Prediction of incident heart failure by serum NT-proBNP level in a community-based cohort

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Abstract

Aims

We investigated which serum amino-terminal pro-B-type-natriuretic peptide (NT-proBNP) levels inform heart failure (HF) risk in a community-based population at increased cardiovascular disease (CVD) risk.

Methods and results

Inclusion criteria were age ≥60 years with one or more of self-reported hypertension, diabetes, heart disease, abnormal heart rhythm, cerebrovascular disease, or renal impairment. Exclusion criteria were known HF, ejection fraction (EF) <50%, or >mild valve abnormality. NT-proBNP levels were measured in 3842 participants on enrolment. HF was diagnosed in 162 participants at a median of 4.5 (interquartile range: 2.7-5.4) years after enrolment, 73 with HF with preserved EF (HFpEF), 53 with HF with reduced EF (HFrEF) and 36 with valvular HF (VHF). Areas under the receiver operating characteristic curve (AUC) for 5-year prediction of total HF were similar for NT-proBNP alone (0.79, 95% confidence interval: 0.74, 0.83) and a 7-parameter multivariable model (0.82, 0.77, 0.86, *P*=0.035). NT-proBNP cut points of 11, 16, and 25 pmol/L for individuals aged 60-69, 70-79, and ≥80 years, respectively, achieved sensitivities >76% and specificities of 47%-69% for 5-year prediction of total HF in men and women in all three age groups. Sensitivities were ≥75% in most subgroups according to body mass index, estimated glomerular filtration rate, and the presence or absence of atrial fibrillation, pacemaker, or CVD, and for the prediction of HFpEF, HFrEF and VHF.

Conclusion

Age-specific serum NT-proBNP levels inform prognosis, and hence therapeutic decisions, regarding HF risk in individuals at increased CVD risk.

Key words NT-proBNP; Natriuretic peptides; Incident heart failure; Prevention; Epidemiology; Risk factors

Introduction

The burden of heart failure (HF) continues to increase despite decreasing age- and sex-standardised incidence of HF because of increasing age and population size.[1] At age 45 years, lifetime risks for symptomatic HF through age 95 years are 30% to 42% in white males, 20% to 29% in black males, 32% to 39% in white females, and 24% to 46% in black females.[2] HF imposes a significant economic burden with older Americans hospitalised more for HF than for any other medical condition.[3] There is, therefore, need for improved measures for HF prevention.

Essential to any HF prevention strategy is a means to identify individuals at increased risk who can be offered preventative therapies. Preferably this method of identification of high risk individuals would be easy for the clinician to obtain and implement. Serum B-type-natriuretic peptide (BNP) and amino-terminal pro-BNP (NT-proBNP) levels predict incident HF in individuals without HF at baseline,[4-7] and recent American College of Cardiology (ACC), American Heart Association (AHA), Heart Failure Society of America (HFSA), and Canadian Cardiovascular Society (CCS) guidelines recommend the use of natriuretic peptide levels to select patients for implementation of HF prevention strategies.[8,9] However, there is uncertainty how natriuretic peptide levels might best inform prognostic and therapeutic decisions. In assessing a biomarker's performance in the identification of increased HF risk, several questions arise.[10] These include the cut point that best separates high from low HF risk, and how well the biomarker discriminates risk according to sex, age, HF subtypes, and in the presence of multimorbidity. Additional questions include the biomarker's discrimination of HF risk in comparison with a multivariable model, how far into the future the prediction applies and how frequently biomarker measurement should be repeated. To address these questions for NT-proBNP as a biomarker for HF risk we performed serial NT-

proBNP measurements in participants of the SCReening Evaluation of the Evolution of New HF (SCREEN-HF) study, a self-selected community-based population at increased cardiovascular disease (CVD) risk.[6,11]

Methods

Participant recruitment to the SCREEN-HF study has been previously described.[6,11] Briefly, the SCREEN-HF study was a community-based evaluation of the use of serum NT-proBNP level to identify individuals with cardiac dysfunction (as assessed by echocardiography) and increased risk of HF and other cardiovascular events. Participants were predominantly members of private health fund Bupa, recruited from Melbourne and Shepparton, Victoria, Australia. To determine whether NT-proBNP level could help identify individuals at increased risk of HF from a population with risk factors of HF, but without known heart failure or well recognised HF risk due to known reduced LVEF or significant valve abnormality, we recruited participants aged ≥60 years with one or more of self-reported treatment for hypertension or diabetes for ≥2 years, myocardial infarction (MI) or other ischaemic or valvular heart disease, irregular or rapid heart rhythm, cerebrovascular disease, or renal impairment. Exclusion criteria were previously diagnosed HF, previous valve surgery or documented valve abnormality graded >mild, or left ventricular ejection fraction (LVEF) <50% on previous echocardiography or other cardiac imaging. Of the 4054 individuals enrolled at the baseline visit (Visit 1), 3842 met the inclusion and exclusion criteria and had serum NT-proBNP measurement. The SCREEN-HF study was approved by the Alfred Human Research Ethics Committee and written informed consent was obtained from all participants. The study was registered at ClinicalTrials.gov NCT00400257, NCT00604006, and NCT01581827.

The collection of baseline clinical information has been described previously.[6,11] Participants were followed up at study visits and by telephone. A flow chart of participant visits and NT-proBNP measurement is shown in Figure 1. NT-proBNP levels were measured in 3842 participants on enrolment, and repeated at Visit 2 (n=3053) and Visit 3 (n=2284). Visit 2 was 1.3 (median,

interquartile range, IQR: 0.5-1.9) years after enrolment and Visit 3 was 5.6 (IQR: 4.9-6.1) years after enrolment. Details of symptoms, interim clinical events and medication were collected, echocardiography performed and the participant examined for signs of HF during Visits 2 and 3. Additionally, details of interim clinical events, symptoms, and medication were collected by telephone interview approximately 4 and 7 years following enrolment. The capture of incident HF has been described previously.[6] All cases of HF were adjudicated by two HF specialists, with differences in opinion adjudicated by a third HF specialist, according to European Society of Cardiology (ESC) criteria of 2012.[12] The adjudicators were provided with all available information including reports of imaging studies; however, they were not informed of the baseline NT-proBNP level, although they were informed of any NT-proBNP and BNP levels measured as part of usual care. Based on cardiac imaging and assessment of LVEF at the time of, or after, HF diagnosis, non-valvular HF was categorised as either HF with reduced LVEF (HFrEF, LVEF <50%) or HF with preserved LVEF (HFpEF, LVEF e 50%), and valvular HF (VHF) was diagnosed when HF was attributed to valvular dysfunction graded as severe. HFpEF cases had relevant structural heart disease and/or diastolic dysfunction, according to the 2012 ESC guidelines.[12]

Body mass index (BMI) was calculated as the ratio of weight to height squared (kg/m^2). Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[13] Serum NT-proBNP was measured by electrochemiluminescence immunoassay using an Elecsys instrument (Roche Diagnostics, Basel, Switzerland) with a lower limit of detection of 0.6 pmol/L (to convert pmol/L to pg/ml, multiply by 8.457).

Statistical analysis

Continuous variables were summarised as means (standard deviations) or medians (IQR). Categorical variables were summarised as numbers (percentages). Comparisons between participant groups were performed with the use of Student's t-tests for continuous variables that were approximately normally distributed, with or without log transformation, or with the use of Mann-Whitney U tests. Categorical variables were compared with the use of chi-square tests or Fisher's exact tests.

Baseline data were complete for the 162 participants who developed HF, except for one with missing blood pressure and heart rate. Of 3680 participants who did not develop HF during follow-up, the maximum number with missing data was 13 for platelet count. In multivariable analysis, the maximum number with missing data was 21. Participants were omitted from particular analyses if the required variables were missing.

Individuals were censored at the date of last contact or development of HF or death, whichever came first. Incidence rate data were analysed using Poisson regression. Area under the curve (AUC) statistics were estimated from time-dependent receiver operating characteristic (ROC) curves and presented with 95% confidence intervals (CI).[14] ROC curves were estimated for the prediction of HF by NT-proBNP alone, and also for the prediction of total HF by a 7-parameter multivariable model constructed using coefficients obtained from a semiparametric proportional hazards model for the subdistribution of competing risk, with non-HF related death as competing risk.[15] This multivariable model has been described previously,[6] and the 7 parameters were baseline age, log BMI, diabetes, MI, obstructive sleep apnoea (OSA), smoking status, and serum NT-proBNP

quintile. NT-proBNP quintile was used in the multivariable model because of non-linearity for the association of NT-proBNP with log-hazard in the subdistribution model.[6] Optimism in AUC estimates was quantified with bootstrapping, following the method described by Steyerberg.[10] A two-sided *P* value of less than 0.05 was considered to indicate statistical significance. Data were analysed with SPSS software version 22 and with R software version 1.0.153.

