Natriuretic peptides and integrated risk assessment for cardiovascular disease: an individual-participant-data meta-analysis

Natriuretic Peptides Studies Collaboration*

Summary

Background [A: Please add a sentence on the background to your study/why the study was done] We assessed whether or not evaluation of N-terminal-pro-B-type natriuretic peptide (NT-proBNP) concentration could enable integrated cardiovascular disease primary prevention by predicting heart failure and enhancing coronary heart disease and stroke risk assessment.

Methods In this individual-participant-data meta-analysis, we collected individual-participant data from relevant prospective cohorts of participants without a history of cardiovascular disease via both de-novo NT-proBNP concentration measurement of stored samples and a systematic search of the literature (PubMed, Scientific Citation Index Expanded, and Embase) for articles published up to Sept 4, 2014, using search terms related to natriuretic peptide family members and the primary outcomes, with no language restrictions. We calculated risk ratios and measures of risk discrimination and reclassification across predicted 10 year risk categories (ie, <5%, 5% to <7.5%, and ≥7.5%), adding NT-proBNP concentration assessment to age, sex, smoking status, systolic blood pressure, history of diabetes, and total and HDL cholesterol concentrations. Primary outcomes were effects of NT-proBNP concentration assessment on a combination of coronary heart disease and stroke and of coronary heart disease, stroke, and heart failure. We calculated hazard ratios in prospective studies with Cox proportional hazard regression models and odds ratios in nested case-control studies using logistic regression models, collectively referred to as risk ratios (for a comparison of the top third vs bottom third of NT-proBNP concentrations, adjusted for conventional risk factors). [A: Please check all methodological detail added to methods section correct]

Findings We recorded 5500 coronary heart disease, 4002 stroke, and 2212 heart failure outcomes among 95 617 participants in 40 prospective studies. Risk ratios were 1.76 (95% CI 1.56–1.98) for the combination of coronary heart disease and stroke and 2.00 (1.77–2.26) for the combination of coronary heart disease, stroke, and heart failure. [A: Deleted secondary outcomes as only primary outcomes reported in the summary] Addition of information about NT-proBNP concentration to a model containing conventional risk factors was associated with a C-index increase of 0.027 (0.019–0.036) for the combination of coronary heart disease and stroke and of coronary heart disease, stroke, and heart failure. Interpretation In people without baseline cardiovascular disease, NT-proBNP concentration assessment strongly predicted first-onset heart failure and augmented coronary heart disease and stroke prediction, suggesting that NT-proBNP concentration assessment could be used to integrate heart failure into cardiovascular disease primary prevention.

Funding British Heart Foundation, Austrian Science Fund, Medical Research Council, National Institute for Health Research, and European Commission Framework Programme 7 [A: Full names correct?].

Copyright © The Author(s). Published by Elsevier Ltd. This is an Open Access article under the XX license. [A: Which licence type have you chosen?]

Introduction Cardiovascular disease guidelines recommend strategies that predict and prevent composite endpoints for coronary heart disease and stroke.4 A rationale for this combined approach is to enhance efficiency of cardiovascular disease screening by capitalising on shared risk factors and preventive interventions, even though coronary heart disease and stroke have different causes. Such a rationale could be extended to heart failure. The age-specific incidence of heart failure is increasing; it is a common initial presentation of cardiovascular disease.5 Furthermore, statins and antihypertensive treatments might, in addition to their benefits for primary prevention of coronary heart disease and stroke, be effective at reducing the risk of new-onset heart failure. Practical advantages of a strategy that integrates heart failure prediction into cardiovascular disease risk assessment could exist since coronary heart
Research in context

Evidence before this study
We hypothesised that integrated cardiovascular disease risk assessment strategies could be extended to primary prevention of heart failure through measurement of N-terminal-pro-B-type natriuretic peptide (NT-proBNP) concentration. In a systematic review of the published literature, we identified a few dozen prospective studies of natriuretic peptides and incident coronary heart disease or stroke outcomes. We attempted a synthesis of these results in a previous literature-based review, but we found that using published results was insufficiently powered or detailed or both to enable reliable assessment of whether or not NT-proBNP concentration measurement could augment cardiovascular disease risk assessment. Furthermore, investigators of very few population-based prospective studies had reported on associations between NT-proBNP concentration and first-onset heart failure.

