N-terminal pro brain natriuretic peptide but not copeptin improves prediction of heart failure over other routine clinical risk parameters in older men with and without cardiovascular disease: population-based study

S. Goya Wannamethee1*, Paul Welsh2, Peter H. Whincup3, Lucy Lennon1, Olia Papacosta1, and Naveed Sattar2

1Department of Primary Care and Population Health, UCL, London, UK; 2Institute of Cardiovascular & Medical Sciences, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, UK; and 3Department of Population Health Sciences and Education, St George’s, University of London, London, UK

Received 10 April 2013; revised 29 May 2013; accepted 14 June 2013

Aims Measurement of NT-proBNP and copeptin may help identify those at high risk of heart failure (HF). However, the value of NT-proBNP and copeptin has been little studied in the older population in primary care. This study aims to examine the use of NT-proBNP and copeptin in improving risk prediction and stratification of HF in older men with and without cardiovascular disease (CVD).

Methods and results This was a prospective study of 3870 men aged 60–79 years with no diagnosed HF followed up for a mean period of 11 years, during which there were 254 incident HF cases. NT-proBNP was associated with HF in those with and without established CVD [diagnosed myocardial infarction (MI), angina, or stroke]. NT-proBNP improved prediction beyond routine conventional risk factors (age, obesity, diabetes, hypertension, history of MI, and history of angina) and the Health ABC Heart Failure Score in all men and in men with and without established CVD (P<0.0001 for improvement in c-statistics). The net reclassification index (NRI) beyond conventional risk factors was 18.8% overall (27.4% for men without CVD and 17.4% for men with CVD). In contrast, copeptin was associated with HF in men with CVD only and did not improve prediction of HF after inclusion of conventional risk factors (P = 0.95 for improvement in c-statistics).

Conclusion NT-proBNP, but not copeptin, significantly improves prediction and risk stratification of HF beyond routine clinical parameters obtained in general practice settings in older men both with and without established CVD.

Keywords NT-proBNP • Copeptin • Heart failure • Epidemiology

Introduction

Heart failure (HF) constitutes a major and increasing burden of morbidity and mortality in older people, leading to high healthcare costs. Identifying high risk individuals to target HF prevention in primary care remains a priority. Current guidelines have stimulated efforts to focus on identifying those with stage A (presence of risk factors) and stage B HF (asymptomatic ventricular dysfunction detectable on echocardiography), in order to implement early interventions to prevent progression to stage C (overt HF). Although echocardiography provides effective non-invasive assessment of HF, routine echocardiographic screening is expensive and not currently recommended for use in the general population. The optimal strategy for identifying people at high risk in the general population remains unclear, though the use of blood markers in primary care settings to identify those at high risk of developing HF is potentially

*Corresponding author. Department of Primary Care and Population Health, University College London, Royal Free Campus, London NW3 2PF, UK. Tel: +44 20 7794 0500, ext. 34765, Fax: +44 20 7472 6871, Email: g.wannamethee@ucl.ac.uk

doi:10.1093/eurjhf/hft124

First published online on 30 July 2013, doi:10.1093/eurjhf/hft124.

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promising.7 The aetiology of HF involves interplay between myocardial ischaemia and remodelling, fibrosis, inflammation, and neurohormonal activation.8 NT-proBNP, a peptide released from myocardium in response to ventricular wall stress and dysfunction, has emerged as a strong predictor of incident HF in high risk populations7 and in the general population.6,9–12 In recent years, there has been interest in the neurohormones in the cascade of the arginine vasopressin (AVP) axis in the pathogenesis of HF.11 Plasma C-terminal provasopressin (copeptin), the C-terminal part of the AVP precursor peptide, is a vasoconstrictor that is secreted from the posterior pituitary in response to changes in plasma osmolarity and reduced cardiac output as part of a defence mechanism to preserve circulatory homeostasis.13,14 Copeptin has been established as a reliable marker of circulating AVP concentration in routine clinical practice.13,14 Higher levels of copeptin have been associated with increased risk of death in patients with HF,13,14 and copeptin has been shown to predict HF in patients with prior myocardial infarction (MI).15 A recent report has highlighted the potential value of combined measurements of copeptin and NT-proBNP in elderly patients presenting in primary care with early symptoms of HF in predicting cardiovascular disease (CVD) mortality.14 However, copeptin was not shown to predict HF in the general middle-aged population,8 and the use of copeptin in predicting HF in the elderly, where most cases of HF occur, has not been established.

