Ethics Committee, Melbourne, Australia (project number 245/06).

Statistical methods

Data analysis was undertaken using Stata SE version 11.0. Approximately normally distributed variables were summarized with mean and standard deviation. Other continuous variables were summarized with median and inter-quartile range. Logistic regression models with dichotomised ventricular dysfunction as outcome were used to investigate the relationship between risk factors, log transformed NT-proBNP and ventricular structure and function. Inter-observer reproducibility was summarized with concordance correlation coefficients [38].

RESULTS

Letters of invitation and questionnaires were sent to 44,000 health fund members who were 60 years or older (Figure 1). Approximately 25% of questionnaires (n=11,046) were returned. Consecutive respondents were then telephone screened (n=9,256) until 3,550 met inclusion and exclusion criteria. Questionnaires were returned by 4,527 members who did not meet inclusion and exclusion criteria, and 1,179 members met criteria but declined to enroll in study.

Three thousand five hundred and fifty participants enrolled after giving informed written consent and attended for visit 1. Fifteen participants who attended for visit 1 were found to have exclusion criteria (pre-existing HF) and were excluded. Of 710 participants in the top NT-proBNP quintile 664 attended the second visit. The 46 participants who declined and withdrew from further involvement in the study had a higher BMI than those who continued (29±5kg/m^2 versus 28±5kg/m2; p=0.01), but there was little difference in their age, gender, medical history or NT-proBNP levels.

Population characteristics

Characteristics of the entire SCREEN HF cohort and those at highest risk are presented in Table 2. The mean±SD age of the cohort was 70±7 years (range 59 to 92 years) and 55% were male. Participants attending for echocardiogram from the top NT-proBNP quintile, when compared to the remainder of the cohort, were on average older, 74±7 years (p<0.001), had higher mean systolic BP (p=0.007) but they had a lower mean diastolic BP (p<0.001) and BMI (p<0.001). A history of coronary artery disease (OR 2.3, 95% CI: 1.9-2.8; p<0.001), stroke (OR 1.4, 95% CI: 1.1-1.7; p=0.002), or atrial fibrillation (OR 5.4, 95% CI 4.2-6.7; p<0.001) were more commonly reported in participants with a plasma NT-pro-BNP level >30pmol/L, as was the presence of multiple HF risk factors (OR 1.6, 95% CI: 1.5-1.7; p<0.001). In contrast, a history of hypertension (OR 0.7, 95% CI: 0.6-0.9; p=0.04) was less commonly reported, and there was no difference in past medical history of diabetes or obesity in the elevated NT-proBNP group.

Left ventricular systolic function

Forty-four participants (6.6%; 95% CI: 4 to 8%) in the top NT-proBNP quintile who underwent echocardiogram (n=664) had impaired left ventricular function (LVEF ≤45%).

Over seventy percent of them were male, and more than half had a background of coronary artery disease (Table 2).

In univariate logistic regression analysis, male gender, coronary artery disease, hypertension and log transformed NT-proBNP were associated with impaired ejection fraction (Table 3). In multivariate regression analysis, left ventricular ejection fraction, after adjustment for age, sex, and HF risk factors, was independently associated with male gender ($p<0.001$), a history of hypertension ($p=0.02$) and log transformed NT-proBNP ($p<0.001$) (Table 3).

Left ventricular diastolic function

In the top NT-proBNP quintile, diastolic function could be categorized in 454 participants. It could not be estimated in 210 participants, with diastolic dysfunction indeterminate in 49 individuals based on ultrasound parameters, and could not be estimated for the remaining 161 due to rhythm, significant mitral valve disease, or echocardiogram quality.

Moderate to severe diastolic dysfunction was observed in 127 participants (24%; 95% CI 20 to 27%), almost 60% of who were female and 80% had a reported history of hypertension (Table 2). Results in Table 4 show that diabetes and log transformed NT-proBNP were the only HF risk factors associated with poor diastolic function ($p=0.01$ and $p<0.001$, respectively), and this persisted after adjustment for age, gender and other HF risk factors ($p=0.02$ & $p<0.001$, respectively).

