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Title Page

The potential role of NT-proBNP in screening for and predicting prognosis in heart failure: a survival analysis.

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Abstract

Objectives: To determine the potential role of N-terminal B type natriuretic peptide (NT-proBNP) in screening for and predicting prognosis in heart failure by examining diagnosis and survival of patients with a raised NT-proBNP at screening.

Design: Survival analysis.

Setting: Prospective sub-study of the Echocardiographic Heart of England Screening study (ECHOES) to investigate ten-year survival in participants with a NT-proBNP level at baseline.

Participants: 594 participants took part in the sub-study. Records of all participants in the ECHOES cohort were flagged during the screening phase which ended 25th February 1999. All deaths until 25th February 2009 were coded.

Outcome measures: Logistic regression was used to examine whether BNP is useful in predicting heart failure at screening after adjustment for age, sex and cohort. Kaplan Meier curves and log rank tests were used to compare survival times of participants according to NT-proBNP level. Cox regression was carried out to assess the prognostic effect of NT-ProBNP after allowing for significant covariates and receiver operator curves were used to determine test reliability.

Results: The risk of heart failure increased almost 18-fold when NT-proBNP was 150pg/ml or above (adjusted odds ratio=17.7 (95% CI 4.9 to 63.5). Ten-year survival in the general population cohort was 61% (95% CI 48% to 71%) for those with NT-proBNP>=150pg/ml and 89% (95% CI 84% to 92%) for those below the cut-off at the time of the initial study. After adjustment for age, sex and risk factors for heart failure, NT-proBNP level >= 150pg/ml was associated with a 58% increase in the risk of death within 10 years (adjusted hazard ratio=1.58, 95% CI 1.09 to 2.30).

Conclusions: Raised NT-proBNP levels, when screening the general population, are predictive of a diagnosis of heart failure (at a lower threshold than guidelines for diagnosing symptomatic patients) and also predicted reduced survival at 10 years.

Keywords
Heart failure, Prognosis, Natriuretic peptides, Screening, Diagnosis

Article Summary

Article focus
To examine the role of natriuretic peptides in predicting a subsequent diagnosis of heart failure and survival over the next decade.

Key messages

In the Echocardiographic Heart of England Screening (ECHOES) study, N-terminal B type natriuretic peptide (NT-proBNP) levels above 150pg/ml were associated with both a diagnosis of heart failure at screening and reduced survival at ten years.

Strengths and limitations of the study

The ECHOES cohort represents a well-phenotyped group with accurate mortality data.

Not all participants in the ECHOES cohort had a NT-proBNP measurement but the characteristics of the subgroup were similar to the whole cohort so are likely to be generalisable.

Manuscript

Introduction

Biomarkers can be useful in diagnosis, treatment monitoring and to inform prognosis.[1 2 3] B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are released by the ventricles of the heart in response to volume and pressure overload. BNP relaxes vascular smooth muscle to reduce ventricular preload and acts on the kidney to increase sodium excretion and induce diuresis.[4] NT-proBNP is an inactive fragment of the cleaved pro-BNP molecule. Both peptides have been investigated for use in diagnosis of heart failure and left ventricular systolic dysfunction (LVSD).[5 6] NT-pro-BNP and BNP assays have been found to be equally reliable for diagnostic use.[7] Raised natriuretic peptide levels have consistently been associated with increased mortality in patients with heart failure.[8 9] There may also be a role for these assays in determining prognosis in patients with and without heart failure.[10]

The Echocardiographic Heart of England Screening (ECHOES) study was a large heart failure screening study carried out in central England.[11] All ECHOES participants underwent a detailed initial clinical assessment to screen for evidence of heart failure. Diagnosis was determined after blinded adjudication by a panel of 3 heart failure specialists using all the clinical and investigation data available from the screening. All deaths were collated from routine mortality data. We previously reported the 10-year prognosis of all patients in the ECHOES study according to presence or absence of heart failure and LVSD.[12] This analysis uses data from ECHOES to examine the role of NT-proBNP in predicting a diagnosis of heart failure at screening and also the relationship between NT-proBNP and survival in the following decade.

Methods

The original ECHOES study screened a total of 6162 participants from sixteen practices in Central England. Four practices were randomly selected from each of the four socio-economic groups defined using the Townsend deprivation score. This resulted in a socio-economically diverse population, likely to be representative of the broader UK population. ECHOES included four separate cohorts: 3960 patients randomly sampled from the general population over age 45; 782 patients with a previous label of heart failure recorded in GP notes; 928 patients on diuretic therapy; and 1062 with known risk factors for heart disease (hypertension, diabetes, angina, history of myocardial infarction). Patients underwent assessment (history, examination, electrocardiogram and echocardiography) to screen for evidence of heart failure.

A substudy involving 594 ECHOES participants was also carried out to investigate the role of NT-proBNP in diagnosis and prognosis of heart failure. Fuller methods are available in an earlier publication[11] but in brief, participants came from 4 general practices, across the Townsend scale; 309 were sampled from the general population, 103 with a previous label of heart failure, 88 on diuretic therapy and 134

with risk factors of heart disease with some patients belonging to more than one cohort.

During the ECHOES study, which ran from March 1995 to February 1999, the records of all participants were flagged by the Office for National Statistics (ONS) Central Register Office. The ONS has provided details of the date and cause of death for all ECHOES participants since then. The final participant in the original ECHOES cohort was screened on 25th February 1999 and all deaths up to the 25th February 2009 had been notified to the research team. This allowed an estimate of 10-year prognosis for patients in ECHOES including those from the NT-proBNP study. All data from the original ECHOES cohort were recorded in a restricted access database. The statistical packages SPSS and Stata 10 were used to analyse the data.

Analytical methods

Area under the receiver operating curves (AUROC) were calculated, for each cohort, to measure the natriuretic peptide's performance in predicting heart failure at screening. Multiple logistic regression was then performed, using all cohorts combined, to examine whether BNP was predictive of heart failure, after adjustment for the sampling structure and other significant predictors. Variables in the final model were selected using the backward elimination method with significance level set at 0.05.

Variables considered in the analysis included NT-proBNP, age, sex, body mass index (BMI), smoking status, blood pressure, individual risk factors for heart failure (hypertension, angina, MI, diabetes), symptoms (tiredness, shortness of breath, ankle oedema), prescribed drugs (beta-blockers, ace inhibitors, ARBs and diuretics); and whether a previous label of heart failure was recoded. Two-way interactions with natriuretic peptide were also considered. The cohort-related variables were kept in the final model to allow for the sampling structure. To improve the precision of the estimates, bootstrapped confidence intervals for odds ratios were calculated using 1000 replications.

Survival analysis was carried out, by each cohort, using Kaplan-Meier curves to demonstrate survival in those with an NT-proBNP level >= 150pg/ml. Log rank tests were used to compare survival between the different groups. The mean survival times were calculated rather than median since data was censored for more than 50% of cases. Estimation of the mean is limited to the largest survival time if data were censored.

Cox regression was then undertaken, using all 594 participants, to assess the prognostic ability of NT-proBNP after allowing for each cohort and other covariates. Variables entered into the starting model are as described previously with the addition of atrial fibrillation, ejection fraction and significant valve disease. Fractional polynomials were considered when comparing models of best fit for continuous variables of age, BMI and blood pressure. The proportional hazards assumption was tested using Schoenfeld residuals.

Results

NT-proBNP levels were measured in 594 participants during the ECHOES study. A heart failure diagnosis was confirmed for 7 (8%) of those in the general population sample; 36 (35%) of those with a previous label of heart failure; 15 (17%) of those on diuretics; and 9 (7%) of those at high risk. Twenty three (43%) of all those with a heart failure diagnosis had an ejection fraction of less than 40% and an additional 10 persons (19%) had ejection fraction of between 40 and 49%.

The baseline characteristics of all participants in the sub-study, broken down by cohort and NT-proBNP 150pg/ml cut-off are shown in table 1. Those in the upper NT-proBNP category were older, had more cardiovascular risk factors and took more medication than those below 150pg/ml. They also, with exception of those from the cohort with previous label of heart failure, had more symptoms of heart failure.

The distributions of NT-proBNP in each cohort are given in table 2. The general population had the lowest values with more than 75% below 150pg/ml. Highest levels were observed in the cohort with a previous label of heart failure.

TABLE 1
TABLE 2

Figures 1 to 4 show the Receiver Operating Curves for assessing the performance of NT-proBNP in diagnosing heart failure in each of the cohorts. The area under the receiver operating curve (AUROC) for NT-proBNP levels above 150 pg/ml was 0.95 (95%CI 0.88 to 1.00) for the general population; 0.83 (0.75 to 0.91) for those with previous label of HF; 0.91(0.82 to 1.00) for those on diuretics; and 0.88 (0.80 to 0.97 for those at risk of heart failure]. The cut-off for NT-proBNP at 150pg/ml had sensitivity of 100% (95% CI (59.0% to 100%)) and specificity of 79.5% (95%CI(74.5% to 83.9%)) in identifying heart failure in the general population sample; [97.2%(85.5% to 99.9%) sensitivity and 29.9%(19.3% to 42.3%) specificity for those with previous label of HF; 93.3%(68.1% to 99.8%) sensitivity and 43.8%(32.2% to 55.9%) specificity for those on diuretics; and 100%(66.4% to 100%) sensitivity and 53.6%(44.5% to 62.6%) specificity for those at high risk]. Other cut-offs were not considered in this analysis due to the high sensitivity and reasonable specificity observed using the chosen cut-off. Overall, a cut-off of 150pg/ml found 100% of heart failure cases and 80% of non-heart failure cases. The percentage of deaths at 10 years with NT-proBNP >=150pg/ml at baseline was 50% in the general population, 86% in HF label group, 71% in the high risk group and 84% in the diuretics group.

FIGURES 1 TO 4

The multiple logistic regression analysis suggests that BNP>150pg/ml is predictive of heart failure (OR=17.7 (95%CI 4.9 to 63.5)) after allowing for cohort related variables (Table 3).

TABLE 3

Cause of death

Cardiovascular disease was the main cause of death in each cohort, ranging from 31% (95%CI 20% to 46%) in the general population to 49% (95% CI 37% to 61%) in the high risk group. The remaining deaths were mainly due to respiratory disease and cancer.

Survival analysis of the general population cohort

There was a statistically significant difference in survival between those who had an NT-proBNP level >= 150pg/ml and those with an NT-proBNP level <150pg/ml in the general population sample (log-rank test, χ^2 =30.4, 1, P<0.0001) as shown in figure 5. Mean survival for those with an NT-proBNP >= 150pg/ml was 8.7 years (95%CI 8.0 to 9.4) compared to 9.9 years (95%CI 9.7 to 10.2) for those with an NT-proBNP <150pg/ml. Ten-year survival was 61% (95%CI 48% to 71%) for those with a NT-proBNP >= 150pg/ml and 89% (95%CI 84% to 92%) for those with NT-proBNP <150pg/ml at the time of the initial study.

FIGURE 5

Survival analysis of the other cohorts

Reduced length of survival was also observed for those above the NT-proBNP cut-off when compared with those below the cut-off in each of the other cohorts (p<0.001). Those sampled with a previous label of HF and with NT-proBNP >= 150pg/ml had a mean survival of 5.8 years (95%CI 5.0 to 6.5) compared to 8.4 years (95%CI 7.1 to 9.7) for those below the cut-off (figure 6). The comparative results for those on diuretics (figure 7) were 7.0 years (6.0 to 7.9) vs 9.5 years (8.7 to 10.4); and those at high risk (figure 8) 8.3 years (7.6 to 9.0) vs. 9.4 years (8.8 to 10.0).

FIGURE 6-8

Cox regression analysis of all cohort data

After adjustment for demographic variables, shortness of breath and NT-proBNP >=150pg/ml was found to increase the risk of death by 58% (HR=1.58 (1.09 to 2.30)).

Table4

Discussion

Summary of main findings

594 participants of the ECHOES study took part in the NT-proBNP substudy. Mean survival time for participants from the general population with an NT-proBNP >= 150pg/ml was over one year less than participants with NT-proBNP < 150pg/ml (8.7 *vs* 9.9 years). The proportion of patients surviving ten years was significantly lower in the group with an NT-proBNP level >= 150pg/ml compared to an NT-proBNP level < 150pg/ml (61% vs 89% respectively in the general population). An NT-proBNP level >= 150pg/ml was strongly predictive of a diagnosis of heart failure at screening and of death in the next ten years.

Strengths and limitations of the study

The ECHOES study represents a unique cohort of patients with well phenotyped heart failure from a community setting. The rigor of clinical assessment means the diagnosis of heart failure is accurate. All participants notes were flagged by ONS to ensure accurate data about date and cause of death were sent to the research team. NT-proBNP levels were not recorded in all participants of the ECHOES study however the baseline characteristics of the NT-proBNP substudy were similar to those of the study population as a whole. Only 3% of participants were non-white which may not accurately reflect the ethnic diversity of the UK population and NT-proBNP levels may vary depending on ethnicity. Renal function was not recorded in this study therefore we were unable to assess the effect of renal impairment on mortality.[13] A cut off of 150pgm/ml was chosen to represent a raised level of NT-proBNP in the substudy however debate exists around the optimal cut off level for NT-proBNP.[14]

Comparison with existing literature

A study by Wang et al investigated the relationship between BNP levels and risk of cardiovascular events or death in 3346 patients from the Framingham cohort who did not have heart failure at baseline.[8] 119 participants died and 79 had a first cardiovascular event during a mean follow-up of 5.2 years. For each one standard deviation increment increase in log BNP level, risk of developing heart failure increased by 77% ($p<0.001$) and risk of death increased by 27% ($p=0.009$).