While NT-proBNP has improved prediction of HF beyond established routine clinical risk factors3–8,10–12 and the Health ABC Heart Failure Score,13,14 the use of NT-proBNP testing in older adults (>60 years old) with and without CVD has been less studied, particularly in a primary care setting. We have therefore examined the clinical utility of NT-proBNP and copeptin in an elderly population of men with and without prevalent CVD. We assessed each biomarker's ability to improve the prediction of HF beyond established clinical HF risk factors (and Health ABC Heart Failure Score) and to what extent they add predictive information beyond inflammatory markers which have been shown to improve risk prediction for HF.17 Finally, we assessed the performance of NT-proBNP and copeptin in improving risk stratification for incident HF.

Methods

The British Regional Heart Study is a prospective study involving 7735 men aged 40–59 years drawn from one general practice in each of 24 British towns, who were screened between 1978 and 1980.18 The population studied was socio-economically representative of British men and comprises predominantly white Europeans (>99%). In 1998–2000, all surviving men, then aged 60–79 years, were invited for a 20th year follow-up examination, on which the current report is based. Ethical approval was obtained from all relevant local research ethics committees, and informed consent has been obtained from the subjects. All men completed a mailed questionnaire providing information on their lifestyle and medical history, had a physical examination, and provided a fasting blood sample. The samples were frozen and stored at −20°C on the day of collection and transferred in batches for storage at −70°C until analysis, carried out after no more than one freeze–thaw cycle. The 12-lead ECGs were recorded using a Siemens Sicard 460 instrument and were analysed using Minnesota Coding definitions at the University of Glasgow ECG core laboratory.19 The men were asked whether a doctor had ever told them that they had angina or MI, HF, or stroke; details of their medications were recorded at the examination. A total of 4252 men (77% of available survivors) attended for examination. Blood measurements, including NT-proBNP and copeptin, were available in 3985 men (94%) at the 20-year follow-up examination (1998–2000). Of these men, we excluded 115 men with prevalent HF, leaving 3870 men for analysis.

Cardiovascular risk factors at 1998–2000

Details of measurement and classification methods for smoking status, body mass index, physical activity, social class, alcohol intake, blood pressure, blood lipids, and forced expiratory volume in 1 s (FEV1) in this cohort have been described.20–22 C-reactive protein (CRP) was assayed by ultrasensitive nephelometry (Dade Behring, Milton Keynes, UK). Predicted glomerular filtration rate (eGFR), a measure of renal function, was estimated from serum creatinine using the Modification of Diet in Renal Disease equation developed by Levy et al.23 eGFR = 186 × creatinine−1.154 × age−0.203. Electrocardiographic LV hypertrophy (LHV) was defined according to relevant Minnesota codes (codes 3.1 or 3.3). Atrial fibrillation was defined according to Minnesota codes 8.3.1 and 8.3.3.

Laboratory methods

Manufacturers' calibrators and controls were used in the measurement of NT-proBNP and copeptin in accordance with their instructions. NT-proBNP was determined using the Elecsys 2010 electrochemiluminescence method (Roche Diagnostics, Burgess Hill, UK).24 The lower limit of sensitivity was 5 pg/mL. Low control coefficient of variation (CV) was 6.7% and high control CV was 4.9%. Data on NT-proBNP were available in 3672 men. Copeptin was measured using an ultrasensitive method on a BRAHMS Kryptor compact plus (B.R.A.H.M.S, Bottisham, UK). The lower limit of sensitivity was 0.9 pmol/L. Low control CV was 4.7% and high control CV was 4.6%. Data on copeptin were available in 3560 men.