Results

Baseline characteristics

The baseline characteristics of SCREEN-HF participants who developed HF, and those who did not develop HF, during follow-up are shown in Table 1. The median follow-up of the 3842 participants was 5.6 (IQR: 4.5-6.3) years and 271 non-HF related deaths were recorded. HF was diagnosed in 162 participants: 73 with HFpEF, 53 with HFrEF and 36 with VHF; 63 were diagnosed on hospitalisation and 99 were diagnosed in the ambulant setting. Excluding hospitalisations for valve surgery, a further 44 participants were hospitalised for HF after HF diagnosis. The median time to HF diagnosis was 4.5 (interquartile range: 2.7-5.4) years, Participants who developed HF were older, with lower diastolic blood pressure, increased pulse pressure, lower heart rate, and were more likely to be obese (BMI e 30 kg/m^2). Participants who developed HF were also more likely to be diabetic, have coronary and/or peripheral artery disease, have arrhythmia, pacemaker and OSA, and be current or former smokers. Furthermore, they had lower baseline eGFR, haemoglobin and platelet count, and higher white cell count, and were more likely to be taking ß-blocker, ACE inhibitor, statin, loop diuretic, clopidogrel, and warfarin therapies.

HF incidence rates were 3.5, 11.4, and 23.4 per 1000 person years for participants aged 60-69, 70-79, and e 80 years, respectively, with significant differences between age groups but similar age-specific rates for men and women.[6]

Baseline serum NT-proBNP levels increased with age (Table 2), and were higher in participants who subsequently developed HF than in those who did not develop HF during follow-up. Baseline NT-proBNP levels (pmol/L) were higher in women (median: 14.2, IQR: 7.8-26.2, n=1744) than in men (median: 10.3, IQR: 5.2-21.1, n=2098, *P*<0.001); however, the baseline NT-proBNP levels were only higher in women than in men who did not develop HF during follow-up, whereas baseline NT-proBNP levels were similar in women and men who subsequently developed HF (Table 2). In addition, baseline NT-proBNP levels (pmol/L) were higher in participants with atrial fibrillation (AF) (median: 29.1, IQR: 13.5-74.2, n=393) than in those without AF on enrolment (median: 11.3, IQR: 5.9-20.9, n=3449, *P*<0.0001), higher in participants with pacemaker (median 37.4, IQR: 14.6-80.8, n=66) than in those without pacemaker (median: 12.0, IQR: 6.2-23.1, n=3776, *P*<0.0001), lower in participants with BMI ≥30 kg/m^2 (median: 11.7, IQR: 5.8-23.0, n=1239) than in those with BMI <30 kg/m^2 (median: 12.4, IQR: 6.5-23.9, n=2600, *P*=0.02), higher in participants with eGFR <60 ml/min/1.73m^2 (median: 18.8, IQR: 9.7-37.8, n=784) than in those with eGFR ≥60 ml/min/1.73m^2 (median: 11.1, IQR: 5.8-20.3, n= 3058, *P*<0.0001), and higher in participants with CVD (median: 15.7, IQR: 7.9-33.5, n=1207) than in those without CVD (median: 10.9, IQR: 5.7-20.0, n=2635, *P*<0.0001).

ROC curves

The ROC curve for the multivariable model had an AUC of 0.82 (95% CI: 0.77, 0.86) for 5 year prediction of total HF, in comparison with 0.79 (0.74, 0.83) for the ROC curve calculated for NT-proBNP level alone (Figure 2A). Although the AUC for NT-proBNP alone was less than that for the multivariable model (*P*=0.035), given the similarity of the AUC for the 7-parameter multivariable model and that for NT-proBNP level alone, and the easier clinical application of NT-

proBNP level alone to prognosis and therapeutic decision making, we chose to further explore the prediction of HF by NT-proBNP level alone.

Prediction of incident HF by NT-proBNP level was similar for men and women (Figure 2B), for participants aged 60-69, 70-79, and ≥80 years on enrolment (Figure 2C), and for HFpEF, HFrEF and VHF (Figure 2D). When ROC curves were calculated for cumulative HF events over time, or for individual years of follow-up, the AUC for NT-proBNP alone was stable for the first 6 years of follow-up (supplementary material online, *Figure* S1).

Optimism of AUC

Bootstrap estimation of the 5-year prediction of total HF by NT-proBNP alone gave a median AUC of 0.78 (95% CI: 0.73-0.83) in comparison with a median AUC of 0.81 (0.76, 0.85) for the 7-parameter multivariable model. The calculated median optimism (bootstrap performance - test performance in the original sample) for the prediction of total HF by NT-proBNP alone was 0.001 (95% CI: -0.049, 0.046). We also assessed optimism by comparing ROC curves for the prediction of total HF by serum NT-proBNP levels measured at either Visit 1 or Visit 2, conducted a median of 1.3 (IQR: 0.5, 1.9) years after Visit 1. Each curve was estimated for a follow-up of 3 years (49 HF events and 3344 survivors without HF for the curve estimated for Visit 1 NT-proBNP levels, and 51 HF events and 2681 survivors without HF for the curve estimated for Visit 2 NT-proBNP levels). The AUC was 0.80 (0.74, 0.86) for both Visit 1 NT-proBNP levels and Visit 2 NT-proBNP levels. Although NT-proBNP levels from different visits were used to construct these two ROC curves, both curves were derived from the same population and 22 HF events were common to both curves.

Trajectory of serum NT-proBNP levels during follow-up

We examined the change in NT-proBNP levels over time to obtain information about how often serum NT-proBNP levels should be measured (Table 3, supplementary material online, *Figure* S2A). Changes in NT-proBNP levels over 1-2 years of follow-up were no different between participants who subsequently did and did not develop HF during follow-up. However, during a median of 4.5-4.8 years between NT-proBNP measurements, NT-proBNP levels increased by a median of 13.2 (IQR: 3.6-55.0) pmol/L, significantly greater than the increase that occurred in participants who did not develop HF during follow-up (median: 3.4, IQR: -0.6-11.9 pmol/L, P<0.0001, Table 3). Much greater increases in NT-proBNP levels occurred after the diagnosis of HF, in comparison with the changes that occurred over the same time period before HF onset (Table 3, supplementary material online, *Figure* S2B).

Cut points for classification of HF risk

Based on the Youden index,[16] which is the maximum sum of sensitivity plus specificity, optimum NT-proBNP cut points were 19 pmol/L for participants (men and women combined) aged 60-69 years, 23 pmol/L for age 70-79 years and 36 pmol/L for age ≥80 years. However, these cut points produced sensitivities of only 63.9% for participants aged 60-69 years, 71.3% for participants aged 70-79 years, and 74.4% for participants ≥80 years of age. Given that our goal was to identify cut points that best inform prognosis and therapeutic decisions in order to prevent HF, we chose cut points that identified at least 75% of participants who subsequently developed HF. Moreover, to assist application of an NT-proBNP threshold to clinical decision making, we wanted the same age-specific thresholds for men and women. We therefore chose NT-proBNP cut points of 11 pmol/L

for persons 60-69 years of age, 16 pmol/L for persons aged 70-79 years and 25 pmol/L for persons aged ≥80 years (Table 4). These cut points achieved relatively stable sensitivities over 6 years of follow-up. Among participants aged 70-79 years, who had the largest number of events, the sensitivity was 100% (4 events), 70% (10 events), 80% (10 events), 100% (11 events), 75% (16 events), and 75% (24 events) during the first, second, third, fourth, fifth and sixth years of follow-up, respectively.

When participants were stratified according to sex, BMI, eGFR, and the presence or absence of AF, pacemaker, and CVD, sensitivities were in most cases >75% (Table 4). These cut-points would have identified 129 (80%) of the 162 participants who developed HF, based on their single baseline NT-proBNP measurement.

When calculated separately for HFpEF, HFrEF, and VHF, the sensitivities for HFpEF were 71.4%, 85.4%, and 77.8%; for HFrEF were 81.8%, 75.9%, and 84.6%; and for VHF were 81.8%, 70.6%, and 87.5%, for ages 60-69, 70-79, and ≥80 years, respectively.