Added value of this study
The Natriuretic Peptides Studies Collaboration involved new NT-proBNP concentration measurements in eight prospective studies as well as collection and harmonisation of individual-participant data from a further 32 relevant prospective cohorts identified by an updated systematic review. This effort enabled a detailed and standardised analysis of primary data for 95,617 participants without a history of cardiovascular disease recruited into 40 prospective studies in 12 different countries.

Implications of all the available evidence
We found that NT-proBNP concentration assessment strongly predicted first-onset heart failure and augmented coronary heart disease and stroke prediction. The incremental predictive ability of NT-proBNP concentration for coronary heart disease and stroke was moderate, but still greater than were those for HDL cholesterol or C-reactive protein concentrations. Our results have suggested that NT-proBNP concentration assessment could serve as a multipurpose biomarker in new approaches that integrate heart failure into cardiovascular disease primary prevention.
The appendix (p 17) provides details of the methods used to collect and harmonise data. Contributing studies classified deaths according to the primary cause (or, in its absence, the underlying cause) on the basis of International Classification of Diseases coding, revisions eight to ten, to at least three digits, or according to study-specific classification systems. We based ascertainment of fatal outcomes on death certificates, sometimes supplemented by additional data, and of non-fatal outcomes on WHO (or similar) criteria for myocardial infarction and on clinical and imaging features for stroke and heart failure (appendix p 18). This article follows Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Individual Patient Data reporting (appendix pp 8–11). The study was designed and done by the Natriuretic Peptides Studies Collaboration’s independent coordinating centre and approved by the Cambridgeshire Ethics Review Committee.

Data analysis
The study involved three interrelated components. First, we characterised cross-sectional associations of NT-proBNP concentration with established and emerging risk factors. Second, we assessed associations of NT-proBNP concentration with first-onset coronary heart disease, stroke, and heart failure, singly and in combination. Third, we quantified the incremental predictive value of assessment of NT-proBNP concentration in addition to conventional risk factors for major cardiovascular disease outcomes. [A: Moved section for more logical placement, ok?]

We focused the principal analyses on NT-proBNP concentration data because NT-proBNP is a more stable analyte than is BNP and encompassed more than 95% of the data in the collaboration (reserving the sparse BNP data for supplementary analyses). We defined two primary outcomes: the effect of NT-proBNP concentration assessment on [A: Correct] a combination of coronary heart disease (defined as fatal or non-fatal myocardial infarction) and stroke and on a combination of coronary heart disease, stroke, and heart failure. Participants contributed only the first cardiovascular disease outcome (whether non-fatal or fatal) recorded during follow-up (ie, we did not include deaths preceded by non-fatal cardiovascular disease events). Secondary outcomes included the component cardiovascular disease outcomes (ie, coronary heart disease, stroke, and heart failure) and the aggregate of death due to additional cardiovascular disease outcomes (including cardiac arrhythmia and sudden death [A: Were these all the additional cardiovascular outcomes?] [A: Were these all the secondary outcomes?]). We censored outcomes if a participant was lost to follow-up, died from non-cardiovascular disease causes, or reached the end of the follow-up period.

We calculated hazard ratios from prospective studies with Cox proportional hazard regression models, stratified by sex, using time-on-study as a timescale. We assessed the proportional hazards assumption, which was satisfied, as previously described. Analyses of case-cohort data involved Prentice weights and robust SEs. We calculated odds ratios from nested case-control studies using logistic regression models. We assumed hazard and odds ratios to represent the same relative risk, collectively describing them as risk ratios. We calculated risk ratios for a comparison of individuals in the top third with those in the bottom third of baseline NT-proBNP values using a two-stage approach, with estimates calculated separately within each study before pooling across studies with multivariate random-effects meta-analysis. To characterise shapes of associations, we calculated pooled risk ratios within overall tenths of NT-proBNP concentration and plotted them against the pooled geometric mean of NT-proBNP concentration within each tenth. We adjusted risk ratios for baseline levels of conventional risk factors. We investigated effect modification by study-level and individual characteristics with meta-regression and formal tests of interaction. We assessed between-study heterogeneity with the $I^2$ statistic.