Follow-up

All men have been followed up from initial examination (1978–1980) for cardiovascular morbidity,25 and follow-up has been achieved for 99% of the cohort. In the present analyses, all-cause mortality and morbidity events are based on follow-up from re-screening in 1998–2000 at mean age 60–79 years to June 2010, a mean follow-up period of 11 years (range 10–12 years). During this period, 1278 men had died. Survival times were censored at date of HF, death from any cause, or end of the study follow-up period (June 2010), whichever occurred first. Fatal coronary heart disease (CHD) events were defined as death with CHD [International Classification of Diseases (ICD) 9th revision, codes 410–414] as the underlying code. A non-fatal MI was diagnosed according to World Health Organization criteria. Evidence of non-fatal MI and HF was obtained by ad hoc reports from general practitioners supplemented by biennial reviews of the patients' practice records (including hospital and clinic correspondence) through to the end of the study period. Incident non-fatal HF was based on a confirmed doctor diagnosis of HF from primary care records and confirmed by a review of available clinical information from primary and secondary care records (including symptoms, signs, investigations, and treatment response) to ensure that the diagnosis was consistent with current recommendations on HF diagnosis.26 The incidence and determinants of HF cases identified using this process have already been reported and are consistent with results from other studies.27 Incident HF included incident non-fatal HF as well as death from HF (ICD 9th revision code 428).
Statistical methods
The distribution of NT-proBNP and copeptin was skewed, and log transformation was used. Cox’s proportional hazards model was used to assess the multivariate-adjusted hazards ratio (HR) (relative risk) in a comparison of quarters of NT-proBNP (copeptin) and for a 1 standard deviation increase in log NT-proBNP (log copeptin). In multivariate analyses, smoking [never, long-term ex-smokers (>15 years), recent ex-smokers (<15 years), and current smokers], social class (manual vs. non-manual), physical activity (four groups), alcohol intake (five groups), diabetes (yes/no), use of antihypertensive treatment (yes/no), pre-existing MI (yes/no), LVH (yes/no), and AF (yes/no) were fitted as categorical variables. Systolic blood pressure, FEV\textsubscript{1}, CRP, eGFR, and NT-proBNP were fitted as continuous variables. Receiver operating characteristic (ROC) curves and areas under the curve (AUC) (c-statistics) were used to assess the ability of NT-proBNP (copeptin) to predict HF beyond a score which included conventional routine risk factors as well as how NT-proBNP predicted beyond the Health ABC Heart Failure Score. Conventional routine risk factors included established risk factors for HF routinely obtained in clinical practice, e.g., age, obesity, hypertension, history of diabetes, history of MI, and history of angina. The Health ABC Heart Failure Score includes age, smoking, eGFR, heart rate, LVH, albumin, systolic blood pressure, history of MI and angina, fasting blood glucose, and antihypertensive treatment. We calculated risk function estimates based on the regression coefficients of the Cox’s models with and without NT-proBNP (copeptin) in the model. Tests for differences between the c-statistics for established risk function models with and without NT-proBNP (copeptin) were performed using an SAS macro (%ROC) with SAS software (version 9.3). To address the issue of how NT-proBNP evaluation may alter the risk stratification of men, all men were categorized according to three risk groups based on their 10 year predicted probabilities, <10%, 10–19%, and ≥20%, obtained from risk function models for HF events with and without NT-proBNP. The 20% cut-off was used as it is estimated that lifetime risk for developing HF is 20%. We evaluated the ability of NT-proBNP to reclassify risk by calculating the net reclassification improvement (NRI) and the integrated discrimination improvement (IDI). We also examined the prognostic value of NT-proBNP in healthy normal subjects, HF stage A subjects (those with traditional risk factors for CVD but without established CVD or HF), and men with pre-existing established CVD (MI, stroke, or angina) based on a previous doctor diagnosis of one or more of these conditions. Stage A subjects included those with obesity, hypertension, cigarette smoking, dyslipidemia (statin use), or diabetes 1 (n = 2411). Healthy normal included those with none of these risk factors and without pre-existing CVD (n = 645).