Discussion

We identified age-specific serum NT-proBNP cut points with the potential to inform prognostic and therapeutic decisions regarding HF risk, achieving a sensitivity of >75% in men and women aged 60-69 years, 70-79 years and ≥80 years, and in most subgroups according to BMI, eGFR, and the presence or absence of AF, pacemaker, or CVD, and for the prediction of HFpEF, HFrEF and VHF. Serum NT-proBNP level alone showed similar discrimination for HFrEF, HFpEF and VHF, and for individuals aged 60-69, 70-79, and ≥80 years of age. Discrimination was robust, with very low optimism, and compares favourably with the Framingham risk score for atherosclerotic CVD (coronary heart disease, cerebrovascular disease, peripheral vascular disease, and HF), for which the AUC was 0.763 for men and 0.793 for women.[17] Moreover, the median of 4.5 years between enrolment and HF diagnosis in our study indicates that NT-proBNP levels have the potential to identify HF risk well in advance of its onset, thereby providing ample opportunity for the institution of HF preventative strategies. Although the 7-parameter prediction model had slightly better discrimination, the use of NT-proBNP alone for the identification of individuals at increased HF risk offers advantages for clinical application. Thus, a pathology laboratory could highlight NT-proBNP levels above the age-specific cut point, drawing a clinician's attention to a patient's increased HF risk. Echocardiographic parameters also predict HF,[18] but NT-proBNP levels provide a less expensive and more convenient means to assess HF risk and may assist in the selection of individuals for whom echocardiography is indicated, thereby allowing a more cost-effective use of echocardiography that may not only refine the prediction of HF risk but also lead to specific preventative strategies, such as valve replacement or repair.

The extensive overlap in baseline NT-proBNP levels between participants who developed HF and those who did not develop HF during follow-up meant that the choice of cut point necessarily involved a compromise between sensitivity and specificity. The specificities of 47%-69% obtained by the NT-proBNP cut points chosen in this study should be interpreted in the context of the lifetime HF risk at age 45 of 20%-46% reported in populations with a much lower baseline prevalence of CVD risk factors than present in SCREEN-HF participants.[2] Only 162 (4.2%) SCREEN-HF participants developed HF during the median follow-up of 5.6 years, and it is likely that a much larger number were destined to develop HF in subsequent years, with a lifetime risk approaching 50%. Any HF prevention strategy needs a lifetime perspective if it is to have maximum impact on HF incidence and prevalence. Given that many of the participants with NT-proBNP levels above the cut point who did not develop HF during the period of follow-up were likely to develop HF in the future, a false positive rate (1-specificity) approaching 50% is appropriate.

Baseline NT-proBNP levels discriminated HF risk over 6 years of follow-up. During 1-2 years of follow-up, change in NT-proBNP levels was not different between those who subsequently developed HF and those who did not develop HF during follow-up. However, over 4-6 years of follow-up, NT-proBNP levels showed a greater increase in those who subsequently developed HF than in those who did not develop HF. Our data therefore indicate that repeating serum NT-proBNP measurement at 4-5 year intervals may provide an efficient means to identify additional individuals at increased risk of HF, as indicated by findings from the Cardiovascular Health Study.[7]

NT-proBNP level is a predictor of not only HF but also other cardiovascular events.[5,7,19-22] The ACC/AHA/HFSA and CCS guidelines on use of natriuretic peptide levels to select patients for implementation of HF prevention strategies are based on the St Vincent's Screening to Prevent Heart Failure (STOP-HF) and the NT-proBNP selected Prevention of cardiac Events in a population of Diabetic Patients without a history of cardiac disease (PONTIAC) studies.[8,9,23,24] The STOP-HF study randomised patients (mean age 68-71 years) with CVD risk factors to either BNP screening and referral to echocardiography and collaborative care between their primary care physician and specialist cardiovascular service if their BNP level was e 50 pg/mL, or to usual primary care without BNP screening. If one assumes 35 pg/mL BNP is equivalent to 125 pg/mL NT-proBNP,[25] then the BNP cut point used in the STOP-HF study (50 pg/mL) was equivalent to 21.4 pmol/L NT-proBNP. However, the BNP cut point chosen in the STOP-HF study was not based on a formal assessment of the relationship between BNP levels and HF incidence. STOP-HF study patients referred to BNP screening had lower combined rates of LV systolic dysfunction, diastolic dysfunction and HF during a mean follow-up of 4.2 years than patients randomised to usual care.[23] The NT-proBNP cut point used in the PONTIAC study was based on the prediction of short-term CVD events in diabetic patients without cardiac disease, where 125 pg/mL NT-proBNP (14.8 pmol/L) achieved a sensitivity of 79.5% and specificity of 60%, and an AUC of 0.785.[22] Type 2 diabetic patients (mean age 68 years) free of cardiac disease with NT-proBNP >125 pg/mL (14.8 pmol/L) randomised to up-titration of renin-angiotensin system antagonist and ß-blocker therapies had a lower rate of hospitalisation or death due to cardiac disease after 2 years than those randomised to usual care in the PONTIAC study.[24] Prediction of HF hospitalisation by NT-proBNP level was also examined in participants of the Cardiovascular Health Study (mean age 73 years), where an NT-proBNP cut point of 190 pg/mL (22.5 pmol/L) achieved a sensitivity of 47.6% and specificity of 75.6%.[7] Thus,

serum NT-proBNP levels performed similarly in the prediction of CVD events in diabetic patients in the PONTIAC study,[22] and in the prediction of HF in SCREEN-HF participants. The STOP-HF and PONTIAC studies demonstrated the potential utility of NT-proBNP-guided therapy to prevent not only HF but also other cardiovascular events. The present study expands on these prior reports by emphasising the effect of age on NT-proBNP levels and defining age-specific cut points that may lead to improved identification of HF risk and improved HF prevention in the general community. As the ACC/AHA/HFSA guidelines state, further studies are needed to determine cost-effectiveness and risk of such screening, as well as its impact on quality of life and mortality rate.[8]

Strengths and limitations of the study

The strengths of our study include the diagnosis of HF in a predominantly ambulant setting and the long duration of observation such that baseline serum NT-proBNP levels were measured well before HF diagnosis. A key limitation of our study was that the inclusion criteria with respect to age and cardiovascular risk factors, together with the SCREEN-HF cohort comprising volunteers who were predominantly members of a health fund, are cause for caution in the generalisation of our findings to the general community. However, the SCREEN-HF cohort was not that dissimilar to the general Australian population aged ≥60 years; of Australians aged 65-74 years, 70% have hypertension,[26] 17% have diabetes,[27] 38.2 % of men and 32.7% of women are obese,[28] 5% have AF,[29] and 53% have CVD.[30] We enrolled a cohort ≥60 years of age with CVD risk factors in order to achieve sufficient events during follow-up. Our inclusion criteria would have captured up to 90% of individuals in the general community at risk of HF,[31] and we therefore believe that the NT-proBNP cut points identified in our study are likely to be applicable to the general community. We excluded individuals known at baseline to have reduced LVEF or significant valve abnormality

because such individuals have well recognised HF risk, and our aim was to identify otherwise unrecognised HF risk in a community cohort. The echocardiographic examinations performed as part of the SCREEN-HF study, and the prediction of echocardiographic findings by NT-proBNP levels, will be the subject of future analyses.

Conclusions and implications

We identified age-specific serum NT-proBNP cut points with the potential to inform prognostic and therapeutic decisions regarding HF risk, achieving a sensitivity of >75% in men and women aged 60-69 years, 70-79 years and ≥80 years, and in most subgroups according to BMI, eGFR, and the presence or absence of AF, pacemaker, or CVD, and for the prediction of HFpEF, HFrEF and VHF. Moreover, these cut points identified increased HF risk for at least 6 years into the future, indicating that an appropriate interval between NT-proBNP measurements to identify HF risk is 4-5 years. Future prospective studies are required to determine whether use of the age-specific serum NT-proBNP cut points identified in our study to guide therapy can delay or prevent HF development.

Supplementary Information

Additional supporting information may be found in the online version of this article.

Figure S1. Change in AUC for the prediction of total incident HF in SCREEN-HF participants by baseline serum NT-proBNP levels over time.

Figure S2. Change in serum NT-proBNP levels over time for individual SCREEN-HF participants who developed heart failure during follow-up.