BNP and NT-proBNP levels also increase with heart failure stage. A study of patients over the age of 45 from the Rochester Epidemiology Study found that mean BNP (rather than NT-proBNP) level was 26pg/ml in patients without heart failure, 32pg/ml in those with risk factors, 53pg/ml in those asymptomatic participants with structural or functional cardiac abnormalities, 137pg/ml in participants with heart failure symptoms and 353pg/ml for participants with severe heart failure. Survival declined progressively for each additional stage of disease.[15]

Another study by Hartmann et al investigated the role of baseline NT-proBNP in predicting mortality and hospitalisation in patients with a diagnosis of heart failure.[9] NT-proBNP levels were recorded in 814 men and 197 women with severe heart failure defined as breathlessness at rest or on minimal exertion and an ejection fraction of less than 25%. They were followed up for a median time of 159 days

(range 1-488 days). A baseline NT-proBNP level above compared to below the median level for the cohort was a strong predictor of all-cause mortality and hospitalisation for heart failure (relative risk 2.4; 95%CI 1.8-3.4; p=0.0001). NT-proBNP has also been found to be an independent predictor of mortality in patients with renal disease.[10]

Implications of future research and practice

In this substudy, participants with a raised NT-proBNP level were more likely to have a confirmed diagnosis of heart failure after screening. Natriuretic peptides are already used in clinical practice to determine the likelihood of heart failure and guide referral for echocardiography however the optimal cut-off level if still unclear.[16 17] The National Institute for Health and Clinical Excellence (NICE) clinical guideline on the management of chronic heart failure recommends an NT-proBNP of 400 pg/ml is used as the threshold to refer for echocardiography in symptomatic patients, whereas the European Society of Cardiology suggest a threshold level of 125 pg/ml to exclude heart failure. Fuat et al showed that a cut-off of 150 pg/ml had a negative predictive value of 92% in a primary care community heart failure clinic, again in symptomatic patients.[18] Our data suggest that the current NICE cut-off is too high and that 150 pg/ml is a more reliable threshold for further investigation, especially since our data includes asymptomatic as well as symptomatic non-presenting patients.

Importantly, participants in the NT-proBNP substudy with a raised NT-proBNP were also more likely to die sooner than participants with a normal NT-proBNP level. These data confirm the potential for incident NT-proBNP tests to indicate patient prognosis in primary care settings as has been confirmed in hospital settings. Assessment of patients to establish the cause of a raised NT-proBNP level such as heart failure or renal disease followed by optimal management using evidence based therapies is crucial to reducing mortality in these high risk patients.

Finally, these data are the first we are aware of that suggest a possible role for natriuretic peptides in population screening for heart failure. Given the late diagnosis in many patients and the asymptomatic nature in early stages, this may be an important finding.

Tables

	General population (n=309)		Previous label of HF (n=103)		On diuretics (n=88)		High risk (n=134)	
Characteristics	NTproBNP < 150 pg/ml (n=240)	NTproBNP >=150pg/ml (n=69)	NTproBNP < 150 pg/ml (n=21)	NTproBNP >=150pg/ml (n=82)	NTproBNP < 150pg/ml (n=33)	NTproBNP >=150pg/ml (n=55)	NTproBNP < 150 pg/ml (n=67)	NTproBNP >=150pg/ml (n=67)
Demographics								
Age at screening [mean (sd) years]	59.6 (8.7)	71.7 (9.7)	72.2 (9.6)	74.7 (8.4)	63.2 (8.8)	74.1 (9.8)	63.2 (8.7)	70.4 (8.2)
Gender, male	130 (54)	31 (45)	9 (43)	47 (57)	24 (73)	26 (47)	43 (64)	33 (49)
Ever Smoked	137 (57)	37 (54)	17 (81)	45 (55)	21 (64)	32 (58)	42 (63)	48 (72)
Body mass index [mean (sd) kg/m^2]	27.0 (4.9)	25.8 (3.8)	31.1 (8.5)	26.6 (4.4)	27.9 (3.5)	26.8 (4.5)	28.4 (4.1)	27.1 (3.8)
Systolic BP [mean(sd)mm/Hg]	149.3 (20.9)	156.1 (23.3)	162.9(18.3)	149.2(26.3)	161.7(22.6)	154.8 (25.2)	155.2 (18.3)	158.7 (23.4)
Diastolic BP [mean(sd)mm/Hg]	85.6 (10.9)	83.6 (9.9)	84.4 (9.5)	78.0 (12.6)	91.7 (10.3)	82.4 (14.2)	83.9 (10.1)	83.6 (11.7)
History								
Diabetes	9 (4)	6 (9)	4 (19)	14 (17)	3 (9)	8 (15)	24 (36)	12 (18)
Myocardial Infarction	5 (2)	7 (10)	4 (19)	26 (32)	2 (6)	8 (15)	16 (24)	36 (54)
Angina	12 (5)	16 (23)	7 (33)	33 (40)	3 (9)	14 (25)	23 (34)	46 (69)
Hypertension	54 (22)	24 (35)	9 (43)	27 (33)	29 (88)	31 (56)	38 (57)	39 (58)
Medication taken								
Diuretics	15 (6)	20 (29)	16 (76)	17 (85)	22 (67)	53 (96)	12 (18)	26 (39)
Ace Inhibitors	12 (5)	5 (7)	4 (19)	39 (48)	10 (30)	20 (36)	19 (28)	18 (27)
ARBs	3 (1)	0 (0)	1 (5)	7 (9)	0 (0)	1 (2)	2 (3)	0 (0)

Beta-blockers	14 (6)	19 (28)	2 (10)	9 (11)	5 (15)	8 (15)	17 (25)	21 (31)
Symptoms								
Shortness of breath	48 (20)	32 (46)	16 (76)	61 (74)	11 (33)	34 (62)	17 (25)	44 (66)
Tired	70 (29)	33 (48)	15 (71)	62 (75)	12 (36)	35 (64)	27 (40)	42 (63)
Ankle swelling	38 (16)	22 (32)	15 (71)	41 (50)	10 (30)	29 (53)	22 (33)	22 (33)
New York Heart Association class								
1	200 (83)	39 (57)	5 (24)	22 (27)	23 (70)	21 (38)	57 (78)	28 (42)
2	35 (15)	23 (33)	11 (52)	30 (37)	7 (21)	21 (38)	10 (15)	29 (43)
3	4 (2)	2 (3)	3 (14)	15 (18)	3 (9)	8 (15)	1 (1)	6 (9)
4	1 (0.4)	5 (7)	2 (10)	15 (18)	0 (0)	5 (9)	4 (6)	4 (6)
Ejection fraction								
<40%	1 (0.4)	4 (6)	1 (5)	20 (24)	1 (3)	6 (11)	1 (1)	9 (13)
40-49%	2 (0.8)	3 (4)	2 (10)	18 (22)	1 (3)	6 (11)	3 (4)	6 (9)
>=50%	237 (98.7)	62 (90)	18 (86)	44 (54)	31 (94)	43 (78)	63 (94)	52 (78)
Diagnosis								
Definite heart failure	0 (0)	7 (10)	1 (5)	35 (43)	1 (3)	14 (25)	0 (0)	9 (13)
Atrial fibrillation	0 (0)	7 (10)	0 (0)	23 (28)	0 (0)	13 (24)	0 (0)	3 (4)
Significant valve disease	0 (0)	5 (7)	1 (5)	9 (11)	0 (0)	7 (13)	0 (0)	3 (4)

Table 1 – Baseline characteristics of patients in the ECHOES NT-proBNP sub-study

Cohort	N	Mean (sd)	Median (IQR)
General population	309	159.7 (334.7)	70.9 (35.3 to 130.1)
Previous label of HF	103	1099.9 (1589.1)	493.6 (204.3 to 1341)
On diuretics	88	653.3 (1149.4)	200 (76.1 to 672.8)
At high risk	134	388.5 (983.1)	160.1 (64.6 to 386.3)

Table 2 Distribution of NT-proBNP in each cohort

Variable	Odds Ratio (95% confidence interval*)	P value
Previous label of HF	3.74 (1.45 to 9.69)	0.007
On diuretics	5.26 (1.70 to 16.31)	0.004
Diabetes	4.91 (1.66 to 14.51)	0.004
Hypertension	0.39 (0.16 to 0.97)	0.04
Angina	1.22 (0.99 to 5.00)	0.053
Myocardial infarction	1.61 (0.67 to 3.86)	0.29
NT-proBNP >=150 pg/ml	17.65 (4.91 to 63.48)	<0.001

*Bootstrapped estimates

Table 3 Logistic regression model to predict heart failure

Variable	Hazard Ratio (95% confidence interval*)	P value
Age	1.10 (1.08 to 1.10)	<0.001
Sex	2.05 (1.43 to 2.95)	<0.001
Previous label of HF	1.75 (1.17 to 2.57)	0.007
On diuretics	0.90 (0.62 to 1.32)	0.59
Diabetes	1.08 (0.65 to 1.88)	0.78
Hypertension	1.37 (0.99 to 1.90)	0.06
Angina	1.04 (0.73 to 1.50)	0.82
Myocardial infarction	1.18 (0.80 to 1.73)	0.40
Shortness of breath	1.64 (1.14 to 2.37)	0.008
NT-proBNP >=150 pg/ml	1.58 (1.09 to 2.30)	0.02

*Bootstrapped estimates

Table 4 Cox regression model of factors associated with mortality

Authors' contributions: F.D.R.H. was principal investigator and established the ECHOES cohort. C.J.T. and F.D.R.H. designed this study. C.J.T. and A.K.R. undertook statistical analysis. C.J.T. and R.I. coded the death data. All authors contributed to the manuscript.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: The NT-proBNP assays for the ECHOES study were provided free of charge by Roche Diagnostics, but Roche were not party to the study design, nor any aspect of the analysis, nor to the write up of this paper. FDRH has received similar indirect research support on other investigator led heart failure research. FDRH has also received occasional fees or expense reimbursement from Roche in the past; no other relationships or activities that could appear to have influenced the submitted work.

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Figures

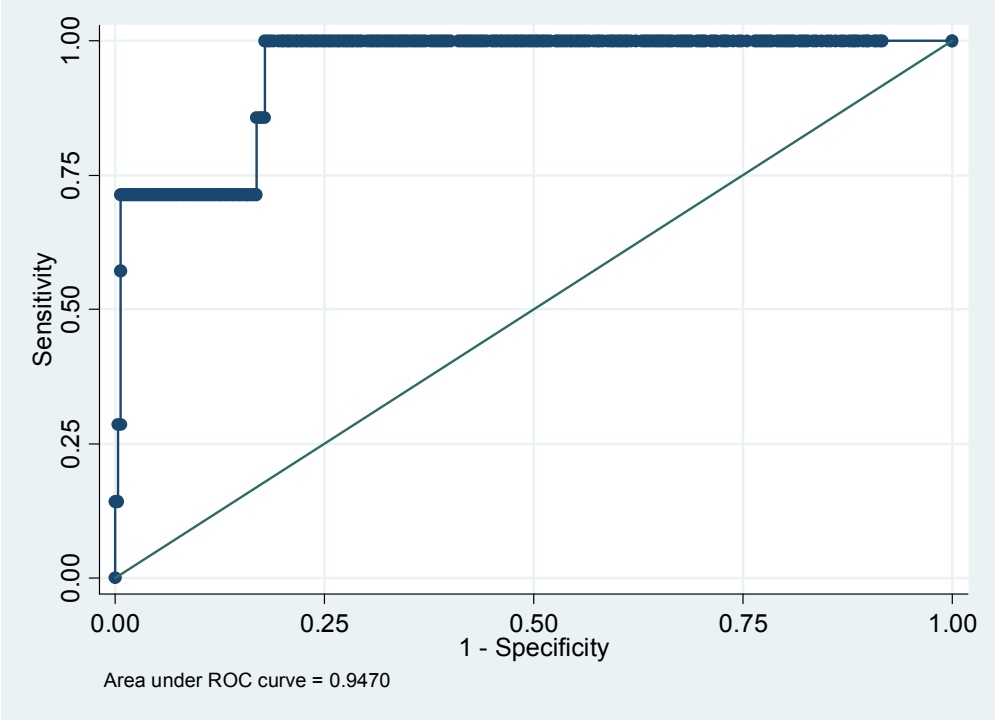

Figure 1 – Receiver operating characteristic curve to show effectiveness of baseline NT-proBNP in predicting a diagnosis of heart failure at screening in the general population cohort