Results
Table 1 shows baseline characteristics of the study population. During the mean follow-up period of 11 years, there were 257 incident HF cases (5.9/1000 person-years) in the 3870 men with no previous diagnosed HF. Mean (geometric) NT-proBNP and copeptin were significantly higher in those with pre-existing CVD (MI, angina, or stroke) (186.8 vs. 81.5 pg/mL; P < 0.0001 and 4.33 vs. 3.92 pmol/L; P = 0.0006, respectively) than men without CVD. The 99th percentiles for NT-proBNP in those with and without CVD were 3254 and 1752 pg/mL, and the corresponding 99th percentiles for copeptin were 36.42 and 22.24 pmol/L, respectively.

Figure 1 shows the Kaplan–Meier estimates of the cumulative incidence of HF by quarters of NT-proBNP and copeptin in all men. Risk of HF increased significantly with increasing quarters of NT-proBNP (log rank test, P < 0.0001) and to a weaker extent with increasing quarters of copeptin (log rank test, P = 0.002).

In all men, risk of HF increased significantly by NT-proBNP quarters after adjustment for age, smoking, physical activity, social class, alcohol intake, systolic blood pressure, prevalent diabetes, history of CHD (angina or MI), use of antihypertensive treatment, and LVH (Table 2). Further adjustment for eGFR, CRP, albumin, FEV\textsubscript{1}, heart rate, and ECG evidence of ischaemia and silent MI had minor effects on the findings. When examined separately in men with and without CVD, the strong positive association between NT-proBNP and HF was broadly comparable in both groups (Table 2). Exclusion of men who developed a non-fatal MI during the follow-up period made minor differences to the findings (data not shown). Raised

| Parameters           | Value     |
|----------------------|-----------|
| Mean age             | 68.61 (5.51) |
| Current smoking      | 12.8%     |
| Ex-smokers           | 58%       |
| Inactive             | 10.6%     |
| Manual               | 53.7%     |
| Heavy drinkers       | 3.8%      |
| BMI, kg/m\textsuperscript{2} | 26.84 (3.62) |
| History of MI        | 10.0%     |
| Silent MI (ECG only) | 2.6%      |
| History of angina    | 13.0%     |
| History of diabetes  | 6.9%      |
| Stroke               | 5.2%      |
| Use of antihypertensive drugs | 32.6% |
| Hypertensives        | 70.7%     |
| Statin use           | 6.9%      |
| Left ventricular hypertrophy | 7.7% |
| Atrial fibrillation  | 3.4%      |
| Systolic BP, mmHg    | 149.34 (24.0) |
| Diastolic BP, mmHg   | 85.34 (11.07) |
| Cholesterol, mmol/L  | 0.01 (11.08) |
| HDL-cholesterol, mmol/L | 1.32 (0.34) |
| Glucose, mmol/L      | 5.87 (5.25–6.10) |
| eGFR, L              | 2.60 (0.65) |
| C-reactive protein, mg/L | 1.72 (0.82–3.43) |
| NT-proBNP, pg/mL     | 97.51 (46–189) |
| Copeptin, pmol/L     | 3.81 (2.44–6.23) |

All results are given as either percentage, mean (SD), or median and interquartile range.

BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; FEV\textsubscript{1}, forced expiratory volume in 1 s; MI, myocardial infarction.

Hypertensive, systolic BP ≥140 or diastolic BP ≥90 or on blood-lowering treatment.
NT-proBNP (i.e. top quarter) was associated with a markedly increased risk of HF in healthy normal men, in those with stage A risk factors, and in men with CVD [adjusted HR 3.34, 95% confidence interval (CI) 1.93–5.70; \( P \leq 0.0001 \); HR 2.25, 95% CI 1.91–2.65; \( P \leq 0.0001 \); and HR 2.13, 95% CI 1.71–2.65; \( P \leq 0.0001 \), respectively].