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References

1. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, Allison M, Hemingway H, Cleland JG, McMurray JJV, Rahimi K. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet* 2018;**391**:572-580.
2. Huffman MD, Berry JD, Ning H, Dyer AR, Garside DB, Cai X, Daviglus ML, Lloyd-Jones DM. Lifetime risk for heart failure among white and black Americans: cardiovascular lifetime risk pooling project. *J Am Coll Cardiol* 2013;**61**:1510-1517.
3. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomidis JS, Khavjou O, Konstam MA, Maddox TM, Nichol G, Pham M, Pina IL, Trogdon JG, American Heart Association Advocacy Coordinating C, Council on Arteriosclerosis T, Vascular B, Council on Cardiovascular R, Intervention, Council on Clinical C, Council on E, Prevention, Stroke C. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail* 2013;**6**:606-619.
4. Campbell DJ, Woodward M, Chalmers JP, Colman SA, Jenkins AJ, Kemp BE, Neal BC, Patel A, MacMahon SW. Prediction of heart failure by amino-terminal-pro-B-type natriuretic peptide and C-reactive protein in subjects with cerebrovascular disease. *Hypertension* 2005;**45**:69-74.
5. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Omland T, Wolf PA, Vasan RS. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med* 2004;**350**:655-663.
6. Gong FF, Jelinek MV, Castro JM, Coller JM, McGrady M, Boffa U, Shiel L, Liew D, Wolfe R, Stewart S, Owen AJ, Krum H, Reid CM, Prior DL, Campbell DJ. Risk factors for incident heart failure with preserved or reduced ejection fraction, and valvular heart failure, in a community-based cohort. *Open Heart* 2018;**5**:e000782.
7. deFilippi CR, Christenson RH, Gottdiener JS, Kop WJ, Seliger SL. Dynamic cardiovascular risk assessment in elderly people. The role of repeated N-terminal pro-B-type natriuretic peptide testing. *J Am Coll Cardiol* 2010;**55**:441-450.
8. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation* 2017;**136**:e137-e161.
9. Moe GW, Ezekowitz JA, O'Meara E, Lepage S, Howlett JG, Fremes S, Al-Hesayen A, Heckman GA, Abrams H, Ducharme A, Estrella-Holder E, Grzeslo A, Harkness K, Koshman SL, McDonald M, McKelvie R, Rajda M, Rao V, Swiggum E, Virani S, Zieroth S, Arnold JM, Ashton T, D'Astous M, Chan M, De S, Dorian P, Giannetti N, Haddad H, Isaac DL, Kouz S, Leblanc MH, Liu P, Ross HJ, Sussex B, White M, Canadian Cardiovascular S. The 2014 Canadian Cardiovascular Society Heart Failure Management Guidelines Focus Update: anemia, biomarkers, and recent therapeutic trial implications. *Can J Cardiol* 2015;**31**:3-16.
10. Steyerberg EW. *Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating*. New York: Springer; 2009. p. 568.
11. Campbell DJ, Coller JM, Gong FF, McGrady M, Prior DL, Boffa U, Shiel L, Liew D, Wolfe R, Owen AJ, Krum H, Reid CM. Risk factor management in a contemporary Australian population at increased cardiovascular disease risk. *Intern Med J* 2018;**48**:688-698.

12. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012;**33**:1787-1847.
13. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J, Ckd EPI. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604-612.
14. Blanche P, Dartigues JF, Jacqmin-Gadda H. Estimating and comparing time-dependent areas under receiver operating characteristic curves for censored event times with competing risks. *Stat Med* 2013;**32**:5381-5397.
15. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;**94**:496-509.
16. Youden WJ. Index for rating diagnostic tests. *Cancer* 1950;**3**:32-35.
17. D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;**117**:743-753.
18. Gong FF, Campbell DJ, Prior DL. Noninvasive Cardiac Imaging and the Prediction of Heart Failure Progression in Preclinical Stage A/B Subjects. *JACC Cardiovasc Imaging* 2017;**10**:1504-1519.
19. Campbell DJ, Woodward M, Chalmers JP, Colman SA, Jenkins AJ, Kemp BE, Neal BC, Patel A, MacMahon SW. Prediction of myocardial infarction by N-terminal-pro-B-type natriuretic peptide, C-reactive protein and renin in subjects with cerebrovascular disease. *Circulation* 2005;**112**:110-116.
20. Campbell DJ, Woodward M, Chalmers JP, Colman SA, Jenkins AJ, Kemp BE, Neal BC, Patel A, MacMahon SW. Soluble vascular cell adhesion molecule 1 and N-terminal pro-B-type natriuretic peptide in predicting ischemic stroke in patients with cerebrovascular disease. *Arch Neurol* 2006;**63**:60-65.
21. Blankenberg S, McQueen MJ, Smieja M, Pogue J, Balion C, Lonn E, Rupprecht HJ, Bickel C, Tiret L, Cambien F, Gerstein H, Munzel T, Yusuf S. Comparative impact of multiple biomarkers and N-terminal pro-brain natriuretic peptide in the context of conventional risk factors for the prediction of recurrent cardiovascular events in the Heart Outcomes Prevention Evaluation (HOPE) Study. *Circulation* 2006;**114**:201-208.
22. Huelsmann M, Neuhold S, Strunk G, Moertl D, Berger R, Prager R, Abrahamian H, Riedl M, Pacher R, Luger A, Clodi M. NT-proBNP has a high negative predictive value to rule-out short-term cardiovascular events in patients with diabetes mellitus. *Eur Heart J* 2008;**29**:2259-2264.
23. Ledwidge M, Gallagher J, Conlon C, Tallon E, O'Connell E, Dawkins I, Watson C, O'Hanlon R, Bermingham M, Patle A, Badabhagni MR, Murtagh G, Voon V, Tilson L, Barry M, McDonald L, Maurer B, McDonald K. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. *JAMA* 2013;**310**:66-74.

24. Huelsmann M, Neuhold S, Resl M, Strunk G, Brath H, Francesconi C, Adlbrecht C, Prager R, Luger A, Pacher R, Clodi M. PONTIAC (NT-proBNP selected prevention of cardiac events in a population of diabetic patients without a history of cardiac disease): a prospective randomized controlled trial. *J Am Coll Cardiol* 2013;**62**:1365-1372.
25. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force M. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129-2200.
26. Australian Institute of Health and Welfare. Cardiovascular disease, diabetes and chronic kidney disease - Australian facts: Risk factors. In. *Cardiovascular, diabetes and chronic kidney disease series no 4 Cat no CDK 4*. Canberra; 2015.
27. Australian Institute of Health and Welfare. *Diabetes compendium*. https://www.aihw.gov.au/reports/diabetes/diabetes-compendium/contents/how-many-australians-have-diabetes. **(14 October 2018)**
28. Australian Institute of Health and Welfare. *An interactive insight into overweight and obesity in Australia*. https://www.aihw.gov.au/reports/overweight-obesity/interactive-insight-into-overweight-and-obesity/contents/how-many-people-are-overweight-or-obese. **(14 October 2018)**
29. Ball J, Thompson DR, Ski CF, Carrington MJ, Gerber T, Stewart S. Estimating the current and future prevalence of atrial fibrillation in the Australian adult population. *Med J Aust* 2015;**202**:32-35.
30. Australian Institute of Health and Welfare. *Cardiovascular health compendium*. https://www.aihw.gov.au/reports/heart-stroke-vascular-disease/cardiovascular-health-compendium/contents/how-many-australians-have-cardiovascular-disease. **(14 October 2018)**
31. Wilhelmsen L, Rosengren A, Eriksson H, Lappas G. Heart failure in the general population of men - morbidity, risk factors and prognosis. *J Intern Med* 2001;**249**:253-261.
32. National Health and Medical Research Council of Australia. *Australian guidelines to reduce health risks from drinking alcohol*. Canberra: Australian Government; 2009.

Legends to figures

Figure 1. Flow chart of participant visits and NT-proBNP measurements for SCREEN-HF participants who did not develop HF and for participants who developed HF during follow-up. NT-proBNP levels were measured in 3842 participants on enrolment, and repeated at Visit 2 (n=3053) and Visit 3 (n= n=2284). Visit 2 was 1.3 (median, interquartile range: 0.5-1.9) years after enrolment and Visit 3 was 5.6 (4.9-6.1) years after enrolment. Twenty three participants developed HF after Visit 3.

Figure 2. Time-dependent receiver operating characteristic (ROC) curves for the prediction of incident HF in SCREEN-HF participants. (*A*) ROC curves for 5-year prediction of total HF by a 7-parameter multivariable model (NT-proBNP quintile, age, log BMI, and diabetes, prior MI, obstructive sleep apnoea and smoking status) and by serum NT-proBNP levels alone (100 HF events). (*B*) ROC curves for 5-year prediction of total HF by serum NT-proBNP levels alone in men (67 HF events) and women (33 events). (*C*) ROC curves for 5-year incidence of total HF in participants aged 60-69 years (25 HF events), 70-79 years (51 HF events), and ≥80 years (24 HF events). (*D*) ROC curves for 5-year prediction of HFpEF (44 HF events), HFrEF (31 HF events) and VHF (25 HF events). ROC curves were censored for event times with competing risks and areas under the curve (AUC) are shown with 95% confidence intervals.[14]

Table 1. Baseline characteristics of SCREEN-HF participants with serum NT-proBNP measurement at baseline who developed new onset heart failure, and of participants who did not develop heart failure during follow-up.