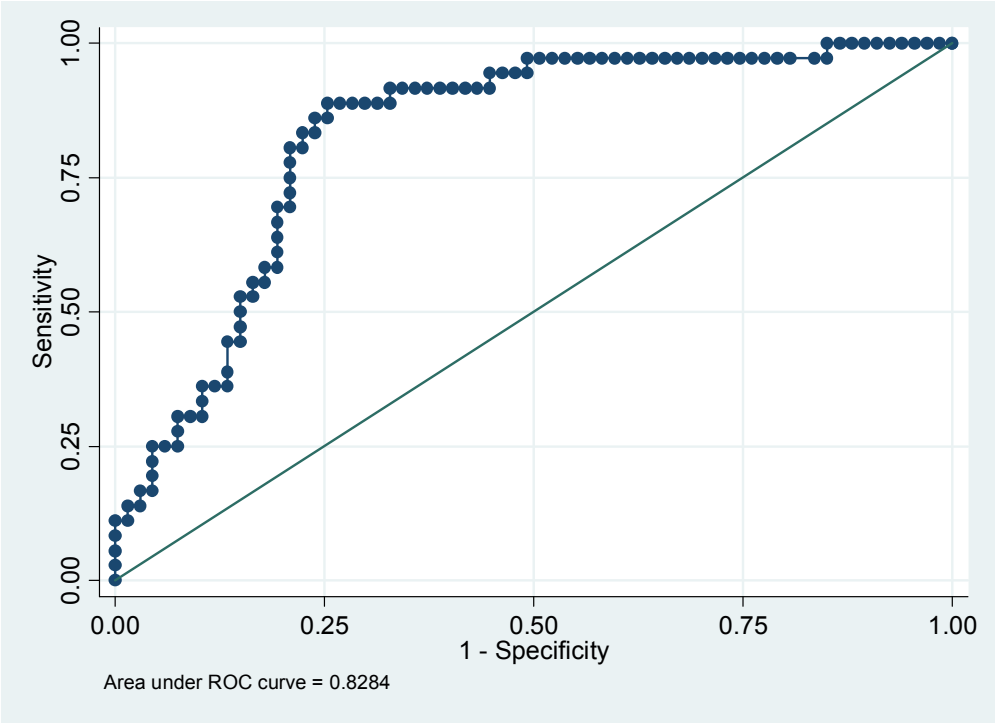

Figure 2. ROC curve for cohort with previous label of heart failure

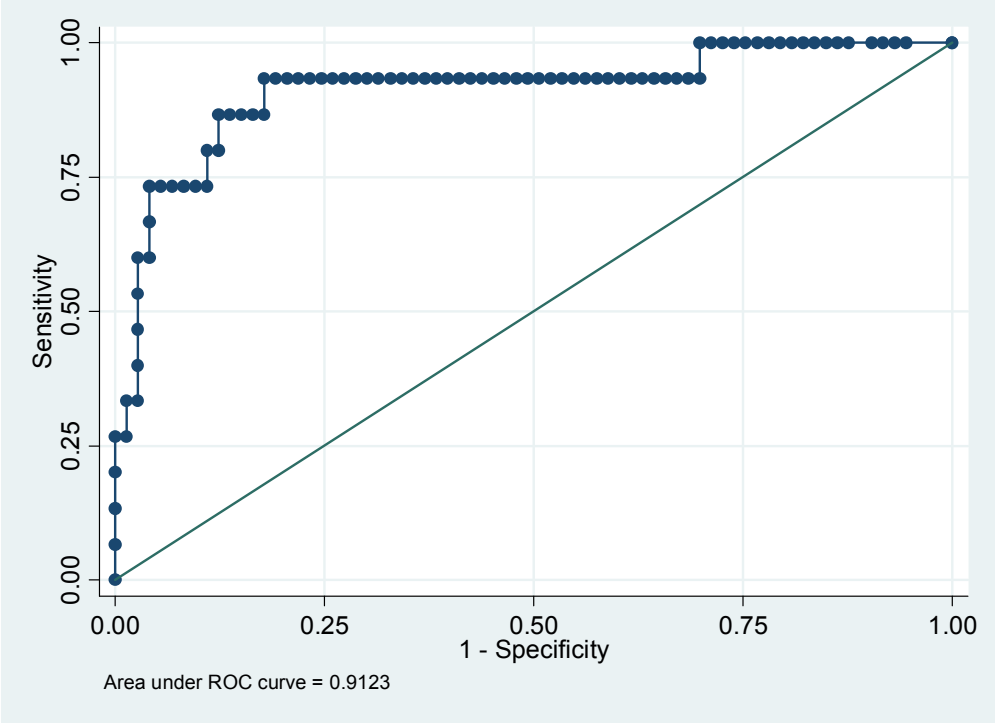

Figure 3. ROC curve for cohort who were on prescribed diuretics

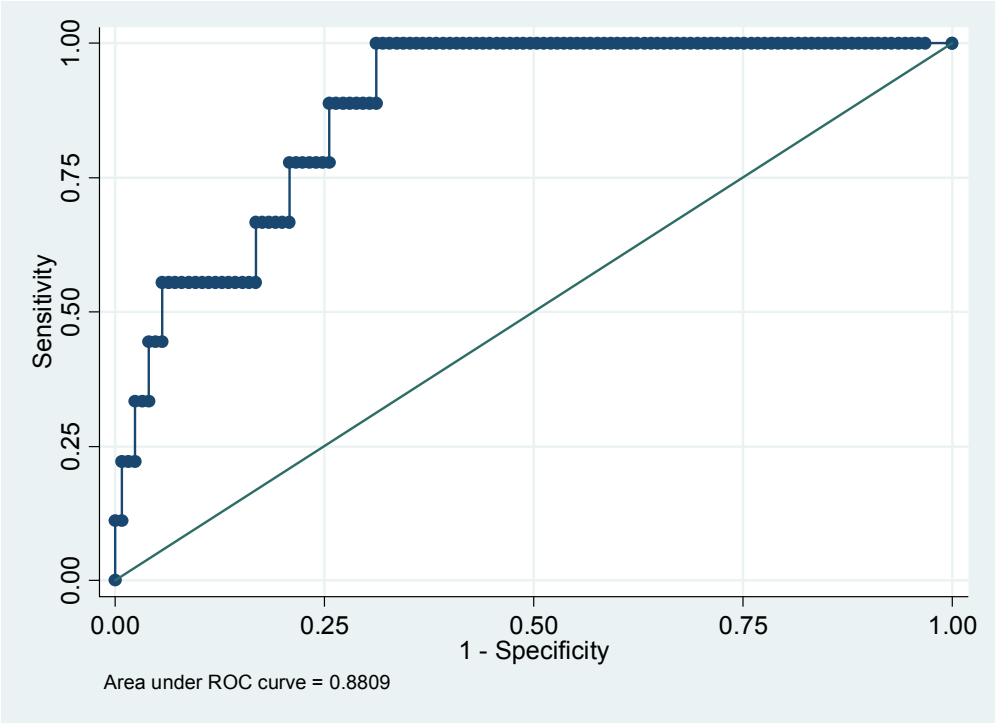

Figure 4 ROC curve for the high risk cohort

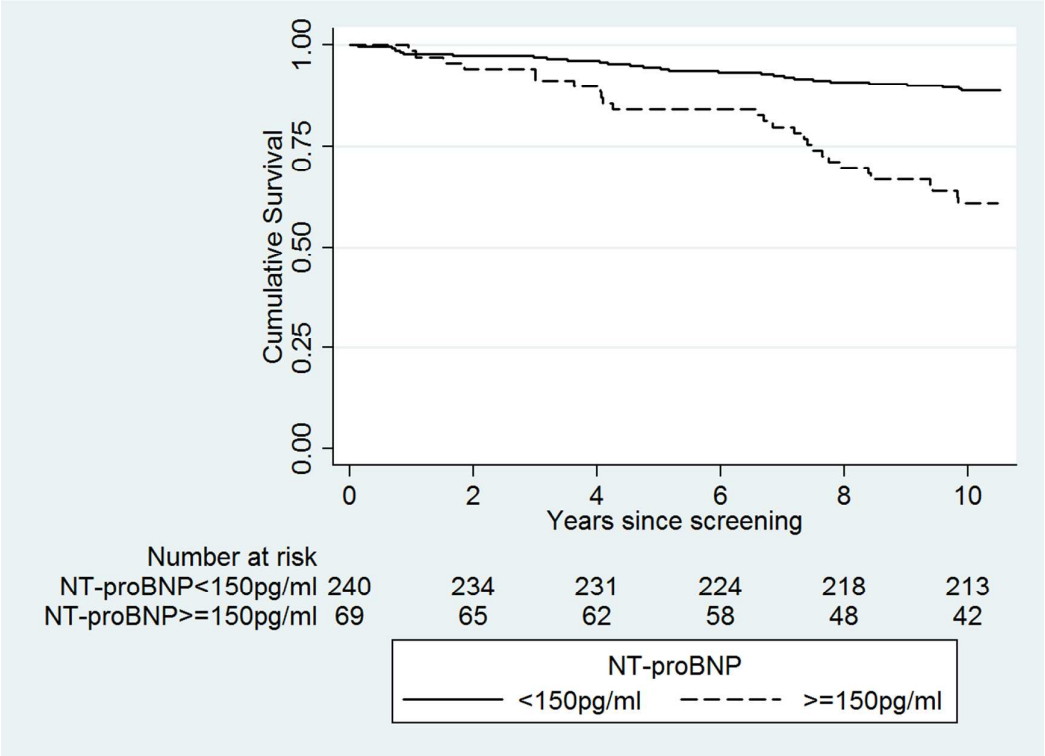

Figure 5 - Kaplan-Meier curve showing NT-proBNP level and ten year survival for the general population cohort.

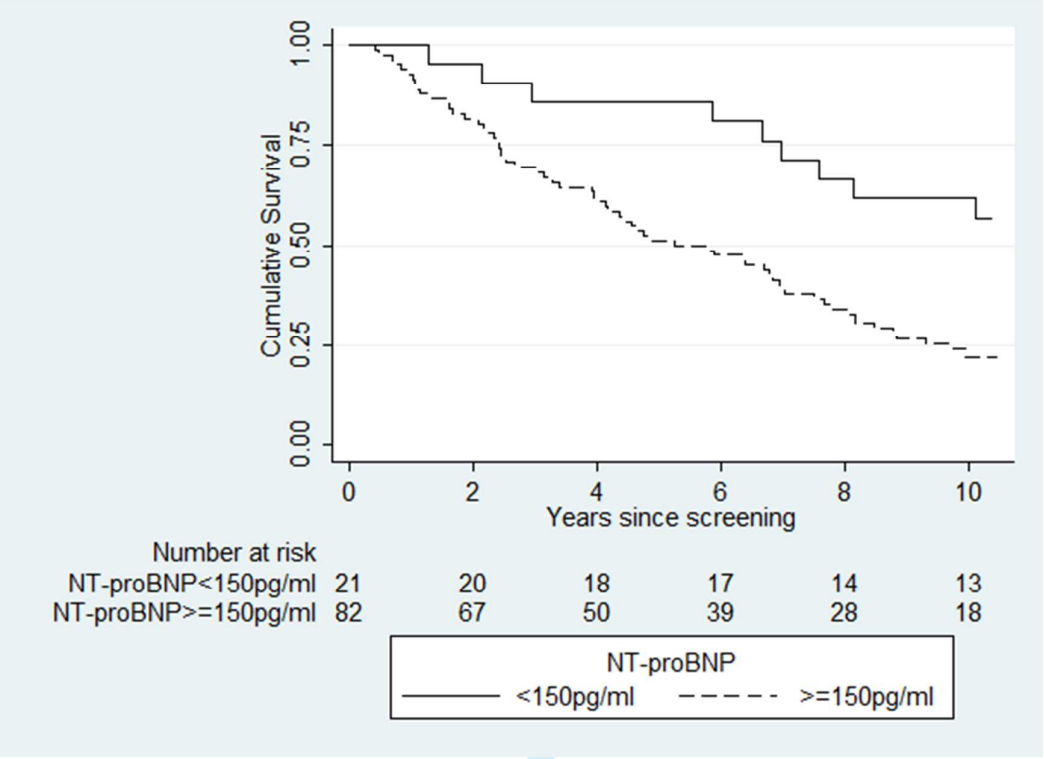

Figure 6 - Kaplan-Meier curve showing NT-proBNP level and ten year survival for the cohort with a previous label of heart failure.

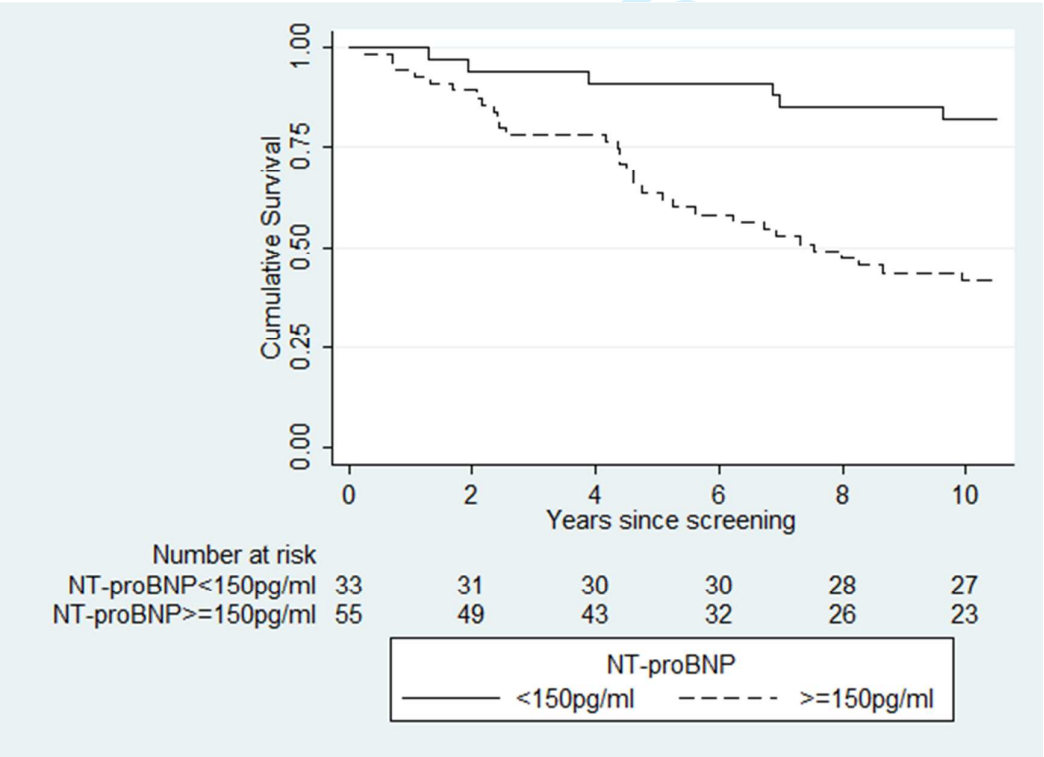

Figure 7 - Kaplan-Meier curve showing NT-proBNP level and ten year survival for the diuretic cohort.

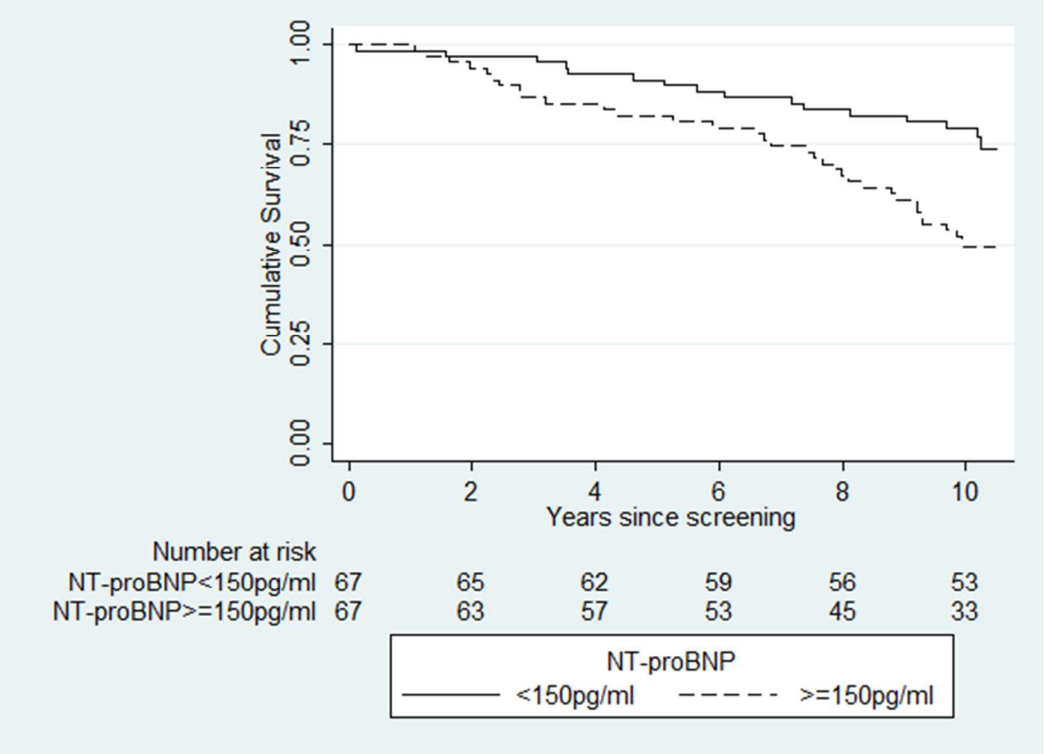

Figure 8 - Kaplan-Meier curve showing NT-proBNP level and ten year survival for the high risk cohort.