The participants (n=51) from the bottom NT-proBNP quintile (very low NT-proBNP, <5.5pmol/L) who underwent echocardiogram where representative of the bottom quintile, with no significant differences in age, gender, medical history, BP, BMI or NT-proBNP

between these 51 individuals and the remaining 659 in the quintile (data not shown). The participants who undertook echocardiography in the bottom quintile, when compared to the top quintile, were younger (67.2 ±4.6 years vs. 74.5±6.8 years; $p<0.001$) and had a higher left ventricular ejection fraction (59.5 ±5.7% vs. 56.5±7.4%; $p=0.003$). In this lower risk group no systolic dysfunction was observed and only 6% (95% CI: 1 to 15%) were observed to have moderate diastolic dysfunction.

DISCUSSION

Significant ventricular dysfunction was documented in 25% of asymptomatic elderly subjects with HF risk factors and a very high NT-proBNP level (>80th centile). The odds of having left ventricular dysfunction almost doubled in those with pre-existing coronary artery disease and, similarly, diabetes. NT-proBNP was associated with both systolic and diastolic impairment.

The burden of systolic dysfunction (6%) we observed was similar to that reported by other researchers, including the MONICA Glasgow study [3] 7.7%, the Olmsted County study [5] 6.0%, ECHOES [15] 5.3% and the Canberra Heart Study [6] 5.9%. Comparison among studies is, however, limited by non-uniform diagnostic criteria and methodology. For example, these other studies, unlike SCREEN-HF, reported both symptomatic and asymptomatic dysfunction, and hence the burden of asymptomatic systolic dysfunction in SCREEN HF is likely greater, reflecting the pre-existing risk factors and elevated biomarker (>80th centile) that defined the group. In contrast, the SCREEN HF subgroup with HF risk factors but very low NT-proBNP (<20th centile) had no systolic, and only a small proportion of diastolic dysfunction. PROBE-HF investigators observed similar results, reporting 4%

moderate to severe diastolic dysfunction and 1% systolic dysfunction in a hypertensive and/or diabetic population [39].

Primary prevention of HF risk factors and targeting existing HF risk factors are both essential strategies to prevent cardiac injury and progression to HF. Nevertheless, many individuals are already living with HF risk factors and asymptomatic dysfunction, and thus screening to differentiate stage A from stage B HF, with the goal of targeting resources and therapy to prevent progression to overt HF, is the next frontier in management [1]. Biomarkers, in particular NT-proBNP and B type natriuretic peptide (BNP), are the most promising measures for screening and are currently used in clinical medicine to triage patients who present with dyspnoea [23-25, 29, 40, 41], in management of HF patients [28, 42-45] and to determine HF prognosis [27, 46, 47].

For the purposes of screening, the role of natriuretic peptides is not yet established [48, 49] and their inclusion in screening is not recommended by major guidelines. While a low plasma NT-proBNP level essentially excludes structural heart disease [39], interpreting elevated NT-proBNP results is more problematic. Several investigators have reported BNP is effective and cost-effective when used to screen for systolic dysfunction [20, 21], but other studies have reported more equivocal results, with a high number of those screened still requiring an echocardiogram. Strategies aiming to improve screening with natriuretic peptide have been investigated. For example, Ng et al. combined major ECG abnormalities (pathological q waves, left bundle branch block, left ventricular hypertrophy, atrial flutter/fibrillation) with NT-proBNP to improve their positive predictive value for the detection of systolic dysfunction [50]. The use of major ECG abnormalities and NT-proBNP significantly reduced the number of screened individuals who required subsequent echocardiograms; however, this

was most effective in those with pre-existing coronary artery disease. In our study, only 50% of SCREEN HF participants with confirmed left ventricular systolic dysfunction had a background of coronary artery disease. Determining the effectiveness of the strategy of combining ECG abnormalities and NT-proBNP to screen in broader populations needs further consideration. This will be particularly important as coronary artery disease prevalence rates decline.

Murtagh and the STOP-HF investigators examined the proportion of diastolic dysfunction responsible for the high rates of false positives when using BNP to screen for systolic dysfunction in an asymptomatic population (≥40 years + HF risk factor) [51]. They observed a significant proportion of diastolic dysfunction in those labeled as "false positives". In the SCREEN HF study, we found a large proportion of the ventricular dysfunction was diastolic dysfunction without co-existent systolic dysfunction.