We developed cardiovascular disease risk prediction models containing information about conventional risk factors with or without NT-proBNP concentration only in cohort and case-cohort studies and quantified improvements in predictive ability using measures of risk discrimination and reclassification. We calculated C-indices and C-index changes within each study before pooling results weighted by the number of outcomes contributed. We calculated measures of risk reclassification (ie, integrated discrimination improvement and categorical and continuous net reclassification improvement) using data from studies in which both fatal and non-fatal events had been recorded. We examined categorical net reclassification of participants across predicted 10 year risk categories using cutoffs defined by the American College of Cardiology (ACC) and American Heart Association (AHA) 2013 (ie, <5%, 5% to <7.5%, and ≥7.5% [A: Correct]), National Institute of Health and Care Excellence 2014,4 American College of Cardiology Foundation and American Heart Association 2010,1 and European Society of Cardiology 2016 guidelines.7 We log-transformed NT-proBNP concentration and modelled it using both linear and quadratic terms (with similar approaches used for the analysis of HDL cholesterol and C-reactive protein [CRP] concentration). We did analyses using Stata software, version 12.1. All p values are two sided. The appendix (pp 5–6) provides further details of the analytical methods used.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. PW, JD, and EDA had full access to all the data in the study and had final responsibility for the decision to submit for publication. [A: Correct?]
Results

Measurement of stored samples from 7129 participants (including 1173 incident cardiovascular disease cases) was done for eight prospective studies (the Reykjavik Offspring Study, the Northern Sweden Health and Disease Study, the Bruneck Study, and the four [A: Five according to eAppendix 17] cohorts contributing to the DAN-MONICA study; appendix p 3) [A: Please provide references for these studies]. We sought individual-participant data from 33 relevant prospective studies. Only one potentially relevant study17 (comprising <3% of the cardiovascular disease outcomes) was unable to contribute data, yielding a total of 40 contributing prospective studies from 12 countries [A: Added from discussion, correct?](of which 30 had been analysed as cohort studies, eight as case-cohort studies, and two as nested case-control studies) and 95 617 participants without a history of cardiovascular disease. Details of the 40 [A: Is this 40 excluding the 45yr1936 and 70yr1914 DANMON cohorts in eAppendix 5? But 4 (or 5) DAN-MONICA cohorts are included above? Please clarify] contributing studies are provided in the appendix (p 12 [A: Corrected citation, ok?]) [A: Please provide the references for these 40 studies for inclusion in the text here]. We based ascertainment of fatal outcomes on death certificates, supplemented in 26 cohorts by additional data. [A: Moved results in this para from methods sections]

51% [A: Please provide absolute data] of participants were women and 64% [A: Please provide absolute data] were from western Europe, and mean age at baseline was 61 years (SD 10). Median NT-proBNP concentration was 64 pg/mL (IQR 30–135; appendix pp 19, 27). NT-proBNP concentrations were approximately linearly associated with BNP concentrations across the range of values (appendix p 28). NT-proBNP and BNP concentrations increased with age and were higher in women, but were only weakly associated with several other characteristics, including ethnicity, history of hypertension, use of antihypertensive medication, systolic blood pressure, total and HDL cholesterol concentration, and estimated glomerular filtration rate (appendix pp 21, 22, 29).

During 809 525 person-years at risk (median follow-up 7·8 years [IQR 5·2–11·8]), 5500 coronary heart disease, 4002 stroke, and 2212 heart failure outcomes occurred. NT-proBNP concentration was non-linearly associated with the risk of each of these diseases (figure 1). Risk ratios (top third vs bottom third of NT-proBNP concentration) adjusted for conventional risk factors were 1·76 (95% CI 1·56–1·98) for the combination of coronary heart disease and stroke; 2·00 (1·77–2·26) for the combination of coronary heart disease, stroke, and heart failure; 1·67 (1·45–1·93) for coronary heart disease; 1·81 (1·58–2·07) for stroke; 3·45 (2·66–4·46) for heart failure; and 3·11 (2·34–4·15) for cardiovascular disease deaths due to additional causes (figure 2; appendix p 30) [A: Moved primary outcome results to before secondary outcome results, ok?]. Risk ratios were somewhat higher for fatal than for non-fatal coronary heart disease (p<0·0001), but similar for ischaemic and haemorrhagic stroke [A: Please provide a p value]. [A: Deleted data repeated in figure 2]

Risk ratios for NT-proBNP concentration did not materially change with further adjustment for body-mass index or estimated glomerular filtration rate, but they reduced somewhat with adjustment for CRP concentration (appendix p 23). Risk ratios for heart failure were higher in men than in women [A: Please