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The potential role of NT-proBNP in screening for and predicting prognosis in heart failure: a survival analysis.

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Title Page

The potential role of NT-proBNP in screening for and predicting prognosis in heart failure: a survival analysis.

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Abstract

Objectives: To determine the potential role of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in screening for and predicting prognosis in heart failure by examining diagnosis and survival of patients with a raised NT-proBNP at screening.

Design: Survival analysis.

Setting: Prospective sub-study of the Echocardiographic Heart of England Screening study (ECHOES) to investigate ten-year survival in participants with a NT-proBNP level at baseline.

Participants: 594 participants took part in the sub-study. Records of all participants in the ECHOES cohort were flagged during the screening phase which ended 25th February 1999. All deaths until 25th February 2009 were coded.

Outcome measures: Logistic regression was used to examine whether NT-proBNP is useful in predicting heart failure at screening after adjustment for age, sex and cohort. Kaplan-Meier curves and log rank tests were used to compare survival times of participants according to NT-proBNP level. Cox regression was carried out to assess the prognostic effect of NT-proBNP after allowing for significant covariates and receiver operator curves were used to determine test reliability.

Results: The risk of heart failure increased almost 18-fold when NT-proBNP was 150pg/ml or above (adjusted odds ratio=17.7, 95% CI 4.9 to 63.5). Ten-year survival in the general population cohort was 61% (95% CI 48% to 71%) for those with NT-proBNP>=150pg/ml and 89% (95% CI 84% to 92%) for those below the cut-off at the time of the initial study. After adjustment for age, sex and risk factors for heart failure, NT-proBNP level >= 150pg/ml was associated with a 58% increase in the risk of death within 10 years (adjusted hazard ratio=1.58, 95% CI 1.09 to 2.30).

Conclusions: Raised NT-proBNP levels, when screening the general population, are predictive of a diagnosis of heart failure (at a lower threshold than guidelines for diagnosing symptomatic patients) and also predicted reduced survival at 10 years.

Keywords
Heart failure, Prognosis, Natriuretic peptides, Screening, Diagnosis

Article Summary

Article focus
To examine the role of natriuretic peptides in predicting a subsequent diagnosis of heart failure and survival over the next decade.

Key messages

In the Echocardiographic Heart of England Screening (ECHOES) study, N-terminal B type natriuretic peptide (NT-proBNP) levels above 150pg/ml were associated with both a diagnosis of heart failure at screening and reduced survival at ten years.

Strengths and limitations of the study

The ECHOES cohort represents a well-phenotyped group with accurate mortality data.

Not all participants in the ECHOES cohort had a NT-proBNP measurement but the characteristics of the subgroup were similar to the whole cohort so are likely to be generalisable.

Manuscript

Introduction

Biomarkers can be useful in diagnosis, treatment monitoring and to inform prognosis.[1 2 3] B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are released by the ventricles of the heart in response to volume and pressure overload. BNP relaxes vascular smooth muscle to reduce ventricular preload and acts on the kidney to increase sodium excretion and induce diuresis.[4] NT-proBNP is an inactive fragment of the cleaved pro-BNP molecule. Both peptides have been investigated for use in diagnosis of heart failure and left ventricular systolic dysfunction (LVSD).[5 6] NT-proBNP and BNP assays have been found to be equally reliable for diagnostic use.[7] Raised natriuretic peptide levels have consistently been associated with increased mortality in patients with heart failure.[8 9] There may also be a role for these assays in determining prognosis in patients with and without heart failure.[10]

The Echocardiographic Heart of England Screening (ECHOES) study was a large heart failure screening study carried out in central England.[11] All ECHOES participants underwent a detailed initial clinical assessment to screen for evidence of heart failure. Diagnosis was determined after blinded adjudication by a panel of 3 heart failure specialists using all the clinical and investigation data available from the screening. All deaths were collated from routine mortality data. We previously reported the 10-year prognosis of all patients in the ECHOES study according to presence or absence of heart failure and LVSD.[12] This analysis uses data from ECHOES to examine the role of NT-proBNP in predicting a diagnosis of heart failure at screening and also the relationship between NT-proBNP and survival in the following decade.

Methods

The original ECHOES study screened a total of 6162 participants from sixteen practices in Central England. Four practices were randomly selected from each of the four socio-economic groups defined using the Townsend deprivation score. This resulted in a socio-economically diverse population, likely to be representative of the broader UK population. ECHOES included four separate cohorts: 3960 patients randomly sampled from the general population over age 45; 782 patients with a previous label of heart failure recorded in GP notes; 928 patients on diuretic therapy; and 1062 with known risk factors for heart disease (hypertension, diabetes, angina, history of myocardial infarction(MI)). The four cohorts were stipulated prior to the study and searches were carried out to find patients in each of these groups using general practice records. Patients underwent assessment (history, examination, electrocardiogram and echocardiography) to screen for evidence of heart failure.

A substudy involving 594 ECHOES participants was also carried out to investigate the role of NT-proBNP in diagnosis and prognosis of heart failure. Fuller methods are available in an earlier publication[11] but in brief, participants came from 4 general practices, across the Townsend scale; 309 were sampled from the general population, 103 with a previous label of heart failure, 88 on diuretic therapy and 134

with risk factors of heart disease with some patients belonging to more than one cohort.

During the ECHOES study, which ran from March 1995 to February 1999, the records of all participants were flagged by the Office for National Statistics (ONS) Central Register Office. The ONS has provided details of the date and cause of death for all ECHOES participants since then. The final participant in the original ECHOES cohort was screened on 25th February 1999 and all deaths up to the 25th February 2009 had been notified to the research team. This allowed an estimate of 10-year prognosis for patients in ECHOES including those from the NT-proBNP study. All data from the original ECHOES cohort were recorded in a restricted access database. The statistical packages SPSS and Stata 10 were used to analyse the data.

Analytical methods

Area under the receiver operating curve (AUROC) was calculated, for each cohort, to measure the natriuretic peptide's performance in predicting heart failure at screening. Multiple logistic regression was then performed, using all cohorts combined, to examine whether BNP was predictive of heart failure, after adjustment for the sampling structure and other significant predictors. Variables in the final model were selected using the backward elimination method with significance level set at 0.05.

Variables considered in the analysis included NT-proBNP, age, sex, body mass index (BMI), smoking status, blood pressure, individual risk factors for heart failure (hypertension, angina, MI, diabetes), symptoms (tiredness, shortness of breath, ankle oedema), prescribed drugs (beta-blockers, ace inhibitors, angiotensin receptor blockers (ARBs) and diuretics); and whether a previous label of heart failure was recoded. Two-way interactions with natriuretic peptide were also considered. The cohort-related variables were kept in the final model to allow for the sampling structure. To improve the precision of the estimates, bootstrapped confidence intervals for odds ratios were calculated using 1000 replications.

Survival analysis was carried out, by each cohort, using Kaplan-Meier curves to demonstrate survival in those with an NT-proBNP level >= 150pg/ml. Log rank tests were used to compare survival between the different groups. The mean survival times were calculated rather than median since data was censored for more than 50% of cases. Estimation of the mean is limited to the largest survival time if data were censored.

Cox regression was then undertaken, using all 594 participants, to assess the prognostic ability of NT-proBNP after allowing for each cohort and other covariates. Variables entered into the starting model are as described previously with the addition of atrial fibrillation, ejection fraction and significant valve disease. Fractional polynomials were considered when comparing models of best fit for continuous variables of age, BMI and blood pressure. The proportional hazards assumption was tested using Schoenfeld residuals.

Results

NT-proBNP levels were measured in 594 participants during the ECHOES study. A heart failure diagnosis was confirmed for 7 (8%) of those in the general population sample; 36 (35%) of those with a previous label of heart failure; 15 (17%) of those on diuretics; and 9 (7%) of those at high risk. Twenty three (43%) of all those with a heart failure diagnosis had an ejection fraction of less than 40% and an additional 10 persons (19%) had ejection fraction of between 40 and 49%.

The baseline characteristics of all participants in the sub-study, broken down by cohort and NT-proBNP 150pg/ml cut-off, are shown in Table 1. Those in the upper NT-proBNP category were older, had more cardiovascular risk factors and took more medication than those below 150pg/ml. They also, with exception of those from the cohort with previous label of heart failure, had more symptoms of heart failure.

The distributions of NT-proBNP in each cohort are given in Table 2. The general population had the lowest values with more than 75% below 150pg/ml. Highest levels were observed in the cohort with a previous label of heart failure.

TABLE 1
TABLE 2

Figures 1 to 4 show the Receiver Operating Curves for assessing the performance of NT-proBNP in diagnosing heart failure in each of the cohorts. The area under the receiver operating curve (AUROC) for NT-proBNP levels above 150 pg/ml was 0.95 (95%CI 0.88 to 1.00) for the general population; 0.83 (0.75 to 0.91) for those with previous label of HF; 0.91(0.82 to 1.00) for those on diuretics; and 0.88 (0.80 to 0.97 for those at risk of heart failure]. The cut-off for NT-proBNP at 150pg/ml had sensitivity of 100% (95% CI 59.0% to 100%) and specificity of 79.5% (95%CI 74.5% to 83.9%) in identifying heart failure in the general population sample; [97.2%(85.5% to 99.9%) sensitivity and 29.9%(19.3% to 42.3%) specificity for those with previous label of HF; 93.3%(68.1% to 99.8%) sensitivity and 43.8%(32.2% to 55.9%) specificity for those on diuretics; and 100%(66.4% to 100%) sensitivity and 53.6%(44.5% to 62.6%) specificity for those at high risk]. A full summary of performance characteristics, including positive and negative predictive values and accuracy, is given in Table 3. Other cut-offs were not considered in this analysis due to the high sensitivity and reasonable specificity observed using the chosen cut-off. Overall, a cut-off of 150pg/ml found 100% of heart failure cases and 80% of non-heart failure cases. The percentage of deaths at 10 years with NT-proBNP >=150pg/ml at baseline was 50% in the general population, 86% in HF label group, 71% in the high risk group and 84% in the diuretics group.

FIGURES 1 TO 4
Table 3

The multiple logistic regression analysis suggests that NT-proBNP>=150pg/ml is predictive of heart failure (OR=17.7 (95%CI 4.9 to 63.5)) after allowing for cohort related variables (Table 4).

TABLE 4

Cause of death

Cardiovascular disease was the main cause of death in each cohort, ranging from 31% (95%CI 20% to 46%) in the general population to 49% (95% CI 37% to 61%) in the high risk group. The remaining deaths were mainly due to respiratory disease and cancer.

Survival analysis of the general population cohort

There was a statistically significant difference in survival between those who had an NT-proBNP level >= 150pg/ml and those with an NT-proBNP level <150pg/ml in the general population sample (log-rank test, χ^2 =30.4, 1, P<0.0001) as shown in Figure 5. Mean survival for those with an NT-proBNP >= 150pg/ml was 8.7 years (95%CI 8.0 to 9.4) compared to 9.9 years (95%CI 9.7 to 10.2) for those with an NT-proBNP <150pg/ml. Ten-year survival was 61% (95%CI 48% to 71%) for those with a NT-proBNP >= 150pg/ml and 89% (95%CI 84% to 92%) for those with NT-proBNP <150pg/ml at the time of the initial study.

FIGURE 5

Survival analysis of the other cohorts

Reduced length of survival was also observed for those above the NT-proBNP cut-off when compared with those below the cut-off in each of the other cohorts (p<0.001). Those sampled with a previous label of heart failure and with NT-proBNP >= 150pg/ml had a mean survival of 5.8 years (95%CI 5.0 to 6.5) compared to 8.4 years (95%CI 7.1 to 9.7) for those below the cut-off (figure 6). The comparative results for those on diuretics (Figure 7) were 7.0 years (6.0 to 7.9) vs 9.5 years (8.7 to 10.4); and those at high risk (Figure 8) 8.3 years (7.6 to 9.0) vs. 9.4 years (8.8 to 10.0).

FIGURE 6-8

Cox regression analysis of all cohort data

Table 5 shows a cox regression model examining factors associated with mortality using data from all 4 cohorts. After adjustment for demographic variables and shortness of breath, NT-proBNP >=150pg/ml was found to increase the risk of death by 58% (HR=1.58 (1.09 to 2.30)).

Table5

Discussion

Summary of main findings

594 participants of the ECHOES study took part in the NT-proBNP substudy. Mean survival time for participants from the general population with an NT-proBNP >= 150pg/ml was over one year less than participants with NT-proBNP < 150pg/ml (8.7 *vs* 9.9 years). The proportion of patients surviving ten years was significantly lower in the group with an NT-proBNP level >= 150pg/ml compared to an NT-proBNP level < 150pg/ml (61% vs 89% respectively in the general population). An NT-proBNP level >= 150pg/ml was strongly predictive of a diagnosis of heart failure at screening and of death in the next ten years.

Strengths and limitations of the study

The ECHOES study represents a unique cohort of patients with well phenotyped heart failure from a community setting. The rigor of clinical assessment means the diagnosis of heart failure is accurate. All participants notes were flagged by ONS to ensure accurate data about date and cause of death were sent to the research team. The ONS records reflect the reason for death in the opinion of the attending clinician, as recorded on the death certificate, but the symptoms of heart failure can be similar to other conditions, particularly respiratory disorders, and clinicians can disagree. The study design also did not allow for interim data collection so non-fatal end points, such as hospitalisation, were not explored.