	HF (n, %) n=162	No HF (n, %) n=3680	*P*-value
Age at enrolment (years)	75 (70-80)	70 (65-75)	<0.0001
Male	98 (60%)	2000 (54%)	0.13
SBP (mmHg)	143±19	141±18	0.06
DBP (mmHg)	79±11	81±10	0.019
PP (mmHg)	65±16	60±15	<0.0001
Heart rate (bpm)	68 (61-76)	70 (63-79)	0.009
BMI (kg/m^2)	29 (26-32)	28 (25-31)	<0.0001
BMI e30 kg/m^2	71 (44%)	1168 (32%)	0.0019
Waist circumference (cm)	104±13	99±13	<0.0001
Hypertension	145 (90%)	3147 (86%)	0.17
Diabetes	44 (27%)	659 (18%)	0.0048
Myocardial infarction	37 (23%)	353 (10%)	<0.0001
Coronary revascularisation	42 (26%)	533 (14%)	0.0002
Stroke/TIA	21 (13%)	399 (11%)	0.37
PVD	15 (9%)	110 (3%)	0.0002
AF	37 (23%)	356 (10%)	<0.0001
Pacemaker	7 (4.3%)	59 (1.6%)	0.020

OSA	21 (13%)	258 (7%)	0.0078
Smoker (current or former)	93 (57%)	1796 (49%)	0.037
Alcohol >2 drinks/day	39 (24%)	723 (20%)	0.19
Biochemistry and haematology			
NT-proBNP (pmol/L)	36.0 (20.0-75.3)	11.8 (6.1-22.2)	<0.0001
eGFR (ml/min/1.73m^2)	67±18	73±17	<0.0001
Haemoglobin (g/dL)	13.7±1.6	14.0±1.3	0.013
WCC (x10^9/L)	7.6 (6.3-8.6)	7.1 (6.1-8.2)	0.008
Platelets (x10^9/L)	218 (180-253)	229 (195-267)	0.009
Medication			
ß-blocker	61 (38%)	827 (22%)	<0.0001
ACE inhibitor	62 (38%)	1125 (31%)	0.045
ARB	70 (43%)	1734 (47%)	0.34
ACE inhibitor or ARB	124 (77%)	2725 (74%)	0.52
CCB	51 (31%)	997 (27%)	0.24
Statin	97 (60%)	1895 (51%)	0.037
Thiazide diuretic	48 (30%)	1133 (31%)	0.79
Loop diuretic	19 (11.7%)	90 (2.4%)	<0.0001
Aspirin	73 (45%)	1528 (42%)	0.37
NSAID	23 (14.2%)	301 (8.2%)	0.013
Clopidogrel	19 (11.7%)	221 (6.0%)	0.0069

Warfarin	20 (12.3%)	158 (4.3%)	<0.0001

Data summarised as means±SD, medians (interquartile range), or n (%). ACE, angiotensin converting enzyme; AF, atrial fibrillation; ARB, angiotensin II type 1 receptor blocker; BMI, body mass index; CCB, calcium channel blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation;[13] HF, heart failure; NSAID, non-steroidal anti-inflammatory drug; OSA, obstructive sleep apnoea; PP, pulse pressure; PVD, peripheral vascular disease; SBP, systolic blood pressure; TIA, transient ischaemic attack; WCC, white cell count. Alcohol >2 drinks/day refers to consumption of more than 2 standard drinks on any day.[32]

Table 2. Baseline serum NT-proBNP levels of SCREEN-HF participants who developed new onset heart failure, and of participants who did not develop heart failure during follow-up.

		Age (years)		
	Total	60-69	70-79	≥80
No heart failure, men and women				
n	3680	1895	1445	340
NT-proBNP (pmol/L, median)	11.8	8.4	14.8	24.7
IQR	6.1-22.2	4.5-15.7	8.1-27.5	15.8-49.1
Developed heart failure, men and women				
n	162	36	87	39
NT-proBNP (pmol/L, median)	36.0	23.2	32.2	70.0
IQR	20.0-75.3	11.6-52.2	19.8-55.5	31.7-107.3
P	<0.0001	<0.0001	<0.0001	<0.0001
No heart failure, men				
n	2000	1024	8.8	168
NT-proBNP (pmol/L, median)	9.8	7.0	12.8	24.2
IQR	5.1-19.5	3.9-13.1	7.0-24.3	15.5-50.0
No heart failure, women				

n	1680	871	637	172
NT-proBNP (pmol/L, median)	13.9	10.2	16.9	26.3
IQR	7.7-24.9	5.9-17.3	10.5-30.6	16.5-48.8
P	<0.0001	<0.0001	<0.0001	0.72
Developed heart failure, men				
n	98	21	58	19
NT-proBNP (pmol/L, median)	38.2	22.6	31.0	87.4
IQR	16.4-78.8	10.1-54.9	16.5-53.5	58.4-121.5
Developed heart failure, women				
n	64	15	29	20
NT-proBNP (pmol/L, median)	35.2	29.2	35.2	41.0
IQR	22.9-71.7	12.3-38.7	23.0-70.3	25.9-87.0
P	0.97	0.85	0.51	0.07

Data summarised as medians and interquartile range (IQR). *P* values calculated with Mann-Whitney U test. There were statistically significant differences in NT-proBNP levels between the three age groups for men and women combined, and also when men and women were analysed separately by Mann-Whitney U test ($P<0.0001$).

Table 3. Change in serum NT-proBNP levels during follow-up in participants who did not develop heart failure during follow-up, and in participants who developed heart failure, before and after heart failure diagnosis.

		Age (years)		
	Total	60-69	70-79	≥80
Change in NT-proBNP levels during 1-2 years of follow-up				
A: No HF, median time between NT-proBNP measurements: 1.5 (IQR: 1.3, 1.7) years				
n	1114	672	379	63
Change in NT-proBNP (pmol/L, median)	0.7	0.5	0.9	2.5
IQR	-2.4-3.7	-2.4-3.2	-2.4-4.4	-1.9-9.8
B: Before HF diagnosis, median time between NT-proBNP measurements: 1.7 (IQR: 1.5, 1.8) years				
n	27	10	13	4
Change in NT-proBNP (pmol/L, median)	1.4	-1.3	2.7	3.2
IQR	-3.6-7.4	-3.8-3.7	-3.9-9.9	-6.1-6.6
P	0.76	0.70	0.67	0.83
Change in NT-proBNP levels during >2 years of follow-up*				
C: No HF, median time between NT-proBNP measurements: 4.5 (IQR: 3.7, 5.6) years				
n	4952	2764	1889	299

Change in NT-proBNP (pmol/L, median)	3.4	2.3	5.0	10.2
IQR	-0.6-11.9	-1.1-8.6	0-15.8	1.3-36.2

D: Before HF diagnosis, median time between NT-proBNP measurements: 4.8 (IQR: 3.5, 5.6) years

n	59	12	37	10
Change in NT-proBNP (pmol/L, median)	13.2	13.2	13.2	30.1
IQR	3.6-55.0	4.6-62.9	0.3-29.4	6.0-67.4
P	<0.0001	0.02	0.06	0.20

E: Change in serum NT-proBNP level between pre- and post-heart failure diagnosis; median time between NT-proBNP measurements: 5.0 (IQR: 3.9, 5.8) years

n	60	14	38	8
Change in NT-proBNP (pmol/L, median)	49.3	53.4	45.0	99.4
IQR	13.7-143.4	6.8-99.8	14.3-144.7	25.9-296.6
P†	0.0012	0.44	0.0036	0.0756

Data summarised as medians and interquartile range (IQR). A and C refer to participants who did not develop HF during follow-up; B and D refer to participants who developed HF, but the data for change in NT-proBNP level were obtained before HF diagnosis; E refers to participants for whom NT-proBNP levels were measured before and after HF diagnosis. *P* values calculated with Mann-Whitney U test.

*, The numbers include follow-up intervals between Visit 1 and Visit 2, between Visit 2 and Visit 3, and between Visit 1 and Visit 3, where these visits were before heart failure (HF) diagnosis.

†, comparison with pre-HF follow-up >2 years (Group D).

Table 4. Sensitivities, specificities, positive and negative predictive values for different NT-proBNP cut points for classification of heart failure risk according to sex, BMI, eGFR and CVD.