Figure 1: Associations of NT-proBNP and HDL-C concentrations with first-onset coronary heart disease, stroke, and heart failure

Risk ratios adjusted for age, smoking status, history of diabetes, systolic blood pressure, and total cholesterol and HDL-C concentration (HDL-C concentration only for NT-proBNP concentration analysis) and, where appropriate, stratified by sex. Analyses involved 47 736 coronary heart disease outcomes (from 34 cohorts), 37 688 stroke outcomes (from 30 cohorts), and 20 213 heat failure outcomes (from 16 cohorts). The size of the circles is proportional to the inverse of the variance of the respective estimate. Error bars are 95% CIs, estimated from floated variances. HDL-C=HDL cholesterol. NT-proBNP=N-terminal-pro-B-type natriuretic peptide.
provide actual data\(^{(p<0.0001)}\) and in studies that had stored samples for 10 years or fewer before analysis \(\text{(p<0.0018; appendix p 32\[]A: Citation added correct?\])}. Otherwise, risk ratios did not vary substantially with levels of conventional risk factors or in other clinically relevant subgroups \(\text{(appendix pp 31–32)\[]A: BMI for heart failure also significantly differed according to eFigure 5\])\}. We observed qualitatively similar findings in analyses that defined thirds separately for men and women, excluded people with high baseline concentrations of NT-proBNP, and excluded the initial 5 years of follow-up \(\text{(appendix p 34\[]A: Citation added correct?\])}. Similar findings were also noted in analyses that compared studies grouped by NT-proBNP concentration assay type or generation \(\text{(appendix p 32\[]A: Why ‘up to’?\])}\}. Continuous net reclassification improvements were 0.154 \((0.111–0.198)\) for the combination of coronary heart disease and stroke and 0.028 \((0.019–0.038)\) for the combination of coronary heart disease, stroke, and heart failure \(\text{(table\})\). Incremental risk prediction afforded by NT-proBNP concentration assessment was greater than that afforded by HDL cholesterol or CRP concentration assessment \(\text{(figure 3, figure 4, table\})\}. NT-proBNP and CRP concentration provided essentially non-overlapping incremental risk discrimination \(\text{(figure 4\})\}. [\text{A: 4 dp is used in figures 3 and 4, is this number of dp necessary? If not, could we reduce? If so, could you please provide all values in this para to 4 dp for consistency\}]."
Please smoking, systolic blood pressure, history of diabetes, and concentration of total cholesterol. †p<0·001

Composite outcomes

Coronary heart disease plus stroke

Conventional risk factors without HDL-concentration* 0·6594 (0·6534 to 0·6654) Reference
plus HDL-C concentration 0·6795 (0·6645 to 0·694) 0·0111 (0·0088 to 0·0134)†
plus HDL-C and NT-proBNP concentration 0·6829 (0·6766 to 0·6894) 0·0120 (0·0096 to 0·0144)†

Coronary heart disease plus stroke plus heart failure

Conventional risk factors without HDL-concentration* 0·7104 (0·7039 to 0·7169) Reference
plus HDL-concentration 0·7148 (0·7084 to 0·7211) 0·0043 (0·0026 to 0·0060)†
plus HDL-C and NT-proBNP concentration 0·7238 (0·7272 to 0·7401) 0·0139 (0·0123 to 0·0222)†

Individual outcomes

Coronary heart disease

Conventional risk factors without HDL-concentration* 0·6615 (0·6535 to 0·6695) Reference
plus HDL-concentration 0·6789 (0·6710 to 0·6867) 0·0174 (0·0134 to 0·0213)†
plus HDL-C and NT-proBNP concentration 0·6909 (0·6832 to 0·6987) 0·0121 (0·0088 to 0·0154)†

Stroke

Conventional risk factors without HDL-concentration* 0·6644 (0·6557 to 0·6730) Reference
plus HDL-concentration 0·6694 (0·6607 to 0·6780) 0·0050 (0·0026 to 0·0074)†
plus HDL-C and NT-proBNP concentration 0·6800 (0·6721 to 0·6879) 0·0114 (0·0076 to 0·0152)†