NT-proBNP levels were not recorded in all participants of the ECHOES study however the baseline characteristics of the NT-proBNP substudy were similar to those of the study population as a whole. Only 3% of participants were non-white which may not fully reflect the ethnic diversity of the UK population and NT-proBNP levels may vary depending on ethnicity. Renal function was not recorded in this study therefore we were unable to assess the effect of renal impairment on mortality.[13] A cut off of 150pgm/ml was chosen to represent a raised level of NT-proBNP in the substudy however debate exists around the optimal cut off level for NT-proBNP.[14]

The study reports a long term follow-up of ten years and over this time both the diagnostic criteria and management of heart failure have changed significantly. The original diagnosis of heart failure in the ECHOES study was based on the European Society of Cardiology guideline 1995 and this definition has been updated several times since then.[15 16 21] At the time, heart failure with reduced ejection fraction was the main recognised type of heart failure and the most common precursor to this was, and remains, ischaemic heart disease. Sixty nine per cent of the heart failure labelled group in this study had a history of angina or MI. In the past 10-15 years, heart failure with preserved ejection fraction, or HF-PEF, has also been recognised as distinct clinical and pathological entity. The atrial fibrillation and/or significant valve disease groups (with normal ejection fraction) in the ECHOES study may have partly captured some HFPEF patients but this group will have largely been excluded. The ECHOES-extension study has rescreened the entire cohort, phenotyping for both HF-REF and HF-PEF, and will report shortly.

Comparison with existing literature

A study by Wang et al investigated the relationship between BNP levels and risk of cardiovascular events or death in 3346 patients from the Framingham cohort who did not have heart failure at baseline.[8] 119 participants died and 79 had a first cardiovascular event during a mean follow-up of 5.2 years. For each one standard deviation increment increase in log BNP level, risk of developing heart failure increased by 77% (p<0.001) and risk of death increased by 27% (p=0.009).

BNP and NT-proBNP levels also increase with heart failure stage. A study of patients over the age of 45 from the Rochester Epidemiology Study found that mean BNP (rather than NT-proBNP) level was 26pg/ml in patients without heart failure, 32pg/ml in those with risk factors, 53pg/ml in those asymptomatic participants with structural or functional cardiac abnormalities, 137pg/ml in participants with heart failure symptoms and 353pg/ml for participants with severe heart failure. Survival declined progressively for each additional stage of disease.[17]

Another study by Hartmann et al investigated the role of baseline NT-proBNP in predicting mortality and hospitalisation in patients with a diagnosis of heart failure.[9] NT-proBNP levels were recorded in 814 men and 197 women with severe heart failure defined as breathlessness at rest or on minimal exertion and an ejection fraction of less than 25%. They were followed up for a median time of 159 days (range 1-488 days). A baseline NT-proBNP level above compared to below the median level for the cohort was a strong predictor of all-cause mortality and hospitalisation for heart failure (relative risk 2.4; 95%CI 1.8-3.4; p=0.0001). NT-proBNP has also been found to be an independent predictor of mortality in patients with renal disease.[10]

Overall, participants labelled with heart failure in the ECHOES cohort had a better prognosis than some other community based studies.[18 19] This may reflect a lower overall risk in the studied population, the introduction of medication known to improve survival, such as ACE inhibitors or B blockers, following screening or a referral bias in that patients in the study may have been more likely to be referred for more intensive heart failure management. A letter was sent to GPs of all study participants with advice on management for participants with a confirmed diagnosis of heart failure.

Implications of future research and practice

In this substudy, participants with a raised NT-proBNP level were more likely to have a confirmed diagnosis of heart failure after screening. Natriuretic peptides are already used in clinical practice to determine the likelihood of heart failure and guide referral for echocardiography however the optimal cut-off level if still unclear.[20 21] The National Institute for Health and Clinical Excellence (NICE) clinical guideline on the management of chronic heart failure recommends an NT-proBNP of 400 pg/ml is used as the threshold to refer for echocardiography in symptomatic patients, whereas the European Society of Cardiology suggest a threshold level of 125 pg/ml to exclude heart failure. Fuat et al showed that a cut-off of 150 pg/ml had a negative predictive value of 92% in a primary care community heart failure clinic, again in

symptomatic patients.[22] Our data suggest that the current NICE cut-off is too high and that 150 pg/ml is a more reliable threshold for further investigation, especially since our data includes asymptomatic as well as symptomatic non-presenting patients.

Importantly, participants in the NT-proBNP substudy with a raised NT-proBNP were also more likely to die sooner than participants with a normal NT-proBNP level. These data confirm the potential for incident NT-proBNP tests to indicate patient prognosis in primary care settings as has been confirmed in hospital settings. Assessment of patients to establish the cause of a raised NT-proBNP level such as heart failure or renal disease followed by optimal management using evidence based therapies is crucial to reducing mortality in these high risk patients.

Finally, these data are the first we are aware of that suggest a possible role for natriuretic peptides in population screening for heart failure. Given the late diagnosis in many patients and the asymptomatic nature in early stages, this may be an important finding.

Authors' contributions: F.D.R.H. was principal investigator and established the ECHOES cohort. C.J.T. and F.D.R.H. designed this study. C.J.T. and A.K.R. undertook statistical analysis. C.J.T. and R.I. coded the death data. All authors contributed to the manuscript.

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Ethical approval: The study received full ethical approval from the local research ethics committee.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: The NT-proBNP assays for the ECHOES study were provided free of charge by Roche Diagnostics, but Roche were not party to the study design, nor any aspect of the analysis, nor to the write up of this paper. FDRH has received similar indirect research support on other investigator led heart failure research. FDRH has also received occasional fees or expense reimbursement from Roche in the past; no other relationships or activities that could appear to have influenced the submitted work.

Data sharing: The complete database for the ECHOES study is stored securely at the University of Birmingham and available on request. All authors have access to the data.

Tables

	General population (n=309)		Previous label of HF (n=103)		On diuretics (n=88)		High risk (n=134)	
Characteristics	NTproBNP < 150 pg/ml (n=240)	NTproBNP >=150pg/ml (n=69)	NTproBNP < 150 pg/ml (n=21)	NTproBNP >=150pg/ml (n=82)	NTproBNP < 150pg/ml (n=33)	NTproBNP >=150pg/ml (n=55)	NTproBNP < 150 pg/ml (n=67)	NTproBNP >=150pg/ml (n=67)
Demographics								
Age at screening [mean (sd) years]	59.6 (8.7)	71.7 (9.7)	72.2 (9.6)	74.7 (8.4)	63.2 (8.8)	74.1 (9.8)	63.2 (8.7)	70.4 (8.2)
Gender, male	130 (54)	31 (45)	9 (43)	47 (57)	24 (73)	26 (47)	43 (64)	33 (49)
Ever Smoked	137 (57)	37 (54)	17 (81)	45 (55)	21 (64)	32 (58)	42 (63)	48 (72)
Body mass index [mean (sd) kg/m^2]	27.0 (4.9)	25.8 (3.8)	31.1 (8.5)	26.6 (4.4)	27.9 (3.5)	26.8 (4.5)	28.4 (4.1)	27.1 (3.8)
Systolic BP [mean(sd)mm/Hg]	149.3 (20.9)	156.1 (23.3)	162.9(18.3)	149.2(26.3)	161.7(22.6)	154.8 (25.2)	155.2 (18.3)	158.7 (23.4)
Diastolic BP [mean(sd)mm/Hg]	85.6 (10.9)	83.6 (9.9)	84.4 (9.5)	78.0 (12.6)	91.7 (10.3)	82.4 (14.2)	83.9 (10.1)	83.6 (11.7)
History								
Diabetes	9 (4)	6 (9)	4 (19)	14 (17)	3 (9)	8 (15)	24 (36)	12 (18)
Myocardial Infarction	5 (2)	7 (10)	4 (19)	26 (32)	2 (6)	8 (15)	16 (24)	36 (54)
Angina	12 (5)	16 (23)	7 (33)	33 (40)	3 (9)	14 (25)	23 (34)	46 (69)
Hypertension	54 (22)	24 (35)	9 (43)	27 (33)	29 (88)	31 (56)	38 (57)	39 (58)
Medication taken								
Diuretics	15 (6)	20 (29)	16 (76)	70 (85)	33 (100)	55 (100)	12 (18)	26 (39)
Ace Inhibitors	12 (5)	5 (7)	4 (19)	39 (48)	10 (30)	20 (36)	19 (28)	18 (27)
ARBs	3 (1)	0 (0)	1 (5)	7 (9)	0 (0)	1 (2)	2 (3)	0 (0)

Beta-blockers	14 (6)	19 (28)	2 (10)	9 (11)	5 (15)	8 (15)	17 (25)	21 (31)
Symptoms								
Shortness of breath	48 (20)	32 (46)	16 (76)	61 (74)	11 (33)	34 (62)	17 (25)	44 (66)
Tired	70 (29)	33 (48)	15 (71)	62 (75)	12 (36)	35 (64)	27 (40)	42 (63)
Ankle swelling	38 (16)	22 (32)	15 (71)	41 (50)	10 (30)	29 (53)	22 (33)	22 (33)
New York Heart Association class								
1	200 (83)	39 (57)	5 (24)	22 (27)	23 (70)	21 (38)	57 (78)	28 (42)
2	35 (15)	23 (33)	11 (52)	30 (37)	7 (21)	21 (38)	10 (15)	29 (43)
3	4 (2)	2 (3)	3 (14)	15 (18)	3 (9)	8 (15)	1 (1)	6 (9)
4	1 (0.4)	5 (7)	2 (10)	15 (18)	0 (0)	5 (9)	4 (6)	4 (6)
Ejection fraction								
<40%	1 (0.4)	4 (6)	1 (5)	20 (24)	1 (3)	6 (11)	1 (1)	9 (13)
40-49%	2 (0.8)	3 (4)	2 (10)	18 (22)	1 (3)	6 (11)	3 (4)	6 (9)
>=50%	237 (98.7)	62 (90)	18 (86)	44 (54)	31 (94)	43 (78)	63 (94)	52 (78)
Diagnosis								
Definite heart failure	0 (0)	7 (10)	1 (5)	35 (43)	1 (3)	14 (25)	0 (0)	9 (13)
Atrial fibrillation	0 (0)	7 (10)	0 (0)	23 (28)	0 (0)	13 (24)	0 (0)	3 (4)
Significant valve disease	0 (0)	5 (7)	1 (5)	9 (11)	0 (0)	7 (13)	0 (0)	3 (4)

Table 1 – Baseline characteristics of patients in the ECHOES NT-proBNP sub-study

Cohort	N	Median (IQR)
General population	309	70.9 (35.3 to 130.1)
Previous label of HF	103	493.6 (204.3 to 1341)
On diuretics	88	200 (76.1 to 672.8)
At high risk	134	160.1 (64.6 to 386.3)

Table 2 Distribution of NT-proBNP in each cohort

Cohort	AUROC	Sensitivity	Specificity	Positive predictive value (PPV)	Negative predictive value (NPV)	Accuracy
General population	0.95 (0.88 to 1.00)	100 (59 to 100)	79.5 (74.5 to 83.9)	10.1 (4.2 to 19.8)	100 (98.5 to 100)	79.9 (75 to 84.3)
Previous label of heart failure	0.83 (0.75 to 0.91)	97.2 (85.5 to 99.9)	29.9 (19.3 to 42.3)	42.7 (31.8 to 54.1)	95.2 (76.2 to 99.9)	53.4 (43.3 to 63.3)
On diuretics	0.91 (0.82 to 1.00)	93.3 (68.1 to 99.8)	43.8 (32.2 to 55.9)	25.5 (14.7 to 39.0)	97.0 (84.2 to 99.9)	52.3 (41.4 to 63.0)
High risk	0.88 (0.80 to 0.97	100 (66.4 to 100)	53.6 (44.5 to 62.6)	13.4 (6.3 to 24.0)	100 (94.6 to 100)	56.7 (47.9 to 65.2)

AUROC: Area under the receiver operating curve

Table 3 Performance characteristics for NT-proBNP (cut-off 150pg/ml)

Variable	Odds Ratio (95% confidence interval*)	P value
Previous label of HF	3.74 (1.45 to 9.69)	0.007
On diuretics	5.26 (1.70 to 16.31)	0.004
Diabetes	4.91 (1.66 to 14.51)	0.004
Hypertension	0.39 (0.16 to 0.97)	0.04
Angina	1.22 (0.99 to 5.00)	0.053
Myocardial infarction	1.61 (0.67 to 3.86)	0.29

NT-proBNP >=150 pg/ml	17.65 (4.91 to 63.48)	<0.001

*Bootstrapped estimates

Table 4 Logistic regression model to predict heart failure

Variable	Hazard Ratio (95% confidence interval*)	P value
Age	1.10 (1.08 to 1.10)	<0.001
Male sex	2.05 (1.43 to 2.95)	<0.001
Previous label of HF	1.75 (1.17 to 2.57)	0.007
On diuretics	0.90 (0.62 to 1.32)	0.59
Diabetes	1.08 (0.65 to 1.88)	0.78
Hypertension	1.37 (0.99 to 1.90)	0.06
Angina	1.04 (0.73 to 1.50)	0.82
Myocardial infarction	1.18 (0.80 to 1.73)	0.40
Shortness of breath	1.64 (1.14 to 2.37)	0.008
NT-proBNP >=150 pg/ml	1.58 (1.09 to 2.30)	0.02

*Bootstrapped estimates

Table 5 Cox regression model of factors associated with mortality (including all study cohorts)

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Title Page

The potential role of NT-proBNP in screening for and predicting prognosis in heart failure: a survival analysis.

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Abstract

Objectives: To determine the potential role of N-terminal pro-B--type natriuretic peptide (NT-proBNP) in screening for and predicting prognosis in heart failure by examining diagnosis and survival of patients with a raised NT-proBNP at screening.

Design: Survival analysis.

Setting: Prospective sub-study of the Echocardiographic Heart of England Screening study (ECHOES) to investigate ten-year survival in participants with a NT-proBNP level at baseline.

Participants: 594 participants took part in the sub-study. Records of all participants in the ECHOES cohort were flagged during the screening phase which ended 25th February 1999. All deaths until 25th February 2009 were coded.

Outcome measures: Logistic regression was used to examine whether NT-proBNP is useful in predicting heart failure at screening after adjustment for age, sex and cohort. Kaplan--Meier curves and log rank tests were used to compare survival times of participants according to NT-proBNP level. Cox regression was carried out to assess the prognostic effect of NT-PproBNP after allowing for significant covariates and receiver operator curves were used to determine test reliability.

Results: The risk of heart failure increased almost 18-fold when NT-proBNP was 150pg/ml or above (adjusted odds ratio=17.7, (95% CI 4.9 to 63.5). Ten-year survival in the general population cohort was 61% (95% CI 48% to 71%) for those with NT-proBNP>=150pg/ml and 89% (95% CI 84% to 92%) for those below the cut-off at the time of the initial study. After adjustment for age, sex and risk factors for heart failure, NT-proBNP level >= 150pg/ml was associated with a 58% increase in the risk of death within 10 years (adjusted hazard ratio=1.58, 95% CI 1.09 to 2.30).