Copeptin correlated significantly but only modestly with NT-proBNP (\( r = 0.18; P \leq 0.0001 \)). Elevated copeptin was associated with increased risk of HF, but this was markedly attenuated after adjustment for conventional risk factors and was no longer significant after further adjustment for blood markers (model 2; Table 3). When stratified by presence of CVD, copeptin was only associated with risk of HF in those with CVD after adjustment for routine clinical risk. However, this association was also attenuated to borderline significance after adjustment for additional risk factors (model 2) and was completely abolished after further adjustment for NT-proBNP (1 SD increase in log copeptin HR 1.09, 95% CI 0.84–1.41; \( P = 0.48 \)).

**Figure 1** Kaplan–Meier curves of cumulative heart failure (HF) incidence by quartiles of NT-proBNP (<42, 42–77, 78–151, ≥152 pg/mL) and by quartiles of copeptin (<2.46, 2.46–3.85, 3.86–6.32, ≥6.33 pmol/L) in men without prevalent HF.
In contrast, the association between NT-proBNP remained highly significant after adjustment for copeptin (1 SD increase in log NT-proBNP HR 2.04, 95% CI 1.56–2.69; P<0.0001).

### Table 2 N-terminal pro brain natriuretic peptide and incident heart failure risk in men with no diagnosed heart failure

|                        | Adjusted HR (95% CI) |
|------------------------|----------------------|
|                        | Age only             | Model 1 | Model 2 | Model 3 |
| All men (n = 3672; 250 cases) |                      |         |         |         |
| 1 (<42)                | 1.00                 | 1.00    | 1.00    | 1.00    |
| 2 (42–77)              | 3.23 (1.69–6.16)     | 2.91 (1.52–5.58) | 2.83 (1.48–5.43) | 2.85 (1.49–5.47) |
| 3 (78–151)             | 4.27 (2.27–8.06)     | 3.51 (1.85–6.64) | 3.39 (1.79–6.42) | 3.38 (1.78–6.41) |
| 4 (≥152)               | 14.22 (7.78–25.98)   | 9.87 (5.31–18.33) | 9.02 (4.84–16.80) | 8.51 (4.54–15.89) |
| 1 SD increase in log NT-proBNP | 2.42 (2.16–2.72) | P<0.0001 | 2.21 (1.93–2.53) | 2.15 (1.88–2.48) | 2.21 (1.93–2.53); 2.26 (1.93–2.65) |
| Men with no CVD (n = 2903; 153 cases) | |         |         |         |
| 1 SD increase in log NT-proBNP | 2.24 (1.93–2.60) | P<0.0001 | 2.17 (1.87–2.52) | 2.14 (1.81–2.54) | 2.01 (1.66–2.43); 1.97 (1.62–2.38) |
| Men with CVD (n = 769; 97 cases) | |         |         |         |
| 1 SD increase in log NT-proBNP | 2.22 (1.75–2.82) | P<0.0001 | 2.33 (1.84–2.96) | 2.12 (1.63–2.75) | 2.42 (1.82–3.21); 2.73 (2.01–3.72) |

Missing data on NT-proBNP; n = 198.
1 SD log NT-proBNP = 1.16.
Model 1: adjusted for age, smoking, physical activity, social class, alcohol intake, LV hypertrophy, systolic blood pressure, antihypertensive drugs, history of MI, angina.
Model 2: adjusted for model 1 + eGFR + FEV1 + albumin + CRP.
Model 3: model 2 + heart rate, AF, ECG evidence of ischaemia and silent MI.
CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume in 1 s; MI, myocardial infarction.