Heart failure

Conventional risk factors without HDL-concentration* 0·7352 (0·7245 to 0·7460) Reference
plus HDL-concentration 0·7368 (0·7259 to 0·7473) 0·0041 (-0·0006 to 0·0035)
plus HDL-C and NT-proBNP concentration 0·7744 (0·7641 to 0·7847) 0·0370 (0·0302 to 0·0445)†

Table 3: Improvement in risk discrimination for first-onset individual and composite cardiovascular disease outcomes by addition of information about NT-proBNP concentration compared with that about HDL-C

<table>
<thead>
<tr>
<th>Composite outcomes</th>
<th>C-index (95% CI)</th>
<th>C-index change (95% CI) versus reference model</th>
<th>C-index change (95% CI) versus preceding model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease plus stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional risk factors without HDL-concentration*</td>
<td>0·6594 (0·6534 to 0·6654)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>plus HDL-C concentration</td>
<td>0·6795 (0·6645 to 0·694)</td>
<td>0·0111 (0·0088 to 0·0134)†</td>
<td></td>
</tr>
<tr>
<td>plus HDL-C and NT-proBNP concentration</td>
<td>0·6829 (0·6766 to 0·6894)</td>
<td>0·0120 (0·0096 to 0·0144)†</td>
<td></td>
</tr>
<tr>
<td>Coronary heart disease plus stroke plus heart failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional risk factors without HDL-concentration*</td>
<td>0·7104 (0·7039 to 0·7169)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>plus HDL-concentration</td>
<td>0·7148 (0·7084 to 0·7211)</td>
<td>0·0043 (0·0026 to 0·0060)†</td>
<td></td>
</tr>
<tr>
<td>plus HDL-C and NT-proBNP concentration</td>
<td>0·7238 (0·7272 to 0·7401)</td>
<td>0·0139 (0·0123 to 0·0222)†</td>
<td></td>
</tr>
</tbody>
</table>

Data are categorical net reclassification improvement (95% CI) versus preceding model. We calculated categorical net reclassification improvement across predicted 10-year cardiovascular disease risk categories defined by the American College of Cardiology and American Heart Association 2013 guidelines.‡

The reference model included information about age, sex, smoking, systolic blood pressure, history of diabetes, and concentration of total cholesterol. †p<0·001

Please provide exact p values for all rows unless p<0·0001

*The reference model included information about age, sex, smoking, systolic blood pressure, history of diabetes, and concentration of total cholesterol. †p<0·001

Figure 3: Improvement in risk discrimination for first-onset individual and composite cardiovascular disease outcomes by addition of information about NT-proBNP concentration compared with that about HDL-C concentration

Analyses involved 4552 coronary heart disease outcomes (from 32 cohorts), 3768 stroke outcomes (from 30 cohorts), 2021 heart failure outcomes (from 16 cohorts), 8323 outcomes for the composite outcome of coronary heart disease plus stroke (from 32 cohorts), and 6582 outcomes for the composite outcome of coronary heart disease plus stroke plus heart failure (from 22 cohorts). HDL-C=HDL cholesterol. NT-proBNP=N-terminal-pro-B-type natriuretic peptide.

In this study, we found that NT-proBNP concentration assessment strongly improves in C-index with NT-proBNP concentration assessment were possibly greater among older individuals (≥60 years) and people with a history of diabetes, who used antihypertensives, and who had a low total cholesterol concentration (bottom third; appendix p 38). Systolic blood pressure was also significantly different according to appendix efigure 12. However, we did not adjust these exploratory analyses for multiple comparisons. In further sensitivity analyses, we found that C-index improvements were similar when the base model additionally included information about ethnicity and antihypertensive treatment (appendix p 39), but somewhat smaller in analyses that excluded people with high baseline concentrations of NT-proBNP or modelled NT-proBNP concentration using a prespecified cutoff value rather than continuous values (appendix p 40).

Net reclassification improvements were similar or larger than were those in the main analysis. A: Correct?

when analysis involved cutoffs for clinical risk categories defined by guidelines other than the 2013 ACC and AHA guidelines (appendix p 26). A: Where are I² results presented?