Conclusions: Raised NT-proBNP levels, when screening the general population, are predictive of a diagnosis of heart failure (at a lower threshold than guidelines for diagnosing symptomatic patients) and also predicted reduced survival at 10 years.

Keywords
Heart failure, Prognosis, Natriuretic peptides, Screening, Diagnosis

Article Summary

Article focus
To examine the role of natriuretic peptides in predicting a subsequent diagnosis of heart failure and survival over the next decade.

Key messages

In the Echocardiographic Heart of England Screening (ECHOES) study, N-terminal B type natriuretic peptide (NT-proBNP) levels above 150pg/ml were associated with both a diagnosis of heart failure at screening and reduced survival at ten years.

Strengths and limitations of the study

The ECHOES cohort represents a well-phenotyped group with accurate mortality data.

Not all participants in the ECHOES cohort had a NT-proBNP measurement but the characteristics of the subgroup were similar to the whole cohort so are likely to be generalisable.

Manuscript

Introduction

Biomarkers can be useful in diagnosis, treatment monitoring and to inform prognosis.[1 2 3] B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are released by the ventricles of the heart in response to volume and pressure overload. BNP relaxes vascular smooth muscle to reduce ventricular preload and acts on the kidney to increase sodium excretion and induce diuresis.[4] NT-proBNP is an inactive fragment of the cleaved pro-BNP molecule. Both peptides have been investigated for use in diagnosis of heart failure and left ventricular systolic dysfunction (LVSD).[5 6] NT-pro-BNP and BNP assays have been found to be equally reliable for diagnostic use.[7] Raised natriuretic peptide levels have consistently been associated with increased mortality in patients with heart failure.[8 9] There may also be a role for these assays in determining prognosis in patients with and without heart failure.[10]

The Echocardiographic Heart of England Screening (ECHOES) study was a large heart failure screening study carried out in central England.[11] All ECHOES participants underwent a detailed initial clinical assessment to screen for evidence of heart failure. Diagnosis was determined after blinded adjudication by a panel of 3 heart failure specialists using all the clinical and investigation data available from the screening. All deaths were collated from routine mortality data. We previously reported the 10-year prognosis of all patients in the ECHOES study according to presence or absence of heart failure and LVSD.[12] This analysis uses data from ECHOES to examine the role of NT-proBNP in predicting a diagnosis of heart failure at screening and also the relationship between NT-proBNP and survival in the following decade.

Methods

The original ECHOES study screened a total of 6162 participants from sixteen practices in Central England. Four practices were randomly selected from each of the four socio-economic groups defined using the Townsend deprivation score. This resulted in a socio-economically diverse population, likely to be representative of the broader UK population. ECHOES included four separate cohorts: 3960 patients randomly sampled from the general population over age 45; 782 patients with a previous label of heart failure recorded in GP notes; 928 patients on diuretic therapy; and 1062 with known risk factors for heart disease (hypertension, diabetes, angina, history of myocardial infarction(MI)). The four cohorts were stipulated prior to the study and searches were carried out to find patients in each of these groups using general practice records. Patients underwent assessment (history, examination, electrocardiogram and echocardiography) to screen for evidence of heart failure.

A substudy involving 594 ECHOES participants was also carried out to investigate the role of NT-proBNP in diagnosis and prognosis of heart failure. Fuller methods are available in an earlier publication[9 11 14] but in brief, participants came from 4 general practices, across the Townsend scale; 309 were sampled from the general population, 103 with a previous label of heart failure, 88 on diuretic therapy and 134

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with risk factors of heart disease with some patients belonging to more than one cohort.

During the ECHOES study, which ran from March 1995 to February 1999, the records of all participants were flagged by the Office for National Statistics (ONS) Central Register Office. The ONS has provided details of the date and cause of death for all ECHOES participants since then. The final participant in the original ECHOES cohort was screened on 25th February 1999 and all deaths up to the 25th February 2009 had been notified to the research team. This allowed an estimate of 10-year prognosis for patients in ECHOES including those from the NT-proBNP study. All data from the original ECHOES cohort were recorded in a restricted access database. The statistical packages SPSS and Stata 10 were used to analyse the data.

Analytical methods

Area under the receiver operating curves (AUROC) was calculated, for each cohort, to measure the natriuretic peptide's performance in predicting heart failure at screening. Multiple logistic regression was then performed, using all cohorts combined, to examine whether BNP was predictive of heart failure, after adjustment for the sampling structure and other significant predictors. Variables in the final model were selected using the backward elimination method with significance level set at 0.05.

Variables considered in the analysis included NT-proBNP, age, sex, body mass index (BMI), smoking status, blood pressure, individual risk factors for heart failure (hypertension, angina, MI, diabetes), symptoms (tiredness, shortness of breath, ankle oedema), prescribed drugs (beta-blockers, ace inhibitors, angiotensin receptor blockers (ARBs) and diuretics); and whether a previous label of heart failure was recoded. Two-way interactions with natriuretic peptide were also considered. The cohort-related variables were kept in the final model to allow for the sampling structure. To improve the precision of the estimates, bootstrapped confidence intervals for odds ratios were calculated using 1000 replications.

Survival analysis was carried out, by each cohort, using Kaplan-Meier curves to demonstrate survival in those with an NT-proBNP level >= 150pg/ml. Log rank tests were used to compare survival between the different groups. The mean survival times were calculated rather than median since data was censored for more than 50% of cases. Estimation of the mean is limited to the largest survival time if data were censored.

Cox regression was then undertaken, using all 594 participants, to assess the prognostic ability of NT-proBNP after allowing for each cohort and other covariates. Variables entered into the starting model are as described previously with the addition of atrial fibrillation, ejection fraction and significant valve disease. Fractional polynomials were considered when comparing models of best fit for continuous variables of age, BMI and blood pressure. The proportional hazards assumption was tested using Schoenfeld residuals.

Results

NT-proBNP levels were measured in 594 participants during the ECHOES study. A heart failure diagnosis was confirmed for 7 (8%) of those in the general population sample; 36 (35%) of those with a previous label of heart failure; 15 (17%) of those on diuretics; and 9 (7%) of those at high risk. Twenty three (43%) of all those with a heart failure diagnosis had an ejection fraction of less than 40% and an additional 10 persons (19%) had ejection fraction of between 40 and 49%.

The baseline characteristics of all participants in the sub-study, broken down by cohort and NT-proBNP 150pg/ml cut-off, are shown in ŧTable 1. Those in the upper NT-proBNP category were older, had more cardiovascular risk factors and took more medication than those below 150pg/ml. They also, with exception of those from the cohort with previous label of heart failure, had more symptoms of heart failure.

The distributions of NT-proBNP in each cohort are given in ŧTable 2. The general population had the lowest values with more than 75% below 150pg/ml. Highest levels were observed in the cohort with a previous label of heart failure.

TABLE 1
TABLE 2

Figures 1 to 4 show the Receiver Operating Curves for assessing the performance of NT-proBNP in diagnosing heart failure in each of the cohorts. The area under the receiver operating curve (AUROC) for NT-proBNP levels above 150 pg/ml was 0.95 (95%CI 0.88 to 1.00) for the general population; 0.83 (0.75 to 0.91) for those with previous label of HF; 0.91(0.82 to 1.00) for those on diuretics; and 0.88 (0.80 to 0.97 for those at risk of heart failure]. The cut-off for NT-proBNP at 150pg/ml had sensitivity of 100% (95% CI (–59.0% to 100%)) and specificity of 79.5% (95%CI(74.5% to 83.9%—)) in identifying heart failure in the general population sample; [97.2%(85.5% to 99.9%) sensitivity and 29.9%(19.3% to 42.3%) specificity for those with previous label of HF; 93.3%(68.1% to 99.8%) sensitivity and 43.8%(32.2% to 55.9%) specificity for those on diuretics; and 100%(66.4% to 100%) sensitivity and 53.6%(44.5% to 62.6%) specificity for those at high risk]. A full summary of performance characteristics, including positive and negative predictive values and accuracy, is given in Table 3. -Other cut-offs were not considered in this analysis due to the high sensitivity and reasonable specificity observed using the chosen cut-off. Overall, a cut-off of 150pg/ml found 100% of heart failure cases and 80% of non-heart failure cases. The percentage of deaths at 10 years with NT-proBNP >=150pg/ml at baseline was 50% in the general population, 86% in HF label group, 71% in the high risk group and 84% in the diuretics group.

FIGURES 1 TO 4
Table 3

The multiple logistic regression analysis suggests that NT-proBNP>=150pg/ml is predictive of heart failure (OR=17.7 (95%CI 4.9 to 63.5)) after allowing for cohort related variables (Table ~~3~~4).

TABLE ~~3~~4

Cause of death

Cardiovascular disease was the main cause of death in each cohort, ranging from 31% (95%CI 20% to 46%) in the general population to 49% (95% CI 37% to 61%) in the high risk group. The remaining deaths were mainly due to respiratory disease and cancer.

Survival analysis of the general population cohort

There was a statistically significant difference in survival between those who had an NT-proBNP level >= 150pg/ml and those with an NT-proBNP level <150pg/ml in the general population sample (log-rank test, χ^2 =30.4, 1, P<0.0001) as shown in ~~f~~Figure 5. Mean survival for those with an NT-proBNP >= 150pg/ml was 8.7 years (95%CI 8.0 to 9.4) compared to 9.9 years (95%CI 9.7 to 10.2) for those with an NT-proBNP <150pg/ml. Ten-year survival was 61% (95%CI 48% to 71%) for those with a NT-proBNP >= 150pg/ml and 89% (95%CI 84% to 92%) for those with NT-proBNP <150pg/ml at the time of the initial study.

FIGURE 5

Survival analysis of the other cohorts

Reduced length of survival was also observed for those above the NT-proBNP cut-off when compared with those below the cut-off in each of the other cohorts (p<0.001). Those sampled with a previous label of ~~HF~~heart failure and with NT-proBNP >= 150pg/ml had a mean survival of 5.8 years (95%CI 5.0 to 6.5) compared to 8.4 years (95%CI 7.1 to 9.7) for those below the cut-off (figure 6). The comparative results for those on diuretics (~~f~~Figure 7) were 7.0 years (6.0 to 7.9) vs 9.5 years (8.7 to 10.4); and those at high risk (~~f~~Figure 8) 8.3 years (7.6 to 9.0) vs. 9.4 years (8.8 to 10.0).

FIGURE 6-8

Cox regression analysis of all cohort data

Table 5 shows a cox regression model examining factors associated with mortality using data from all 4 cohorts. After adjustment for demographic variables and~~,~~ shortness of breath~~, and~~ NT-proBNP >=150pg/ml was found to increase the risk of death by 58% (HR=1.58 (1.09 to 2.30)).

Table4~~5~~

Discussion

Summary of main findings

594 participants of the ECHOES study took part in the NT-proBNP substudy. Mean survival time for participants from the general population with an NT-proBNP >= 150pg/ml was over one year less than participants with NT-proBNP < 150pg/ml (8.7 *vs* 9.9 years). The proportion of patients surviving ten years was significantly lower in the group with an NT-proBNP level >= 150pg/ml compared to an NT-proBNP level < 150pg/ml (61% vs 89% respectively in the general population). An NT-proBNP level >= 150pg/ml was strongly predictive of a diagnosis of heart failure at screening and of death in the next ten years.

Strengths and limitations of the study

The ECHOES study represents a unique cohort of patients with well phenotyped heart failure from a community setting. The rigor of clinical assessment means the diagnosis of heart failure is accurate. All participants notes were flagged by ONS to ensure accurate data about date and cause of death were sent to the research team. The ONS records reflect the reason for death in the opinion of the attending clinician, as recorded on the death certificate, but the symptoms of heart failure can be similar to other conditions, particularly respiratory disorders, and clinicians can disagree. The study design also did not allow for interim data collection so non-fatal end points, such as hospitalisation, were not explored.

NT-proBNP levels were not recorded in all participants of the ECHOES study however the baseline characteristics of the NT-proBNP substudy were similar to those of the study population as a whole. Only 3% of participants were non-white which may not ~~accurately~~ fully reflect the ethnic diversity of the UK population and NT-proBNP levels may vary depending on ethnicity. Renal function was not recorded in this study therefore we were unable to assess the effect of renal impairment on mortality.[13] A cut off of 150pgm/ml was chosen to represent a raised level of NT-proBNP in the substudy however debate exists around the optimal cut off level for NT-proBNP.[14]

The study reports a long term follow-up of ten years and over this time both the diagnostic criteria and management of heart failure have changed significantly. The original diagnosis of heart failure in the ECHOES study was based on the European Society of Cardiology guideline 1995 and this definition has been updated several times since then.[15 16 ~~2117~~] At the time, heart failure with reduced ejection fraction was the main recognised type of heart failure and the most common precursor to this was, and remains, ischaemic heart disease. Sixty nine per cent of the heart failure labelled group in this study had a history of angina or MI. In the past 10-15 years, heart failure with preserved ejection fraction, or HF-PEF, has also been recognised as distinct clinical and pathological entity. The atrial fibrillation and/or significant valve disease groups (with normal ejection fraction) in the ECHOES study may have partly captured some HFPEF patients but this group will have largely been excluded. The ECHOES-extension study has rescreened the entire cohort, phenotyping for both HF-REF and HF-PEF, and will report shortly.

Comparison with existing literature

A study by Wang et al investigated the relationship between BNP levels and risk of cardiovascular events or death in 3346 patients from the Framingham cohort who did not have heart failure at baseline.[85] 119 participants died and 79 had a first cardiovascular event during a mean follow-up of 5.2 years. For each one standard deviation increment increase in log BNP level, risk of developing heart failure increased by 77% (p<0.001) and risk of death increased by 27% (p=0.009).