Using natriuretic peptides to screen for diastolic and systolic dysfunction is likely to improve the effectiveness of any strategy. Diastolic dysfunction underlies much of HF due to preserved ejection fraction, also a common syndrome, but may also underlie those who go on to develop subsequent HF with reduced ejection fraction. The role of screening for diastolic dysfunction, as opposed to systolic dysfunction, is however more complex. This is because, once identified, there are as yet no randomized placebo controlled trials of effective therapy for diastolic dysfunction, and treatment remains empirical. There is some indirect evidence that treating hypertension and regression of left ventricular hypertrophy is associated with improved outcomes. Trials using newer therapeutic agents are underway. Trials using established HF therapies are also in progress. For example, preliminary reports on digoxin use in HF with preserved ejection fraction are promising, and results of the use of

spironalactone in this population, from the TOPCAT investigators, is expected in 2012. Thus, although currently specific therapy directed at diastolic dysfunction is not available, this situation will hopefully change.

In SCREEN HF there was a significant proportion of ventricular dysfunction identified, and underlying risk factor profiles varied with systolic and diastolic dysfunction. NT-proBNP was independently associated with both impaired systolic and moderate to severe diastolic dysfunction. Understanding risk factor profiles and their relationship to ventricular dysfunction and combining this with NT-proBNP may be effective in identifying asymptomatic ventricular dysfunction, but this strategy will need further assessment. The opportunity to identify pre-symptomatic dysfunction and prevent progression to heart failure is important if we are to intervene to halt the rising prevalence of HF.

Limitations

The present study has some limitations. The population was recruited from health fund membership which may affect generalization of the findings to the general population. Inclusion of participants was, however, defined by HF risk factors (age plus underlying pathology), and these should not differ greatly from that of the general population. NT-proBNP and heart failure risk factors were measured simultaneously at study visit 1 and cardiac ultrasound was measured at a second study visit. While this lack of temporal alignment may affect findings, >70% of participants had echocardiogram within 3 months and almost all within 6 months. The direction and significance of associations between biomarker and cardiac ultrasound did not alter with time to echo and this may reflect real world use of a screening blood test.

Conclusion

Using a very high plasma NT-proBNP level we documented over one quarter of high risk elderly participants with ventricular dysfunction. This was independent of conventional risk factors. Targeting high risk asymptomatic populations using a combination of plasma NT-proBNP and HF risk factors may help identify those with left ventricular dysfunction and thus at greatest risk of incident heart failure. This strategy may represent an effective approach to screening for left ventricular dysfunction and further investigation of this approach with clinical outcomes and cost-effectiveness is warranted.

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CONFLICT OF INTEREST

Bupa Australia was involved in funding, study design, and recruitment, but was not involved in collection of data, analysis or interpretation, or writing of the article. Bupa Australia had no control or influence over the decision to submit the final manuscript for publication.