	Age (years)		
	60-69	70-79	≥80
NT-proBNP cut point (pmol/L)	11	16	25
Men and women combined (n=HF/total)	n=36/1931	n=87/1532	n=39/379
Sensitivity	77.8%	79.3%	82.1%
Specificity	61.8%	54.4%	50.3%
Positive predictive value	3.7%	9.5%	15.9%
Negative predictive value	99.3%	97.8%	96.1%
Men (n=HF/total)	n=21/1045	n=58/866	n=19/187
Sensitivity	76.2%	77.6%	84.2%
Specificity	69.2%	59.7%	53.0%
Positive predictive value	4.8%	12.1%	16.8%
Negative predictive value	99.3%	97.4%	96.7%
Women (n=HF/total)	n=15/886	n=29/666	n=20/192
Sensitivity	80%	82.8%	80.0%
Specificity	53.2%	47.7%	47.7%

Positive predictive value	2.9%	6.7%	15.1%
Negative predictive value	99.4%	98.4%	95.3%
BMI <30 kg/m^2 (n=HF/total)	n=20/1236	n=42/1061	n=29/303
Sensitivity	75.0%	83.3%	89.7%
Specificity	62.9%	53.6%	48.5%
Positive predictive value	3.2%	6.9%	15.6%
Negative predictive value	99.4%	98.7%	97.8%
BMI e30 kg/m^2 (n=HF/total)	n=16/693	n=45/471	n=10/75
Sensitivity	81.3%	75.6%	60.0%
Specificity	60.0%	56.3%	58.5%
Positive predictive value	4.6%	15.5%	18.2%
Negative predictive value	99.3%	95.6%	90.5%
eGFR <60 ml/min/1.73m^2 (n=HF/total)	n=6/208	n=31/400	21/176
Sensitivity	66.7%	83.9%	66.7%
Specificity	51.5%	44.2%	41.9%
Positive predictive value	3.9%	11.2%	13.5%
Negative predictive value	98.1%	97.0%	90.3%
eGFR e60 ml/min/1.73m^2 (n=HF/total)	n=30/1723	56/1132	18/203
Sensitivity	80.0%	76.8%	100.0%

Specificity	63.1%	57.9%	57.3%
Positive predictive value	3.7%	8.7%	18.6%
Negative predictive value	99.4%	98.0%	100.0%
No AF on enrolment (n=HF/total)	n=27/1776	n=70/1352	n=28/321
Sensitivity	77.8%	74.3%	78.6%
Specificity	64.4%	57.5%	54.9%
Positive predictive value	3.3%	8.7%	14.3%
Negative predictive value	99.5%	97.6%	96.4%
AF on enrolment (n=HF/total)	n=9/155	n=17/180	n=11/58
Sensitivity	77.8%	100%	90.9%
Specificity	28.1%	30.1%	21.3%
Positive predictive value	6.5%	13.0%	21.3%
Negative predictive value	95.7%	100%	90.9%
No pacemaker on enrolment (n=HF/total)	n=34/1918	n=86/1495	n=35/363
Sensitivity	76.5%	79.1%	82.9%
Specificity	62.0%	55.0%	51.5%
Positive predictive value	3.5%	9.7%	15.4%
Negative predictive value	99.3%	97.7%	96.6%

Pacemaker on enrolment (n=HF/total)	n=2/13	n=1/37	n=4/16
Sensitivity	100%	100%	75.0%
Specificity	27.3%	30.6%	16.7%
Positive predictive value	20.0%	3.8%	23.1%
Negative predictive value	100%	100%	66.7%
No known CVD on enrolment (n=HF/total)	n=23/1477	n=42/961	n=15/197
Sensitivity	78.3%	71.4%	80.0%
Specificity	63.5%	58.8%	55.5%
Positive predictive value	3.3%	7.3%	12.9%
Negative predictive value	99.5%	97.8%	97.1%
Known CVD on enrolment (n=HF/total)	n=13/454	n=45/571	n=24/182
Sensitivity	76.9%	86.7%	83.3%
Specificity	56.5%	46.8%	44.3%
Positive predictive value	5.0%	12.2%	18.5%
Negative predictive value	98.8%	97.6%	94.6%

n = number of participants who developed HF/total number of participants in each category. AF, atrial fibrillation; BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated

glomerular filtration rate. CVD refers to total ischaemic heart, cerebrovascular and peripheral vascular disease.

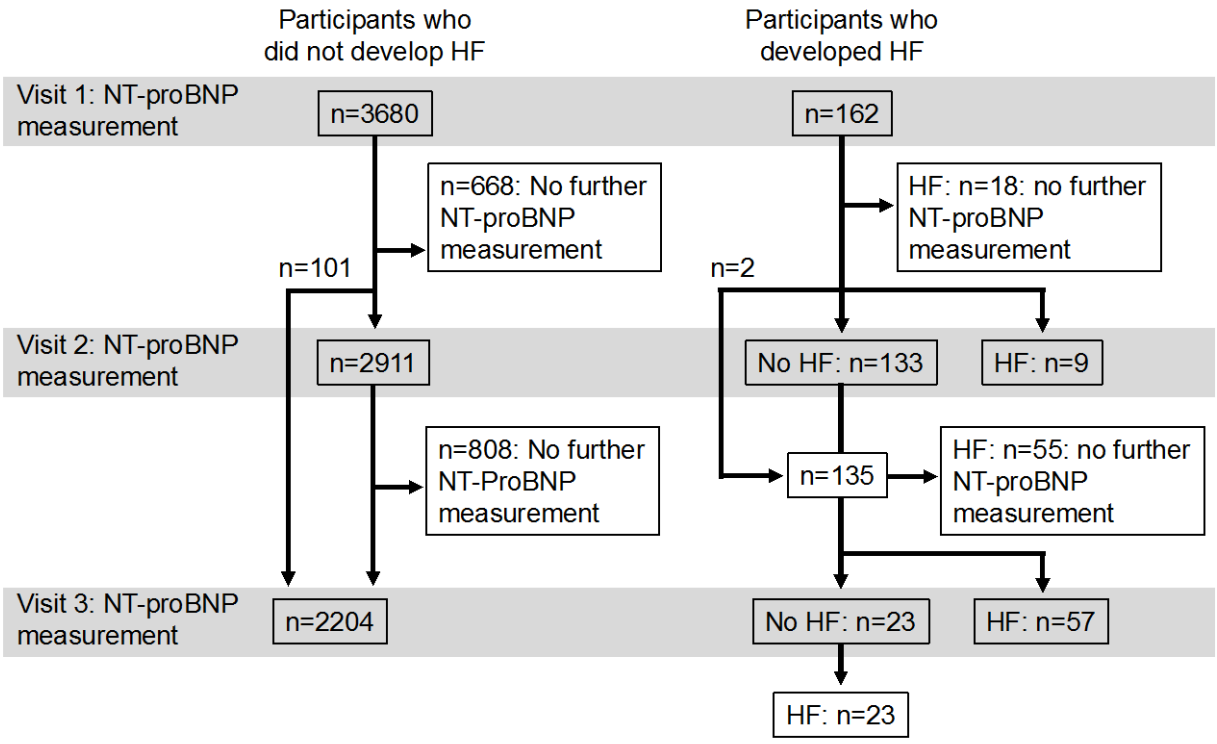

Figure 1. Flow chart of participant visits and NT-proBNP measurements for SCREEN-HF participants who did not develop HF and for participants who developed HF during follow-up. NT-proBNP levels were measured in 3842 participants on enrolment, and repeated at Visit 2 (n=3053) and Visit 3 (n= n=2284). Visit 2 was 1.3 (median, interquartile range: 0.5-1.9) years after enrolment and Visit 3 was 5.6 (4.9-6.1) years after enrolment. Twenty three participants developed HF after Visit 3.