BNP and NT-proBNP levels also increase with heart failure stage. A study of patients over the age of 45 from the Rochester Epidemiology Study found that mean BNP (rather than NT-proBNP) level was 26pg/ml in patients without heart failure, 32pg/ml in those with risk factors, 53pg/ml in those asymptomatic participants with structural or functional cardiac abnormalities, 137pg/ml in participants with heart failure symptoms and 353pg/ml for participants with severe heart failure. Survival declined progressively for each additional stage of disease.[17]

Another study by Hartmann et al investigated the role of baseline NT-proBNP in predicting mortality and hospitalisation in patients with a diagnosis of heart failure.[96] NT-proBNP levels were recorded in 814 men and 197 women with severe heart failure defined as breathlessness at rest or on minimal exertion and an ejection fraction of less than 25%. They were followed up for a median time of 159 days (range 1-488 days). A baseline NT-proBNP level above compared to below the median level for the cohort was a strong predictor of all-cause mortality and hospitalisation for heart failure (relative risk 2.4; 95%CI 1.8-3.4; p=0.0001). NT-proBNP has also been found to be an independent predictor of mortality in patients with renal disease.[107]

Overall, participants labelled with heart failure in the ECHOES cohort had a better prognosis than some other community based studies.[18 19] This may reflect a lower overall risk in the studied population, the introduction of medication known to improve survival, such as ACE inhibitors or B blockers, following screening or a referral bias in that patients in the study may have been more likely to be referred for more intensive heart failure management. A letter was sent to GPs of all study participants with advice on management for participants with a confirmed diagnosis of heart failure.

Implications of future research and practice

In this substudy, participants with a raised NT-proBNP level were more likely to have a confirmed diagnosis of heart failure after screening. Natriuretic peptides are already used in clinical practice to determine the likelihood of heart failure and guide referral for echocardiography however the optimal cut-off level if still unclear.[20 21] The National Institute for Health and Clinical Excellence (NICE) clinical guideline on the management of chronic heart failure recommends an NT-proBNP of 400 pg/ml is used as the threshold to refer for echocardiography in symptomatic patients, whereas the European Society of Cardiology suggest a threshold level of 125 pg/ml to exclude heart failure. Fuat et al showed that a cut-off of 150 pg/ml had a negative

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predictive value of 92% in a primary care community heart failure clinic, again in symptomatic patients.[22] Our data suggest that the current NICE cut-off is too high and that 150 pg/ml is a more reliable threshold for further investigation, especially since our data includes asymptomatic as well as symptomatic non-presenting patients.

Importantly, participants in the NT-proBNP substudy with a raised NT-proBNP were also more likely to die sooner than participants with a normal NT-proBNP level. These data confirm the potential for incident NT-proBNP tests to indicate patient prognosis in primary care settings as has been confirmed in hospital settings. Assessment of patients to establish the cause of a raised NT-proBNP level such as heart failure or renal disease followed by optimal management using evidence based therapies is crucial to reducing mortality in these high risk patients.

Finally, these data are the first we are aware of that suggest a possible role for natriuretic peptides in population screening for heart failure. Given the late diagnosis in many patients and the asymptomatic nature in early stages, this may be an important finding.

Authors' contributions: F.D.R.H. was principal investigator and established the ECHOES cohort. C.J.T. and F.D.R.H. designed this study. C.J.T. and A.K.R. undertook statistical analysis. C.J.T. and R.I. coded the death data. All authors contributed to the manuscript.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: The NT-proBNP assays for the ECHOES study were provided free of charge by Roche Diagnostics, but Roche were not party to the study design, nor any aspect of the analysis, nor to the write up of this paper. FDRH has received similar indirect research support on other investigator led heart failure research. FDRH has also received occasional fees or expense

reimbursement from Roche in the past; no other relationships or activities that could appear to have influenced the submitted work.

Tables

	General population (n=309)		Previous label of HF (n=103)		On diuretics (n=88)		High risk (n=134)	
Characteristics	NTproBNP < 150 pg/ml (n=240)	NTproBNP >=150pg/ml (n=69)	NTproBNP < 150 pg/ml (n=21)	NTproBNP >=150pg/ml (n=82)	NTproBNP < 150pg/ml (n=33)	NTproBNP >=150pg/ml (n=55)	NTproBNP < 150 pg/ml (n=67)	NTproBNP >=150pg/ml (n=67)
Demographics								
Age at screening [mean (sd) years]	59.6 (8.7)	71.7 (9.7)	72.2 (9.6)	74.7 (8.4)	63.2 (8.8)	74.1 (9.8)	63.2 (8.7)	70.4 (8.2)
Gender, male	130 (54)	31 (45)	9 (43)	47 (57)	24 (73)	26 (47)	43 (64)	33 (49)
Ever Smoked	137 (57)	37 (54)	17 (81)	45 (55)	21 (64)	32 (58)	42 (63)	48 (72)
Body mass index [mean (sd) kg/m^2]	27.0 (4.9)	25.8 (3.8)	31.1 (8.5)	26.6 (4.4)	27.9 (3.5)	26.8 (4.5)	28.4 (4.1)	27.1 (3.8)
Systolic BP [mean(sd)mm/Hg]	149.3 (20.9)	156.1 (23.3)	162.9(18.3)	149.2(26.3)	161.7(22.6)	154.8 (25.2)	155.2 (18.3)	158.7 (23.4)
Diastolic BP [mean(sd)mm/Hg]	85.6 (10.9)	83.6 (9.9)	84.4 (9.5)	78.0 (12.6)	91.7 (10.3)	82.4 (14.2)	83.9 (10.1)	83.6 (11.7)
History								
Diabetes	9 (4)	6 (9)	4 (19)	14 (17)	3 (9)	8 (15)	24 (36)	12 (18)
Myocardial Infarction	5 (2)	7 (10)	4 (19)	26 (32)	2 (6)	8 (15)	16 (24)	36 (54)
Angina	12 (5)	16 (23)	7 (33)	33 (40)	3 (9)	14 (25)	23 (34)	46 (69)
Hypertension	54 (22)	24 (35)	9 (43)	27 (33)	29 (88)	31 (56)	38 (57)	39 (58)
Medication taken								
Diuretics	15 (6)	20 (29)	16 (76)	7017 (858521)	3322 (10067)	553 (10096)	12 (18)	26 (39)
Ace Inhibitors	12 (5)	5 (7)	4 (19)	39 (48)	10 (30)	20 (36)	19 (28)	18 (27)

ARBs	3 (1)	0 (0)	1 (5)	7 (9)	0 (0)	1 (2)	2 (3)	0 (0)
Beta-blockers	14 (6)	19 (28)	2 (10)	9 (11)	5 (15)	8 (15)	17 (25)	21 (31)
Symptoms								
Shortness of breath	48 (20)	32 (46)	16 (76)	61 (74)	11 (33)	34 (62)	17 (25)	44 (66)
Tired	70 (29)	33 (48)	15 (71)	62 (75)	12 (36)	35 (64)	27 (40)	42 (63)
Ankle swelling	38 (16)	22 (32)	15 (71)	41 (50)	10 (30)	29 (53)	22 (33)	22 (33)
New York Heart Association class								
1	200 (83)	39 (57)	5 (24)	22 (27)	23 (70)	21 (38)	57 (78)	28 (42)
2	35 (15)	23 (33)	11 (52)	30 (37)	7 (21)	21 (38)	10 (15)	29 (43)
3	4 (2)	2 (3)	3 (14)	15 (18)	3 (9)	8 (15)	1 (1)	6 (9)
4	1 (0.4)	5 (7)	2 (10)	15 (18)	0 (0)	5 (9)	4 (6)	4 (6)
Ejection fraction								
<40%	1 (0.4)	4 (6)	1 (5)	20 (24)	1 (3)	6 (11)	1 (1)	9 (13)
40-49%	2 (0.8)	3 (4)	2 (10)	18 (22)	1 (3)	6 (11)	3 (4)	6 (9)
>=50%	237 (98.7)	62 (90)	18 (86)	44 (54)	31 (94)	43 (78)	63 (94)	52 (78)
Diagnosis								
Definite heart failure	0 (0)	7 (10)	1 (5)	35 (43)	1 (3)	14 (25)	0 (0)	9 (13)
Atrial fibrillation	0 (0)	7 (10)	0 (0)	23 (28)	0 (0)	13 (24)	0 (0)	3 (4)
Significant valve disease	0 (0)	5 (7)	1 (5)	9 (11)	0 (0)	7 (13)	0 (0)	3 (4)

Table 1 – Baseline characteristics of patients in the ECHOES NT-proBNP sub-study

Cohort	N	Median (IQR)
General population	309	70.9 (35.3 to 130.1)
Previous label of HF	103	493.6 (204.3 to 1341)
On diuretics	88	200 (76.1 to 672.8)
At high risk	134	160.1 (64.6 to 386.3)

Table 2 Distribution of NT-proBNP in each cohort

Cohort	AUROC	Sensitivity	Specificity	Positive predictive value (PPV)	Negative predictive value (NPV)	Accuracy
General population	0.95 (0.88 to 1.00)	100 (59 to 100)	79.5 (74.5 to 83.9)	10.1 (4.2 to 19.8)	100 (98.5 to 100)	79.9 (75 to 84.3)
Previous label of heart failure	0.83 (0.75 to 0.91)	97.2 (85.5 to 99.9)	29.9 (19.3 to 42.3)	42.7 (31.8 to 54.1)	95.2 (76.2 to 99.9)	53.4 (43.3 to 63.3)
On diuretics	0.91 (0.82 to 1.00)	93.3 (68.1 to 99.8)	43.8 (32.2 to 55.9)	25.5 (14.7 to 39.0)	97.0 (84.2 to 99.9)	52.3 (41.4 to 63.0)
High risk	0.88 (0.80 to 0.97	100 (66.4 to 100)	53.6 (44.5 to 62.6)	13.4 (6.3 to 24.0)	100 (94.6 to 100)	56.7 (47.9 to 65.2)

AUROC: Area under the receiver operating curve

Table 3 Performance characteristics for NT-proBNP (cut-off 150pg/ml)

Variable	Odds Ratio (95% confidence interval*)	P value
Previous label of HF	3.74 (1.45 to 9.69)	0.007
On diuretics	5.26 (1.70 to 16.31)	0.004
Diabetes	4.91 (1.66 to 14.51)	0.004
Hypertension	0.39 (0.16 to 0.97)	0.04
Angina	1.22 (0.99 to 5.00)	0.053
Myocardial infarction	1.61 (0.67 to 3.86)	0.29

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NT-proBNP >=150 pg/ml	17.65 (4.91 to 63.48)	<0.001

*Bootstrapped estimates

Table ~~3~~4 Logistic regression model to predict heart failure

Variable	Hazard Ratio (95% confidence interval*)	P value
Age	1.10 (1.08 to 1.10)	<0.001
Male ~~S~~sex	2.05 (1.43 to 2.95)	<0.001
Previous label of HF	1.75 (1.17 to 2.57)	0.007
On diuretics	0.90 (0.62 to 1.32)	0.59
Diabetes	1.08 (0.65 to 1.88)	0.78
Hypertension	1.37 (0.99 to 1.90)	0.06
Angina	1.04 (0.73 to 1.50)	0.82
Myocardial infarction	1.18 (0.80 to 1.73)	0.40
Shortness of breath	1.64 (1.14 to 2.37)	0.008
NT-proBNP >=150 pg/ml	1.58 (1.09 to 2.30)	0.02

*Bootstrapped estimates

Table ~~4~~5 Cox regression model of factors associated with mortality (including all study cohorts)

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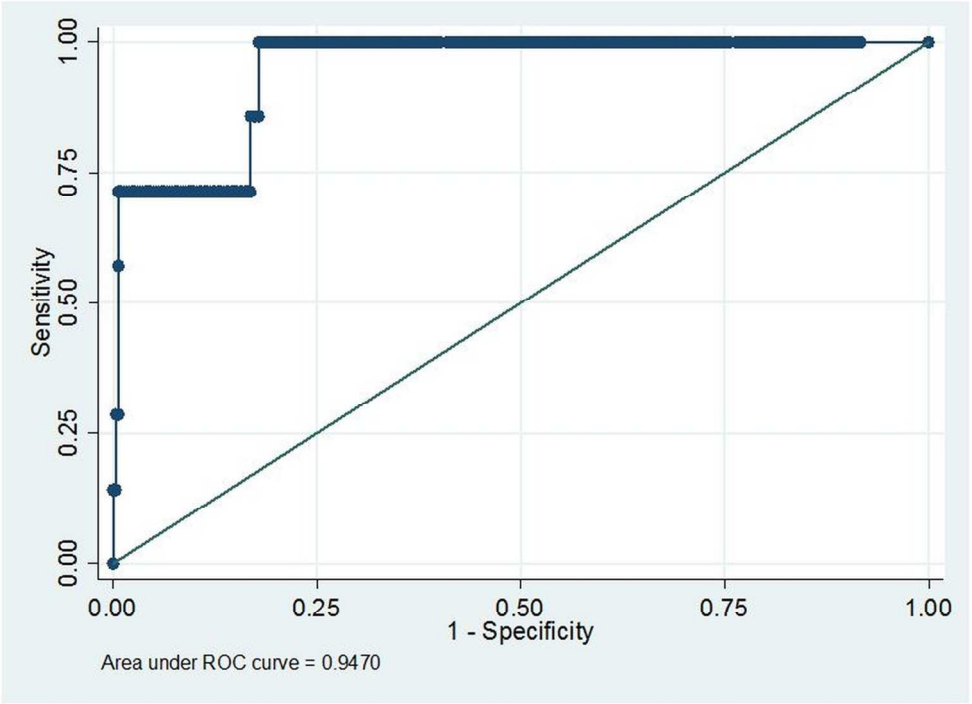

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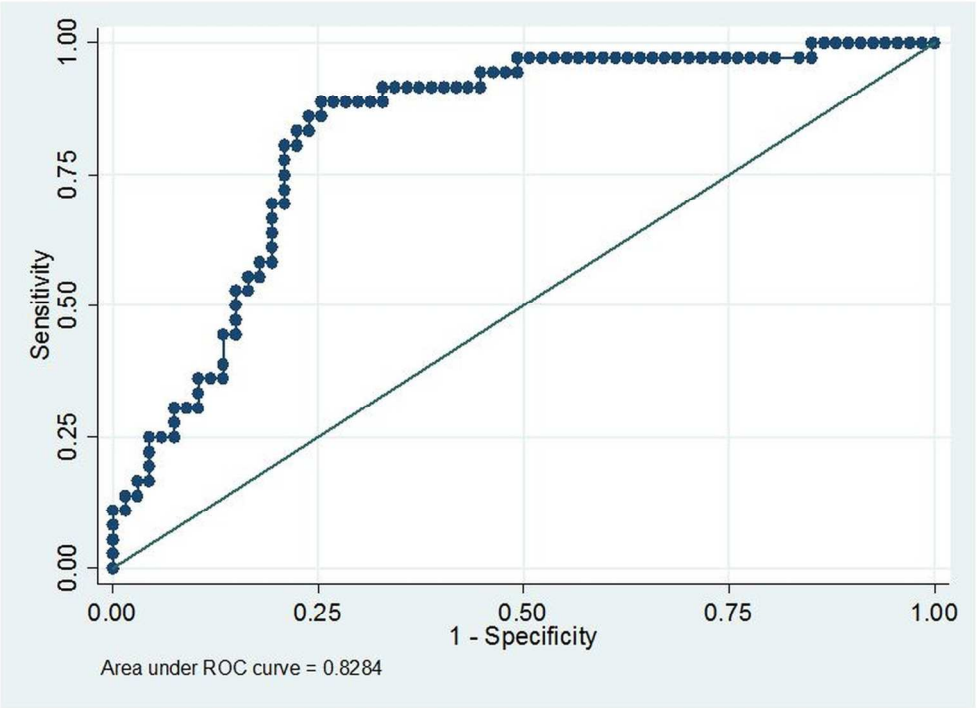