Discussion

[A: Deleted repetitive text] In this study, we found that NT-proBNP concentration assessment strongly
predicted first-onset heart failure and augmented coronary heart disease and stroke prediction, suggesting that NT-proBNP concentration assessment could serve as a multipurpose biomarker in new approaches that integrate heart failure into cardiovascular disease primary prevention. A key observation was our study’s demonstration of graded associations between NT-proBNP concentration and the incidence of coronary heart disease, stroke, and heart failure. The continuous nature of these associations suggests that NT-proBNP concentration measurement is potentially suitable for population-level risk assessment. We also made the surprising observation that NT-proBNP concentration predicts stroke at least as strongly as it does coronary heart disease, by contrast with the idea that NT-proBNP concentration is predominantly a coronary biomarker. The stroke associations that we noted could partly be explained by associations previously reported between NT-proBNP concentration and stroke risk factors (eg, left ventricular hypertrophy and atrial fibrillation) but further work is needed to elucidate the common pathobiology for coronary heart disease, stroke, and heart failure reflected by preceding NT-proBNP concentration. Furthermore, we found that NT-proBNP concentration predicted deaths due to additional cardiovascular causes, such as cardiac arrhythmia and sudden death. Collectively, these results encourage evaluation of NT-proBNP concentration for prediction of an even wider range of cardiovascular disease outcomes than that we studied.

Our conclusions on the incremental predictive ability of assessment of NT-proBNP concentration were strengthened by broadly concordant results when we studied varying cardiovascular disease outcomes and used different measures of risk discrimination and reclassification. Importantly, the modest improvements that we observed in risk reclassification with NT-proBNP concentration assessment applied similarly across the absolute risk thresholds used in different clinical guidelines. In particular, NT-proBNP concentration assessment improved the specificity of risk prediction by appropriately downclassifying the clinical risk category of many individuals who did not go on to develop cardiovascular disease outcomes. Hence, addition of NT-proBNP concentration measurement to cardiovascular disease risk assessment could improve targeting of preventive treatments (such as statins) and allocation of resources for detailed screening (such as comprehensive tests for heart failure at specialised cardiology clinics), as exemplified by previous natriuretic peptide-guided trials in patients with diabetes or heart failure. Data from future studies are needed to establish the cost-effectiveness and feasibility of NT-proBNP concentration screening for prediction of first composite cardiovascular disease outcomes, analogous with previous work on left ventricular systolic dysfunction.

Figure 4: Improvement in risk discrimination for first-onset individual and composite cardiovascular outcomes by addition of information about CRP and NT-proBNP concentration to a model with conventional risk factors

 Analyses involved 4120 coronary heart disease outcomes (from 27 cohorts), 3487 stroke outcomes (from 26 cohorts), 1606 heart failure outcomes (from 13 cohorts), 7618 outcomes for the composite outcome of coronary heart disease plus stroke (from 28 cohorts), and 5492 outcomes for the composite outcome of coronary heart disease plus stroke plus heart failure (from 18 cohorts). CRP=C-reactive protein. NT-proBNP=N-terminal-pro-B-type natriuretic peptide.

<table>
<thead>
<tr>
<th>Composite outcomes</th>
<th>C-index (95% CI)</th>
<th>C-index change (95% CI) versus reference model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease plus stroke</td>
<td>0.6601 (0.6539 to 0.6663)</td>
<td>Reference</td>
</tr>
<tr>
<td>Conventional risk factors*</td>
<td>0.6636 (0.6574 to 0.6698)</td>
<td>0.0035 (0.0016 to 0.0054)†</td>
</tr>
<tr>
<td>plus NT-proBNP concentration</td>
<td>0.6715 (0.6663 to 0.6777)</td>
<td>0.0114 (0.0089 to 0.0139)‡</td>
</tr>
<tr>
<td>Coronary heart disease plus stroke plus heart failure</td>
<td>0.6979 (0.6909 to 0.7049)</td>
<td>Reference</td>
</tr>
<tr>
<td>Conventional risk factors*</td>
<td>0.7070 (0.6980 to 0.7169)</td>
<td>0.0072 (0.0047 to 0.0094)‡</td>
</tr>
<tr>
<td>plus NT-proBNP concentration</td>
<td>0.7283 (0.7193 to 0.7373)</td>
<td>0.0204 (0.0168 to 0.0239)‡</td>
</tr>
</tbody>
</table>