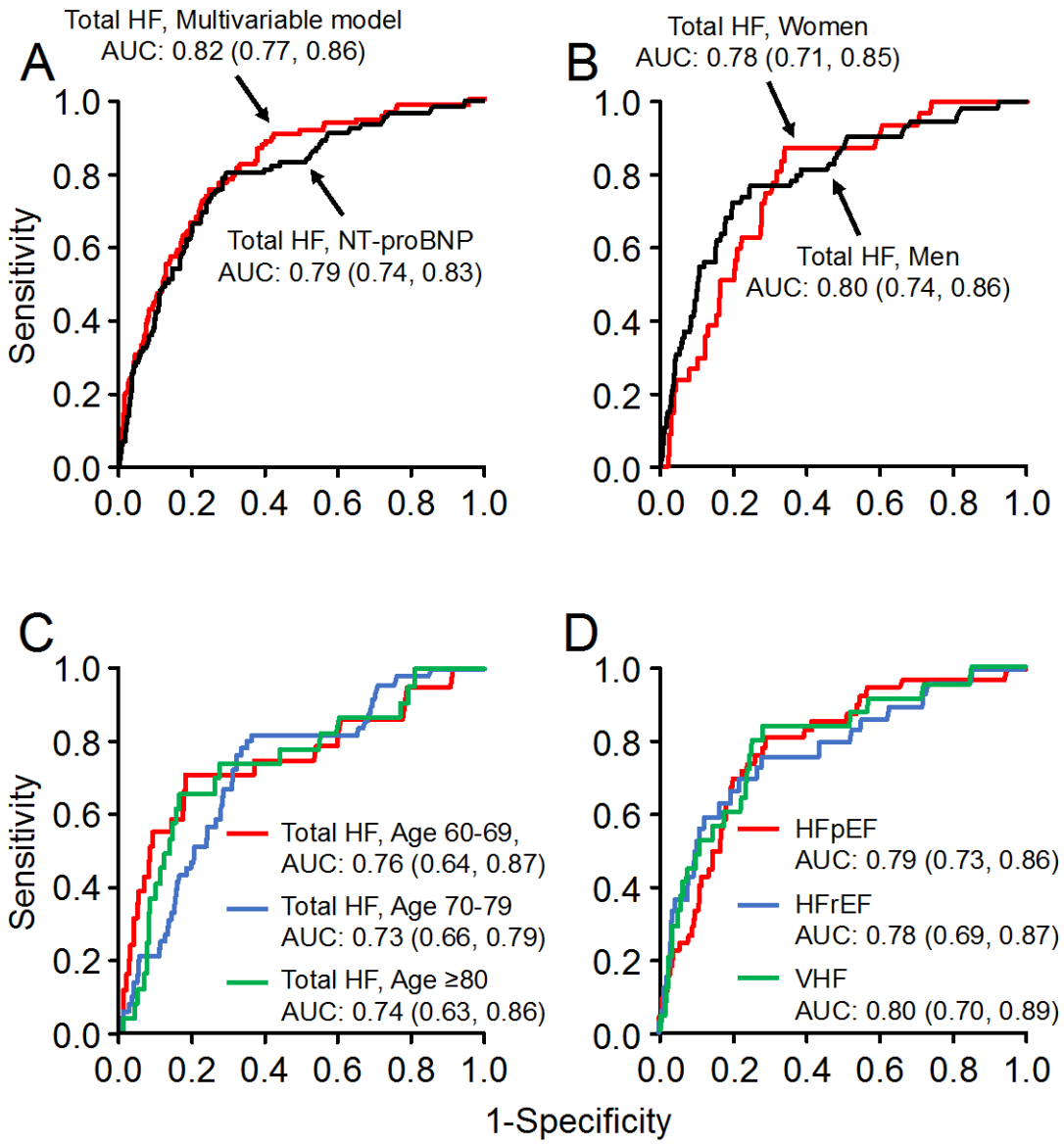

Figure 2. Time-dependent receiver operating characteristic (ROC) curves for the prediction of incident HF in SCREEN-HF participants. (*A*) ROC curves for 5-year prediction of total HF by a 7-parameter multivariable model (NT-proBNP quintile, age, log BMI, and diabetes, prior MI, obstructive sleep apnoea and smoking status) and by serum NT-proBNP levels alone (100 HF events). (*B*) ROC curves for 5-year prediction of total HF by serum NT-proBNP levels alone in men (67 HF events) and women (33 events). (*C*) ROC curves for 5-year incidence of total HF in

participants aged 60-69 years (25 HF events), 70-79 years (51 HF events), and ≥80 years (24 HF events). (*D*) ROC curves for 5-year prediction of HFpEF (44 HF events), HFrEF (31 HF events) and VHF (25 HF events). ROC curves were censored for event times with competing risks and areas under the curve (AUC) are shown with 95% confidence intervals.[14]

Supporting Information

Figure S1. Change in AUC for the prediction of total incident HF in SCREEN-HF participants by baseline serum NT-proBNP levels over time. (*A*) Change in AUC for cumulative events over 6 years of follow-up. AUC (95% confidence interval) for cumulative events were 0.83 (0.65, 1.0), 0.78 (0.68, 0.88) , 0.80 (0.74, 0.86), 0.83 (0.78, 0.87), 0.79 (0.74, 0.83), and 0.77 (0.73, 0.81) for years 1, 2, 3, 4, 5, and 6 respectively. (*B*) Change in AUC for each of the first 6 years of follow-up. AUC for each year of follow-up were of 0.83 (0.65, 1.0), 0.76 (0.64, 0.88) , 0.82 (0.74, 0.89), 0.88 (0.83, 0.92), 0.72 (0.62, 0.82), and 0.78 (0.71, 0.84) for years 1, 2, 3, 4, 5, and 6 respectively. ROC curves were censored for event times with competing risks.[14] Error bars represent 95% confidence intervals.

Figure S2. Change in serum NT-proBNP levels over time for individual SCREEN-HF participants who developed heart failure during follow-up. (*A*) Change in NT-proBNP levels before diagnosis of heart failure for participants who had two or more NT-proBNP measurements ≥ 12 months apart. Each line represents a single individual. (*B*) Change in NT-proBNP levels from the NT-proBNP measurement before heart failure diagnosis to the NT-proBNP measurement after heart failure diagnosis. Each line represents a single individual. Also shown in (*A*) and (*B*) are the baseline NT-proBNP levels (median and interquartile range) for participants aged 60-69, 70-79, and ≥ 80 years who did not develop heart failure during follow-up (blue) and participants who did develop heart failure during follow-up (red).

Table 4. Sensitivities, specificities, positive and negative predictive values for different NT-proBNP cut points for classification of heart failure risk according to sex, BMI, eGFR and CVD.

	Age (years)		
	60-69	70-79	≥80
NT-proBNP cut point (pmol/L)	11	16	25
Men and women combined (n=HF/total)	n=36/1931	n=87/1532	n=39/379
Sensitivity	77.8%	79.3%	82.1%
Specificity	61.8%	54.4%	50.3%
Positive predictive value	3.7%	9.5%	15.9%
Negative predictive value	99.3%	97.8%	96.1%
Men (n=HF/total)	n=21/1045	n=58/866	n=19/187
Sensitivity	76.2%	77.6%	84.2%
Specificity	69.2%	59.7%	53.0%
Positive predictive value	4.8%	12.1%	16.8%
Negative predictive value	99.3%	97.4%	96.7%
Women (n=HF/total)	n=15/886	n=29/666	n=20/192
Sensitivity	80%	82.8%	80.0%
Specificity	53.2%	47.7%	47.7%
Positive predictive value	2.9%	6.7%	15.1%
Negative predictive value	99.4%	98.4%	95.3%

BMI <30 kg/m^2 (n=HF/total)	n=20/1236	n=42/1061	n=29/303
Sensitivity	75.0%	83.3%	89.7%
Specificity	62.9%	53.6%	48.5%
Positive predictive value	3.2%	6.9%	15.6%
Negative predictive value	99.4%	98.7%	97.8%
BMI e30 kg/m^2 (n=HF/total)	n=16/693	n=45/471	n=10/75
Sensitivity	81.3%	75.6%	60.0%
Specificity	60.0%	56.3%	58.5%
Positive predictive value	4.6%	15.5%	18.2%
Negative predictive value	99.3%	95.6%	90.5%
eGFR <60 ml/min/1.73m^2 (n=HF/total)	n=6/208	n=31/400	21/176
Sensitivity	66.7%	83.9%	66.7%
Specificity	51.5%	44.2%	41.9%
Positive predictive value	3.9%	11.2%	13.5%
Negative predictive value	98.1%	97.0%	90.3%
eGFR e60 ml/min/1.73m^2 (n=HF/total)	n=30/1723	56/1132	18/203
Sensitivity	80.0%	76.8%	100.0%
Specificity	63.1%	57.9%	57.3%
Positive predictive value	3.7%	8.7%	18.6%
Negative predictive value	99.4%	98.0%	100.0%

No AF on enrolment (n=HF/total)	n=27/1776	n=70/1352	n=28/321
Sensitivity	77.8%	74.3%	78.6%
Specificity	64.4%	57.5%	54.9%
Positive predictive value	3.3%	8.7%	14.3%
Negative predictive value	99.5%	97.6%	96.4%
AF on enrolment (n=HF/total)	n=9/155	n=17/180	n=11/58
Sensitivity	77.8%	100%	90.9%
Specificity	28.1%	30.1%	21.3%
Positive predictive value	6.5%	13.0%	21.3%
Negative predictive value	95.7%	100%	90.9%
No pacemaker on enrolment (n=HF/total)	n=34/1918	n=86/1495	n=35/363
Sensitivity	76.5%	79.1%	82.9%
Specificity	62.0%	55.0%	51.5%
Positive predictive value	3.5%	9.7%	15.4%
Negative predictive value	99.3%	97.7%	96.6%
Pacemaker on enrolment (n=HF/total)	n=2/13	n=1/37	n=4/16
Sensitivity	100%	100%	75.0%
Specificity	27.3%	30.6%	16.7%
Positive predictive value	20.0%	3.8%	23.1%
Negative predictive value	100%	100%	66.7%

No known CVD on enrolment (n=HF/total)	n=23/1477	n=42/961	n=15/197
Sensitivity	78.3%	71.4%	80.0%
Specificity	63.5%	58.8%	55.5%
Positive predictive value	3.3%	7.3%	12.9%
Negative predictive value	99.5%	97.8%	97.1%
Known CVD on enrolment (n=HF/total)	n=13/454	n=45/571	n=24/182
Sensitivity	76.9%	86.7%	83.3%
Specificity	56.5%	46.8%	44.3%
Positive predictive value	5.0%	12.2%	18.5%
Negative predictive value	98.8%	97.6%	94.6%

n = number of participants who developed HF/total number of participants in each category. AF, atrial fibrillation; BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate. CVD refers to total ischaemic heart, cerebrovascular and peripheral vascular disease.