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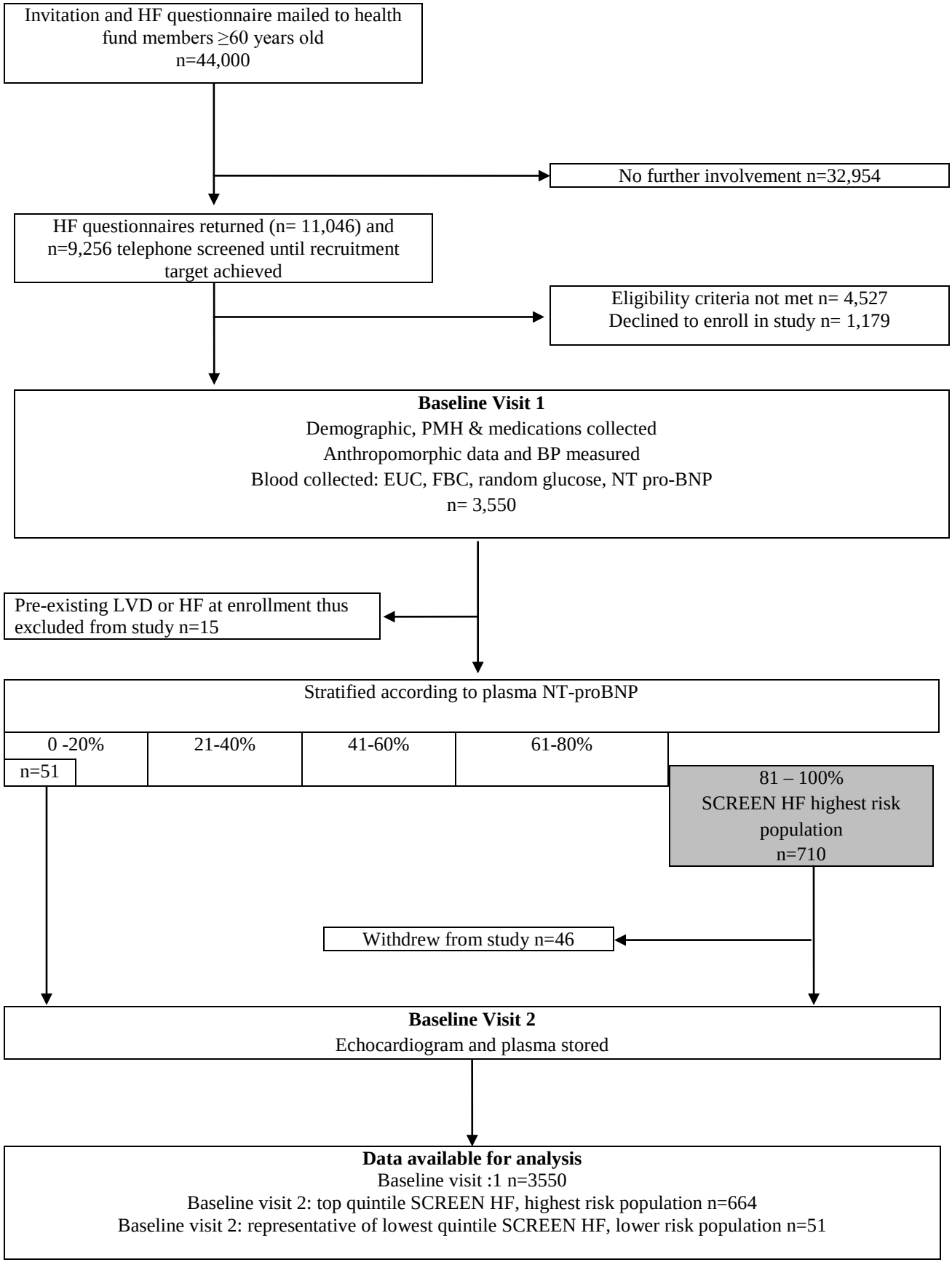

Figure 1: SCREEN-HF study design

Table 1: Doppler criteria for the classification of left ventricular diastolic function

	Diastolic Function			
Doppler measures	**Normal**	**Mild dysfunction**	**Moderate dysfunction**	**Severe dysfunction**
Mitral inflow	0.75<E/A<1.5 DT>160ms	E/A<0.75	0.75<E/A<1.5 DT>160ms	E/A>1.5 DT<160ms
Pulmonary venous inflow	S≥D MV Adur>PV Adur	S≥D MV Adur>PV Adur	S<D MV Adur+30ms<PV Adur	S<D MV Adur+30ms<PV Adur
Mitral annular TDI	E/e'<10	E/e'<10	E/e'≥10	E/e'≥10

A minimum of two Doppler criteria required to be diagnosed as moderate or severe diastolic dysfunction. TDI, tissue Doppler imaging; E, peak early mitral inflow velocity; A, peak mitral filling velocity at atrial contraction; DT, deceleration time of the mitral E wave; e', peak velocity of the mitral annulus motion during early diastole; MV Adur, duration of the mitral A wave; PV Adur, duration of the pulmonary venous reversal wave during atrial contraction; S, peak velocity of the pulmonary venous forward flow during systole; D, peak velocity of the pulmonary venous forward flow during diastole.

Table 2: Demographics of entire cohort, top NT-proBNP quintile and by left ventricular dysfunction.