### Table 3 Copeptin and incident heart failure risk in men with no diagnosed heart failure

|                        | Adjusted HR (95% CI) |
|------------------------|----------------------|
|                        | Age only             | Model 1 | Model 2 |
| All men (n = 3560; 234 cases) |                      |         |         |
| 1 (<2.46)              | 1.00                 | 1.00    | 1.00    |
| 2 (2.46–3.85)          | 1.10 (0.73–1.65)     | 1.04 (0.69–1.56) | 1.03 (0.68–1.55) |
| 3 (3.86–6.32)          | 1.44 (0.99–2.12)     | 1.27 (0.86–1.87) | 1.17 (0.79–1.73) |
| 4 (>6.32)              | 1.72 (1.18–2.51)     | 1.35 (0.92–1.99) | 1.18 (0.79–1.76) |
| 1 SD increase in log copeptin | 1.31 (1.12–1.54) | P = 0.001 | 1.19 (1.04–1.52) | 1.13 (0.97–1.42) |
| Men with no CVD (n = 2807; 139 cases) | |         |         |
| 1 SD increase in log copeptin | 1.20 (1.01–1.65) | P = 0.03 | 1.07 (0.87–1.40) | 1.02 (0.85–1.23) |
| Men with CVD (n = 753; 95 cases) | |         |         |
| 1 SD increase in log copeptin | 1.43 (1.19–1.72) | P = 0.0002 | 1.33 (1.10–1.61) | 1.24 (0.99–1.53) |

Missing data on copeptin; n = 310.
1 SD log copeptin = 0.71.
Model 1: adjusted for age, smoking, physical activity, social class, alcohol intake, LV hypertrophy, systolic blood pressure, antihypertensive drugs, history of MI, angina.
Model 2: adjusted for model 1 + eGFR + FEV1 + albumin + CRP.
CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume in 1 s; MI, myocardial infarction.

Table 4 shows the c-statistics for the conventional risk score and the Health ABC Heart Failure Score, and the improvement in c-statistics in models with and without NT-proBNP, copeptin, or
Table 4 Improvement in c-statistics for conventional models and the Health ABC Heart Failure Score models with and without N-terminal pro brain natriuretic peptide, copeptin and C-reactive protein

|                          | c-Statistics         | P-value improvement |
|--------------------------|----------------------|---------------------|
| All men                  | 0.706 (0.672–0.739)  | –                   |
| ABC risk score           | 0.764 (0.735–0.794)  | P<0.0001            |
| ABC risk score + NT-proBNP | 0.768 (0.739–0.798) | P<0.0001            |
| Conventional risk factors| 0.708 (0.676–0.741) | –                   |
| Conventional risk factors + NT-proBNP | 0.704 (0.670–0.740) | P = 0.95           |
| Conventional risk factors + copeptin | 0.706 (0.672–0.739) | P = 0.67           |
| Conventional risk factors + CRP | 0.773 (0.744–0.800) | P<0.0001            |
| Conventional risk factors + CRP + NT-proBNP | 0.767 (0.635–0.722) | –                   |
| Conventional risk factors + NT-proBNP | 0.753 (0.715–0.792) | P<0.0001            |
| Conventional risk factors + NT-proBNP | 0.684 (0.642–0.727) | –                   |
| Conventional risk factors + NT-proBNP | 0.760 (0.723–0.799) | P<0.0001            |
| Conventional risk factors + NT-proBNP | 0.704 (0.650–0.758) | –                   |
| Conventional risk factors + NT-proBNP | 0.744 (0.695–0.792) | P = 0.03            |
| Conventional risk factors | 0.663 (0.608–0.718) | –                   |
| Conventional risk factors + NT-proBNP | 0.725 (0.673–0.776) | P = 0.004           |

Conventional risk factors include age, obesity, hypertension, history of diabetes, history of MI and history of angina.

Clinical risk factors included age, smoking, eGFR, heart rate, LV hypertrophy, albumin, systolic blood pressure, history of MI and angina, fasting glucose, and antihypertensive treatment.

CRP, C-reactive protein; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction.