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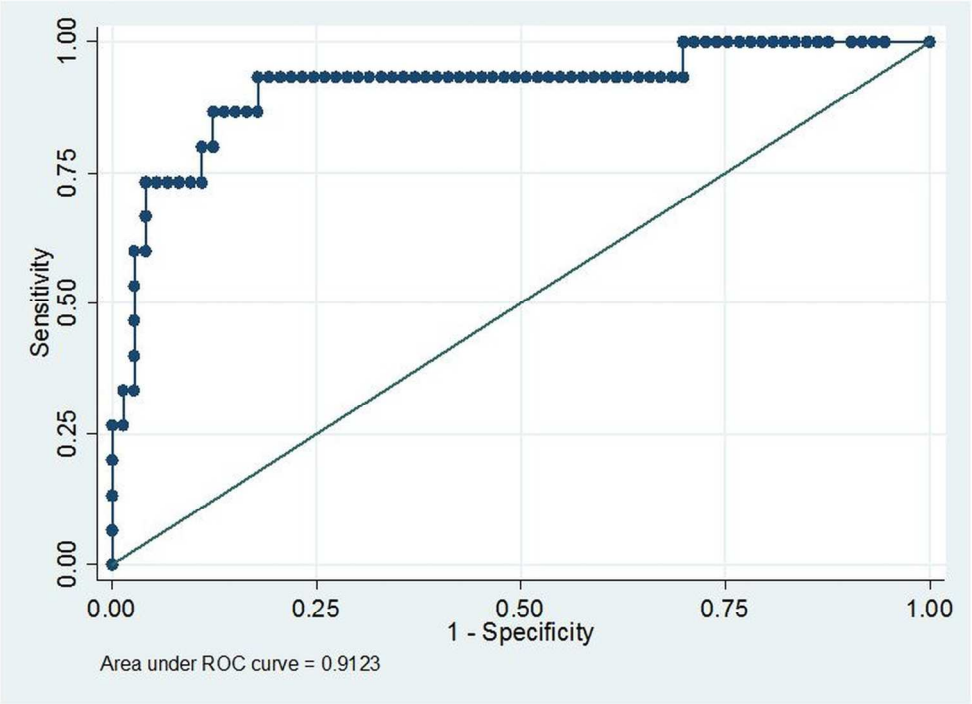

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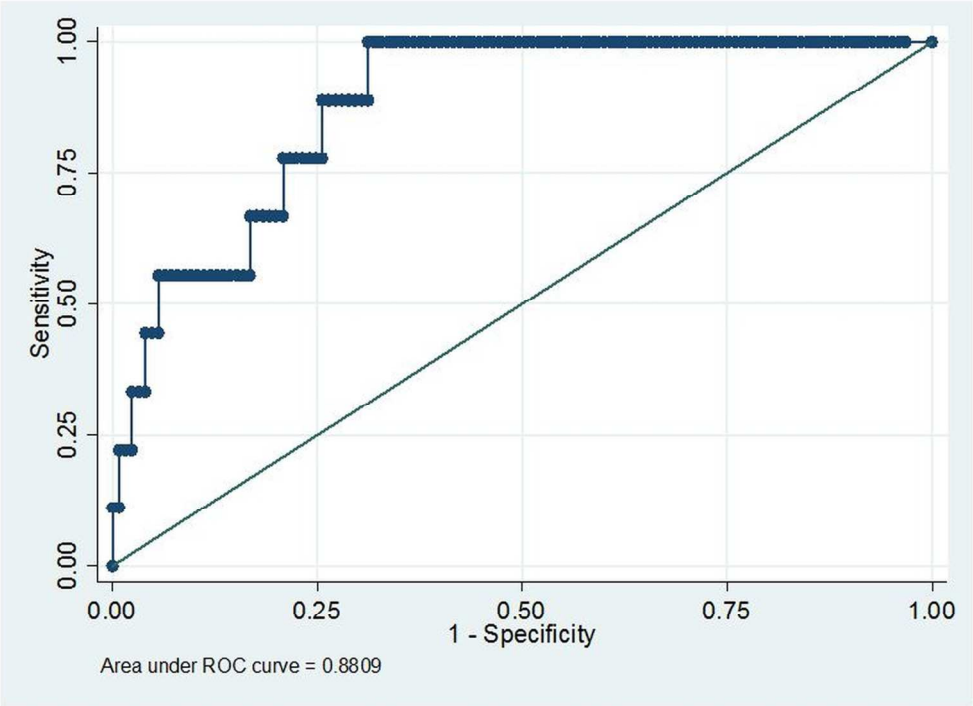

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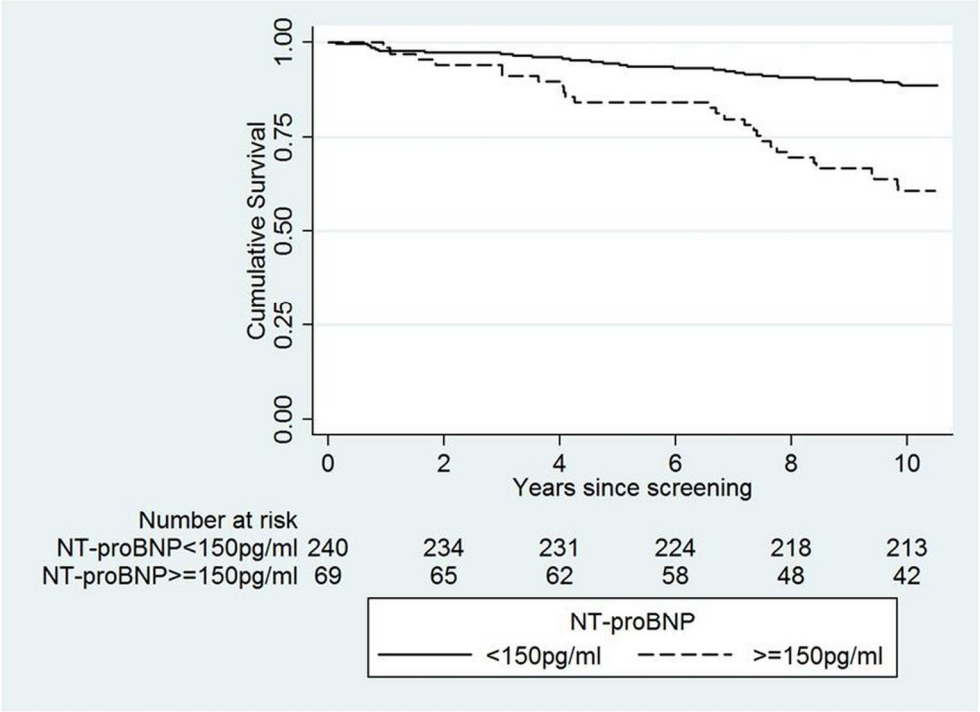

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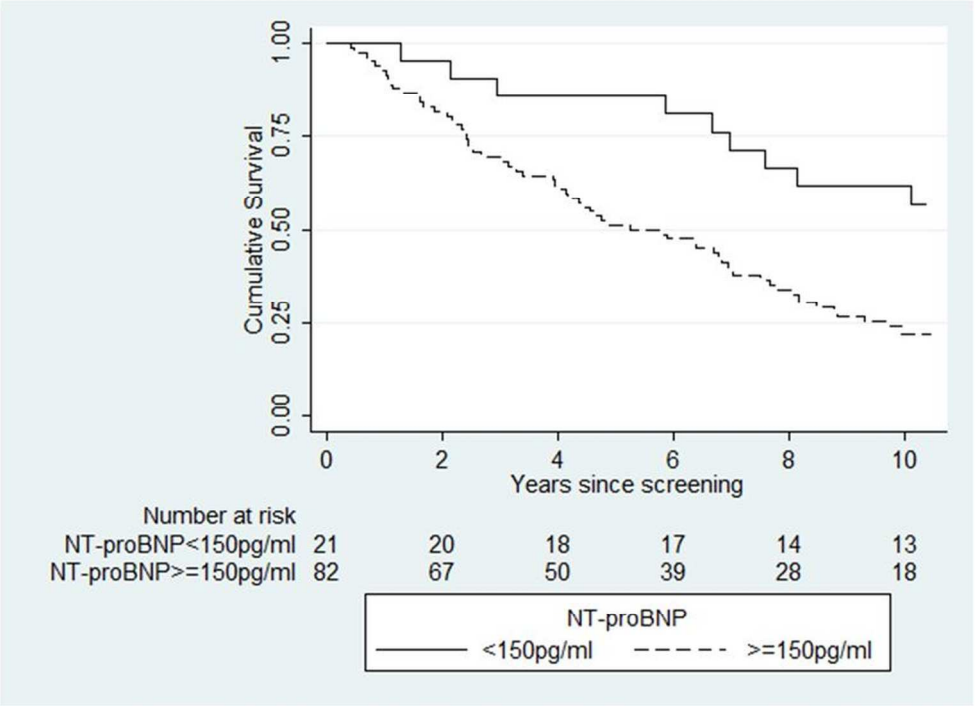

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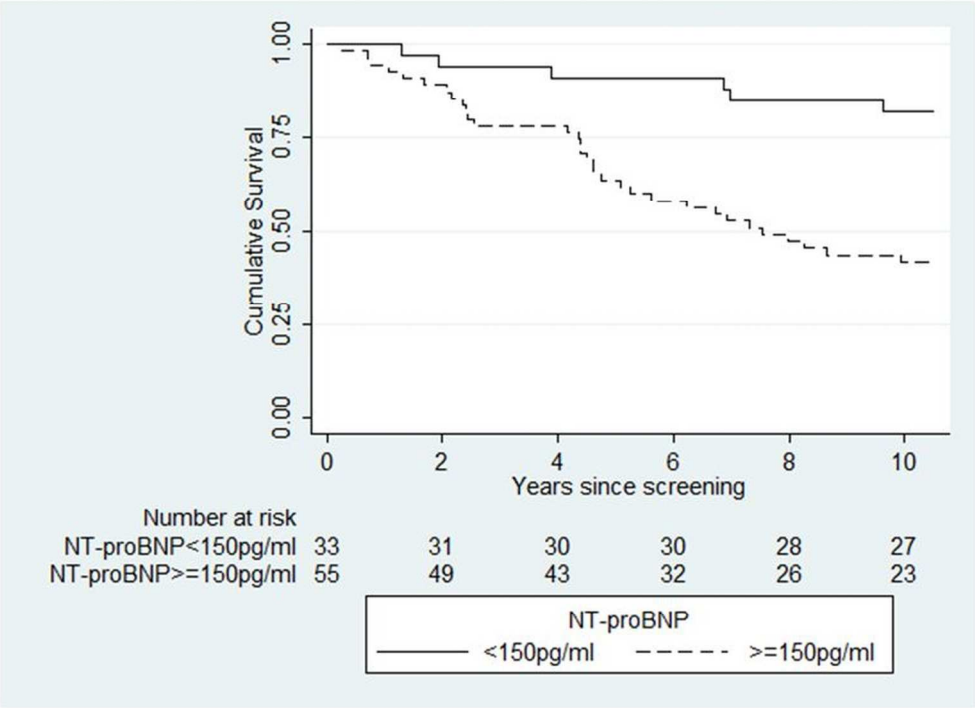

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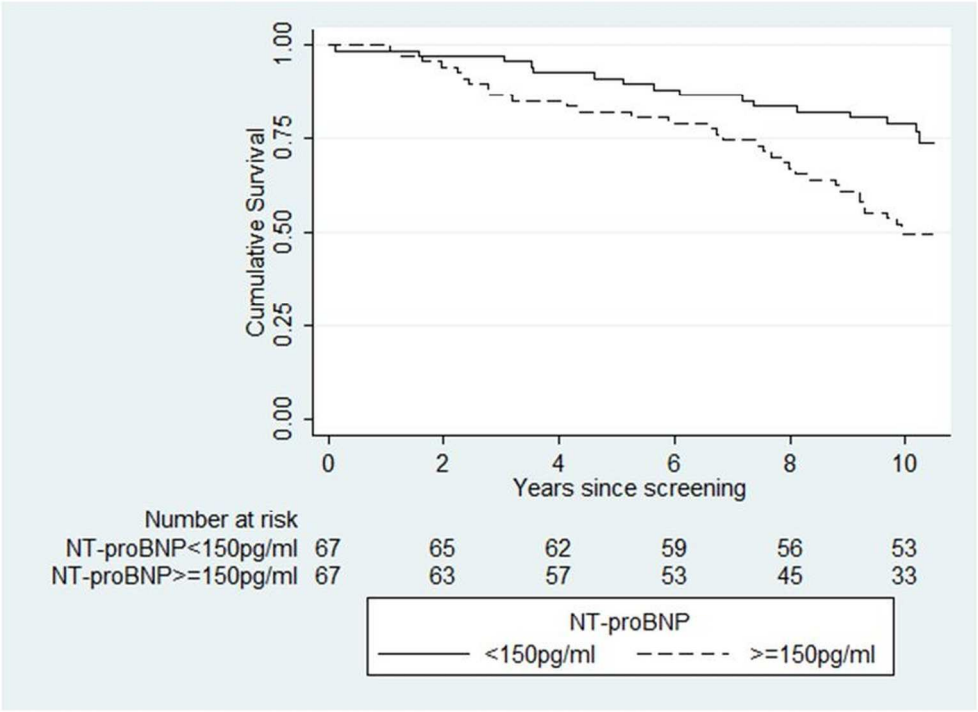

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