Permission Note

All material is original to this submission

Table 1. Baseline characteristics of SCREEN-HF participants with serum NT-proBNP measurement at baseline who developed new onset heart failure, and of participants who did not develop heart failure during follow-up.

	HF (n, %) n=162	No HF (n, %) n=3680	*P*-value
Age at enrolment (years)	75 (70-80)	70 (65-75)	<0.0001
Male	98 (60%)	2000 (54%)	0.13
SBP (mmHg)	143±19	141±18	0.06
DBP (mmHg)	79±11	81±10	0.019
PP (mmHg)	65±16	60±15	<0.0001
Heart rate (bpm)	68 (61-76)	70 (63-79)	0.009
BMI (kg/m^2)	29 (26-32)	28 (25-31)	<0.0001
BMI e30 kg/m^2	71 (44%)	1168 (32%)	0.0019
Waist circumference (cm)	104±13	99±13	<0.0001
Hypertension	145 (90%)	3147 (86%)	0.17
Diabetes	44 (27%)	659 (18%)	0.0048
Myocardial infarction	37 (23%)	353 (10%)	<0.0001
Coronary revascularisation	42 (26%)	533 (14%)	0.0002
Stroke/TIA	21 (13%)	399 (11%)	0.37
PVD	15 (9%)	110 (3%)	0.0002
AF	37 (23%)	356 (10%)	<0.0001
Pacemaker	7 (4.3%)	59 (1.6%)	0.020
OSA	21 (13%)	258 (7%)	0.0078
Smoker (current or former)	93 (57%)	1796 (49%)	0.037

Alcohol >2 drinks/day	39 (24%)	723 (20%)	0.19
Biochemistry and haematology			
NT-proBNP (pmol/L)	36.0 (20.0-75.3)	11.8 (6.1-22.2)	<0.0001
eGFR (ml/min/1.73m^2)	67±18	73±17	<0.0001
Haemoglobin (g/dL)	13.7±1.6	14.0±1.3	0.013
WCC (x10^9/L)	7.6 (6.3-8.6)	7.1 (6.1-8.2)	0.008
Platelets (x10^9/L)	218 (180-253)	229 (195-267)	0.009
Medication			
ß-blocker	61 (38%)	827 (22%)	<0.0001
ACE inhibitor	62 (38%)	1125 (31%)	0.045
ARB	70 (43%)	1734 (47%)	0.34
ACE inhibitor or ARB	124 (77%)	2725 (74%)	0.52
CCB	51 (31%)	997 (27%)	0.24
Statin	97 (60%)	1895 (51%)	0.037
Thiazide diuretic	48 (30%)	1133 (31%)	0.79
Loop diuretic	19 (11.7%)	90 (2.4%)	<0.0001
Aspirin	73 (45%)	1528 (42%)	0.37
NSAID	23 (14.2%)	301 (8.2%)	0.013
Clopidogrel	19 (11.7%)	221 (6.0%)	0.0069
Warfarin	20 (12.3%)	158 (4.3%)	<0.0001

Data summarised as means±SD, medians (interquartile range), or n (%). ACE, angiotensin converting enzyme; AF, atrial fibrillation; ARB, angiotensin II type 1 receptor blocker; BMI, body mass index; CCB, calcium channel blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation;[13] HF, heart failure; NSAID, non-steroidal

anti-inflammatory drug; OSA, obstructive sleep apnoea; PP, pulse pressure; PVD, peripheral vascular disease; SBP, systolic blood pressure; TIA, transient ischaemic attack; WCC, white cell count. Alcohol >2 drinks/day refers to consumption of more than 2 standard drinks on any day.[27]

Table 2. Baseline serum NT-proBNP levels of SCREEN-HF participants who developed new onset heart failure, and of participants who did not develop heart failure during follow-up.

		Age (years)		
	Total	60-69	70-79	≥80
No heart failure, men and women				
n	3680	1895	1445	340
NT-proBNP (pmol/L, median)	11.8	8.4	14.8	24.7
IQR	6.1-22.2	4.5-15.7	8.1-27.5	15.8-49.1
Developed heart failure, men and women				
n	162	36	87	39
NT-proBNP (pmol/L, median)	36.0	23.2	32.2	70.0
IQR	20.0-75.3	11.6-52.2	19.8-55.5	31.7-107.3
P	<0.0001	<0.0001	<0.0001	<0.0001
No heart failure, men				
n	2000	1024	8.8	168
NT-proBNP (pmol/L, median)	9.8	7.0	12.8	24.2
IQR	5.1-19.5	3.9-13.1	7.0-24.3	15.5-50.0
No heart failure, women				
n	1680	871	637	172
NT-proBNP (pmol/L, median)	13.9	10.2	16.9	26.3
IQR	7.7-24.9	5.9-17.3	10.5-30.6	16.5-48.8

P	<0.0001	<0.0001	<0.0001	0.72
Developed heart failure, men				
n	98	21	58	19
NT-proBNP (pmol/L, median)	38.2	22.6	31.0	87.4
IQR	16.4-78.8	10.1-54.9	16.5-53.5	58.4-121.5
Developed heart failure, women				
n	64	15	29	20
NT-proBNP (pmol/L, median)	35.2	29.2	35.2	41.0
IQR	22.9-71.7	12.3-38.7	23.0-70.3	25.9-87.0
P	0.97	0.85	0.51	0.07

Data summarised as medians and interquartile range (IQR). *P* values calculated with Mann-Whitney U test. There were statistically significant differences in NT-proBNP levels between the three age groups for men and women combined, and also when men and women were analysed separately by Mann-Whitney U test ($P<0.0001$).

Table 3. Change in serum NT-proBNP levels during follow-up in participants who did not develop heart failure during follow-up, and in participants who developed heart failure, before and after heart failure diagnosis.

		Age (years)		
	Total	60-69	70-79	≥80
Change in NT-proBNP levels during 1-2 years of follow-up				
A: No HF, median time between NT-proBNP measurements: 1.5 (IQR: 1.3, 1.7) years				
n	1114	672	379	63
Change in NT-proBNP (pmol/L, median)	0.7	0.5	0.9	2.5
IQR	-2.4-3.7	-2.4-3.2	-2.4-4.4	-1.9-9.8
B: Before HF diagnosis, median time between NT-proBNP measurements: 1.7 (IQR: 1.5, 1.8) years				
n	27	10	13	4
Change in NT-proBNP (pmol/L, median)	1.4	-1.3	2.7	3.2
IQR	-3.6-7.4	-3.8-3.7	-3.9-9.9	-6.1-6.6
P	0.76	0.70	0.67	0.83
Change in NT-proBNP levels during >2 years of follow-up*				
C: No HF, median time between NT-proBNP measurements: 4.5 (IQR: 3.7, 5.6) years				
n	4952	2764	1889	299
Change in NT-proBNP (pmol/L, median)	3.4	2.3	5.0	10.2

IQR	-0.6-11.9	-1.1-8.6	0-15.8	1.3-36.2

D: Before HF diagnosis, median time between NT-proBNP measurements: 4.8 (IQR: 3.5, 5.6) years

n	59	12	37	10
Change in NT-proBNP (pmol/L, median)	13.2	13.2	13.2	30.1
IQR	3.6-55.0	4.6-62.9	0.3-29.4	6.0-67.4
P	<0.0001	0.02	0.06	0.20

E: Change in serum NT-proBNP level between pre- and post-heart failure diagnosis; median time between NT-proBNP measurements: 5.0 (IQR: 3.9, 5.8) years

n	60	14	38	8
Change in NT-proBNP (pmol/L, median)	49.3	53.4	45.0	99.4
IQR	13.7-143.4	6.8-99.8	14.3-144.7	25.9-296.6
P†	0.0012	0.44	0.0036	0.0756

Data summarised as medians and interquartile range (IQR). A and C refer to participants who did not develop HF during follow-up; B and D refer to participants who developed HF, but the data for change in NT-proBNP level were obtained before HF diagnosis; E refers to participants for whom NT-proBNP levels were measured before and after HF diagnosis. *P* values calculated with Mann-Whitney U test.

*, The numbers include follow-up intervals between Visit 1 and Visit 2, between Visit 2 and Visit 3, and between Visit 1 and Visit 3, where these visits were before heart failure (HF) diagnosis.

†, comparison with pre-HF follow-up >2 years (Group D).

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