Discussion

In this study of older men, NT-proBNP markedly improved prediction of HF beyond the established Health ABC Heart Failure Score and beyond established routine clinical parameters, whereas copeptin and CRP did not. NT-proBNP improved sensitivity in the prediction of HF, and thus improved risk classification among those who experienced HF. Our finding extends those of previous studies by examining the prognostic value of NT-proBNP and improvement in risk prediction in those with and without CVD separately within the same general older population and comparing the predictive value of NT-proBNP with other markers including in particular copeptin, but also CRP. The findings that NT-proBNP improved prediction even in asymptomatic men suggests that it is detecting men with subclinical cardiac dysfunction (or capturing other risk pathways relevant to HF risk) in men not considered to be at elevated risk.

The association between NT-proBNP and HF is not explained by conventional risk factors for HF; symptoms of general poor health (lung function, renal dysfunction, and inflammation), heart rate, and presence of AF or evidence of ischaemia on ECG, and the association is not mediated by the development of an MI. NT-proBNP has been shown to be associated with the development of AF, a strong risk factor for HF. We did not have information on AF during follow-up and it is possible that part of the association may be mediated by the development of AF. Although we did not have echocardiographic measures, previous studies have shown the association between NT-proBNP and HF to be independent of LV mass.
Measurement of NT-proBNP is not currently recommended for CHD risk assessment in asymptomatic adults. While several studies have evaluated the performance of NT-proBNP for the purpose of reclassifying HF risk in the general population, few have examined the performance of NT-proBNP separately in those without established CVD and in those with established CVD. Our study suggests that measurement of NT-proBNP improves risk prediction and stratification over models that consider clinical variables alone as well as the Health ABC Heart Failure Score in both asymptomatic men and men with established CVD. Of interest, work in part from our group suggests that NT-proBNP deserves greater consideration for general CVD risk screening.

In contrast, copeptin showed much weaker associations with HF than NT-proBNP in this older population and was not associated with increased HF risk in men with CVD after taking into account clinical risk factors and NT-proBNP. Although copeptin has been shown to be a potentially useful prognostic marker of mortality in addition to NT-proBNP and in addition to high-sensitivity troponin in HF patients, copeptin was not a useful predictor of HF in this older population without HF. This is consistent with a previous report showing no association between copeptin and HF in a middle-aged population. The majority of men in this study (96.9%) had levels below the reference limit (97.5 percentile) of 16.8 pmol/L seen in a healthy population. Thus copeptin does not appear to predict incident HF, but raised copeptin is a useful prognostic marker when HF is present and in those in whom the majority (> 55%) were seen to have levels above this reference range.

Our study is not without some limitations. It was based on an older, predominantly white, male population of European origin, so that the results cannot be generalized directly to women, or to younger populations or other ethnic groups. The current findings are based on doctor-diagnosed HF, which is likely to underestimate the true incidence of HF in this study population. However, the other risk factor associations with HF risk in this report and in our previous report on obesity and HF generally agree with previous data and therefore suggest potential external validity for our findings. Echo-cardiographic measurements were not carried out in the present study and we were not therefore able to differentiate systolic and diastolic HF. Like other studies, our reclassification model is not based on any current clinical guidelines, although it serves to illustrate the way in which NT-proBNP might usefully improve risk models as they develop.

In conclusion, we have shown that NT-proBNP but, importantly, not copeptin significantly improves prediction and risk stratification of HF beyond routine clinical parameters obtained in general practice settings in both older men with and without established CVD, suggesting potential for optimizing chronic HF therapy or to prevent its development. Further large studies are needed to determine the practicality and process as well as the potential cost-effectiveness of performing NT-proBNP testing in selected older adults in the general population to detect high risk subjects for HF.

Funding
The British Regional Heart Study is a British Heart Foundation (BHF) research group and receives support from the BHF Programme grant (RG/08/013/25942). P.W. is supported by BHF fellowship FS/12/62/29889. Copeptin measurements were funded by the NIHR School for Primary Care Research.