**Individual outcomes**

<table>
<thead>
<tr>
<th>Coronary heart disease</th>
<th>C-index (95% CI)</th>
<th>C-index change (95% CI) versus reference model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional risk factors*</td>
<td>0.6688 (0.6606 to 0.6770)</td>
<td>Reference</td>
</tr>
<tr>
<td>plus CRP concentration</td>
<td>0.6733 (0.6641 to 0.6814)</td>
<td>0.0045 (0.0016 to 0.0074)†</td>
</tr>
<tr>
<td>plus NT-proBNP concentration</td>
<td>0.6805 (0.6723 to 0.6886)</td>
<td>0.0117 (0.0082 to 0.0152)‡</td>
</tr>
<tr>
<td>Stroke</td>
<td>C-index (95% CI)</td>
<td>C-index change (95% CI) versus reference model</td>
</tr>
<tr>
<td>Conventional risk factors*</td>
<td>0.6592 (0.6501 to 0.6683)</td>
<td>Reference</td>
</tr>
<tr>
<td>plus CRP concentration</td>
<td>0.6617 (0.6526 to 0.6708)</td>
<td>0.0024 (-0.0000 to 0.0049)</td>
</tr>
<tr>
<td>plus NT-proBNP concentration</td>
<td>0.6698 (0.6607 to 0.6789)</td>
<td>0.0105 (0.0066 to 0.0145)‡</td>
</tr>
<tr>
<td>Heart failure</td>
<td>C-index (95% CI)</td>
<td>C-index change (95% CI) versus reference model</td>
</tr>
<tr>
<td>Conventional risk factors*</td>
<td>0.7199 (0.7075 to 0.7323)</td>
<td>Reference</td>
</tr>
<tr>
<td>plus CRP concentration</td>
<td>0.7346 (0.7256 to 0.7455)</td>
<td>0.0147 (0.0090 to 0.0204)‡</td>
</tr>
<tr>
<td>plus NT-proBNP concentration</td>
<td>0.7650 (0.7532 to 0.7769)</td>
<td>0.0451 (0.0357 to 0.0546)‡</td>
</tr>
</tbody>
</table>

†p<0.01  ‡p<0.001 [A: Please provide exact p values for all rows unless p<0.0001].
To provide clinical context, we compared incremental improvements afforded by NT-proBNP concentration assessment with those afforded by HDL cholesterol, a widely used biomarker in cardiovascular disease risk assessment (this comparison is additionally relevant because HDL cholesterol concentration, like NT-proBNP concentration, is a biomarker of unknown relevance to the cause of cardiovascular disease\textsuperscript{19,20}). We found that improvements in risk discrimination with NT-proBNP concentration were greater than those provided by HDL cholesterol, even though our evaluation was skewed in favour of HDL cholesterol concentration since we added HDL cholesterol concentration only to other conventional risk factors (omitting NT-proBNP concentration), whereas we added NT-proBNP concentration to conventional risk factors, including HDL cholesterol concentration. Furthermore, in a head-to-head comparison, we found that the improvement in risk discrimination with NT-proBNP concentration was about three times greater than was the improvement in risk discrimination using CRP concentration. The idea that NT-proBNP concentration captures information about non-traditional cardiovascular disease pathways\textsuperscript{20,21} was supported by our observation that NT-proBNP concentration was uncorrelated or weakly correlated with the established and emerging risk factors that we studied. Our study had major strengths. Because of its considerable statistical power, we could provide precise estimates, even for analyses that involved categorisation of NT-proBNP concentrations. More than 90% of the NT-proBNP concentration data in our analysis were generated with use of a common gold-standard assay. We recorded information about the incidence of various cardiovascular disease outcomes using well validated endpoint definitions. We centrally analysed individual-participant data, which were harmonised from prospective studies with extended follow-up, enabling time-to-event analyses, exclusion of people with a baseline history of cardiovascular disease (including heart failure), and adoption of a uniform approach to statistical analyses. To enhance validity further, we restricted analyses to people with complete information about a set of relevant risk factors. Our primary analysis excluded participants with a reported baseline history of heart failure and, moreover, the findings were robust to exclusion of participants with high baseline NT-proBNP concentrations. The generalisability of our findings was enhanced by inclusion of data from 12 countries and by the robustness of results to various sensitivity analyses.