	Entire cohort	Top quintile NT-proBNP >30pmol/L	ALVDD	ALSVD
	n=3550	n=664	n=127	n=44
Age (years)	70.4±6.6	74±7	75±6	74±7
Male	1961 (55%)	352 (53%)	55 (43%)	32 (72%)
Laboratory profile				
NT-proBNP (pmol/L)	13 (7-26)	54 (39-88)	53 (39-79)	86 (57-151)
Creatinine (umol/L)	81 (70-95)	86 (73-103)	87 (73-105)	90 (79-103)
Haemoglobin (g/L)	13.9 (1.3)	14 (9-18)	13 (9-18)	14 (11-18)
Anthropomorphic data and blood pressure				
Body mass index (kg/m^2)	28.3±4.6	27.8±4.8	27.9±5.0	28.8±5.1
Systolic BP (mmHg)	141±18	142±20	144±20	141±17
Diastolic BP (mmHg)	80±10	78±11	76±11	78±10
Pulse pressure (mmHg)	60±15	64±17	68±16	63±15
Medical History				
Coronary artery disease	836 (24%)	247 (37%)	50 (39%)	23 (52%)
Diabetes	654 (18%)	120 (18%)	32 (25%)	12 (27%)
Hypertension	3018 (85%)	541(81%)	106 (83%)	31 (70%)
Stroke	388 (11%)	112 (17%)	23 (18%)	12 (27%)
Atrial fibrillation	352 (10%)	169 (27%)	N/A	15 (37%)
Obesity (BMI≥$30kg/m^2$)	1119 (32%)	193 (29%)	37 (29%)	14 (32%)

Values are mean±standard deviation, median (inter-quartile range), or number (%).

Top quintile NT-proBNP – participants with NT-proBNP >30mmol/L and who completed echocardiogram; ALVDD – asymptomatic moderate to severe diastolic dysfunction; ALVSD – asymptomatic left ventricular systolic dysfunction (ejection fraction 45%); N/A – not available.

Table 3: Univariate logistic regression analyses with outcome of left ventricular systolic dysfunction (LVEF<45%) and explanatory variables of HF risk factors. Multivariate linear regression analyses of left ventricular ejection fraction and HF risk factors.

	Left ventricular function					
	LVEF <45%			LVEF (%)		
	OR	*95% CI*	*Unadjusted p value*	*Coefficient*	*95% CI*	*Adjusted* p value*
Age (years)	1.0	1.0 to 1.1	0.90	0.02	-0.06 to 0.1	0.7
Male gender	2.5	1.3 to 4.7	0.01	-2.7	-3.8 to -1.7	<0.0001
CAD	2.2	1.1 to 4.1	0.01	-0.6	-1.7 to 0.4	0.2
Diabetes	1.7	0.8 to 3.3	0.14	-0.4	-1.7 to 0.9	0.2
Hypertension	0.5	0.3 to 1.0	0.04	1.6	0.2 to 2.9	0.02
BMI $\geq$30kg/m^2	1.1	0.6 to 2.2	0.70	-0.9	-2.1 to 0.2	0.1
logNT-proBNP	2.5	1.7 to 3.6	<0.0001	-1.4	-2.0 to -0.9	<0.0001

LVEF - left ventricular ejection fraction; CAD – coronary artery disease; logNT-proBNP – log transformed NT-proB natriuretic peptide. *Adjusted for all variables in the table.

Table 4: Univariate and multivariate logistic regression analyses of associations between HF risk factors and the outcome moderate to severe diastolic dysfunction.

	Moderate to severe diastolic dysfunction					
	Unadjusted odds ratio	*95% CI*	*Unadjusted p value*	*Adjusted odds ratio**	*95% CI*	*Adjusted* p value*
Age (years)	1.0	1.0 to 1.1	0.08	1.0	1.0 to 1.0	0.5
Male gender	0.8	0.5 to 1.2	0.3	0.7	0.5 to 1.1	0.1
CAD	1.3	0.8 to 1.9	0.3	1.1	0.7 to 1.7	0.8
Diabetes	1.8	1.1 to 2.9	0.01	1.9	1.1 to 3.1	0.02
Hypertension	0.9	0.5 to 1.5	0.6	0.8	0.4 to 1.4	0.4
BMI≥30kg/m^2	1.1	0.7 to 1.6	0.8	1.1	0.7 to 1.8	0.7
logNT-proBNP	1.7	1.3 to 2.3	<0.0001	1.7	1.3 to 2.3	<0.0001

CAD – coronary artery disease; logNT-proBNP – log transformed NT-proB natriuretic peptide. *Adjusted for all variables in the table.