Conflict of interest: none declared.
17. Kalogeropoulos A, Georgiopoulou V, Patsy BM, Rodondi N, Smith AL, Harrison DG, Lu Y, Hoffmann U, Bauer DC, Newman AB, Kritchevsky SB, Harris TB, Butler J. Health ABC Study Investigators. Inflammatory markers and incident heart failure risk in older adults. J Am Coll Cardiol 2010;55:2129 – 2137.

18. Shaper AG, Popocic SJ, Walker M, Cohen NM, Wale CJ, Thomson AG, et al. British Regional Heart Study: cardiovascular risk factors in middle-aged men in 24 towns. BMJ 1981;283:179 – 186.

19. Macfarlane PW, Devine B, Latif S, McLaughlin S, Shoat DB, Watts MP. Methodology of ECG interpretation in the Glasgow program. Methods Inf Med 1990;29:354 – 361.

20. Wannamethee SG, Lowe GDO, Whincup PH, Rumley A, Walker M, Lennon L. Physical activity and hemostatic and inflammatory variables in elderly men. Circulation 2002;105:1785 – 1790.

21. Wannamethee SG, Lowe GDO, Whincup PH, Rumley A, Lennon L, Lowe GD. C-reactive protein and incident heart failure in older men with and without pre-existing coronary heart disease. Circulation 2002;106:3165 – 3170.

22. Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Sattar N. Obesity and risk of incident heart failure in older men with and without pre-existing coronary heart disease: does keptin have a role? J Am Coll Cardiol 2011;58:1870 – 1877.

23. Levy AS, Bosch JP, Lewis JR, Greene T, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1990;112:410 – 417.

24. Wannamethee SG, Welsh P, Doolin O, Packard C, Cobbe S, Cobbe S, Greenland P, et al. AHA Guideline for assessment of cardiovascular risk in asymptomatic adults: executive summary. J Am Coll Cardiol 2008;52:157 – 172.

25. Walker M, Saeed A, Lennon L, Whincup PH, Smith AL, Harrison DG, et al. 25. Walker M, Shaper AG, Lennon L, Whincup PH, Rumley A, Walker M, Lennon L. Physical activity and hemostatic and inflammatory variables in elderly men. Circulation 2002;105:1785 – 1790.

26. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Filippatos G, Fonseca C, Gómez-Sanchez MA, Janssens T, Kobal L, Lip GY, Maggioni AP, Parkhomenko A, Pfeffer M, Popescu BA, Rennick PK, Rutten FH, Schwitter J, Seferovic P, St John Sutton M, Voors AA, Zannad F, Zijlstra F, Zoccali C. 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 J Heart Fail 2012;14:803 – 869.

27. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D’Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D. Framingham Heart Study: Lifetime risk for developing congestive heart failure: the Framingham Heart Study. Circulation 2002;106:3068 – 3072.

28. Pencina MJ, D’Agostino RB Sr, D’Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157 – 172.

29. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, et al. American Heart Association/American College of Cardiology Foundation. American Heart Association/American College of Cardiology Foundation: ACC/AHA Guideline on the Evaluation and Management of High Blood Pressure in Adults. JAMA 2013;310:507 – 520.

30. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, et al. American Heart Association/American College of Cardiology Foundation. American Heart Association/American College of Cardiology Foundation: ACC/AHA 2007 guidelines for the management of patients with ST-elevation myocardial infarction. Circulation 2007;116:267 – 314.

31. Tentzeris I, Jarai R, Farhan S, Perkmann E, Schwarz MA, Gabriele J, Wojta J, Huber K. Complementary role of copeptin and high-sensitivity troponin in predicting outcome in patients with stable chronic heart failure. Eur J Heart Fail 2011;13:726 – 733.

32. Reichlin T, Hochholzer W, Schmutz J, Winkler S, Altmann M, Schmidt A, et al. The role of copeptin in chronic heart failure: results from 15-year follow-up of WOSCOPS. Circulation 2010;122:e584 – e636.