Our study had potential limitations. Misclassification of heart failure outcomes could have led to underestimation of associations between NT-proBNP concentration and heart failure risk and, conversely, overestimation of associations with non-heart failure outcomes. Most of our data were derived from people of European continental ancestry. We could not compare the performance of NT-proBNP concentration with cardiac troponin, coronary calcium scoring, or other biomarkers apart from HDL cholesterol and CRP concentrations. [A: Deleted repetitive text]

Contributors
PW, JD, and EDA drafted the report. PW did literature searches and analysed data. All investigators shared data and had opportunities to interpret results and critically revise the report. All members of the writing committee provided critical revisions. All members of the coordinating centre collected, harmonised, analysed, and interpreted data. The data management team collected and harmonised data.

Writing committee
Peter Willeit (University of Cambridge, Cambridge, UK and Medical University Innsbruck, Innsbruck, Austria); Stephen Kapogiannis (University of Cambridge, Cambridge, UK); Paul Welsh\textsuperscript{*} (University of Glasgow, Glasgow, UK); Adam S Butterworth\textsuperscript{*} (University of Cambridge, Cambridge, UK); Rajiv Chowdhury (University of Cambridge, Cambridge, UK); Sarah A Spackman (University of Cambridge, Cambridge, UK); Lisa Pennells (University of Cambridge, Cambridge, UK); Pei Gao (University of Cambridge, Cambridge, UK and Peking University, Beijing, China); Stephen Burgess (University of Cambridge, Cambridge, UK); Daniel F Freitag (University of Cambridge, Cambridge, UK); Michael Sweeting (University of Cambridge, Cambridge, UK); Angela M Wood (University of Cambridge, Cambridge, UK); Nancy R Cook (Brigham and Women’s Hospital and Harvard Medical School, Boston, MA, USA); Suzanne Judd (University of Alabama at Birmingham, Birmingham, AL, USA); Stella Troupet (Leiden University Medical Centre, Leiden, Netherlands); Vijay Narbholi (Michael E DeBakey Baylor College of Medicine and Houston Methodist DeBakey Heart and Vascular Center, Houston, TX, USA); Michael Hecht Olsen (Odense University Hospital, Odense, Denmark); Brendan M Everett (Brigham and Women’s Hospital and Harvard Medical School, Boston, MA, USA); Frank Kee (Queen’s University Belfast, Belfast, UK); Johan Arnlöv (Uppsala University, Uppsala, Sweden); Veikko Salomaa (National Institute for Health and Welfare, Helsinki, Finland); Daniel Levy (National Institutes of Health, Bethesda, MD, USA); Jussi Kauhanen (University of Eastern Finland, Kuopio, Finland); Jari A Laukkanen (University of Eastern Finland, Kuopio, Finland); Maryam Kaveousi (Erasmus Medical Center, Rotterdam, Netherlands); Toshiharu Ninomiya (Kyushu University, Fukuoka, Japan); Juan-Pablo Casas (Farr Institute of Health Informatics, University College London, London, UK); Lior B Daniels (University of California San Diego, San Diego, CA, USA); Lars Lind (Uppsala University, Uppsala, Sweden); Caroline N Kistorp (University of Copenhagen, Copenhagen, Denmark); Jens Rosenberg (Copenhagen University Hospital Glostrup, Glostrup, Denmark); Thomas Mueller (Konventhospital Barnherrzige Bruder, Linz, Austria); Speranza Ruhattu (University Sapienza of Rome, Rome, Italy and Istituto di Ricovero e Cura a Carattere Scientifico Neuromed, Pozzilli, Italy); Demosthenes B Panagiotakos (Harokopio University of Athens, Athens, Greece); Oscar H Franco (Erasmus Medical Center, Rotterdam, Netherlands); James A de Lemos (University of Texas Southwestern Medical School, Dallas, TX, USA); Andreas Luchner (Universitätsklinikum Regensburg, Regensburg, Germany and Klinikum St Marien, Amberg, Germany); Jorge R Rizer (Albert Einstein College of Medicine, Bronx, NY, USA); Stefan Kiechl (Medical University Innsbruck, Innsbruck, Austria); Jukka T Salonen (Metabolic Analytical Services, Helsinki, Finland); S Goya Warnamuthu (University College London, London, UK); Rudolf A de Roer (University of Groningen, Groningen, Netherlands); Borbir G Nordestgaard (University of Copenhagen, Copenhagen, Denmark); Jonas Andersson (Umeå University, Umeå, Sweden); Torben Jørgensen (Research Centre for Prevention and Health, Glostrup, Denmark); Olle Melander (Malmö University Hospital, Malmö, Sweden); Christie M Ballantyne (Baylor College of Medicine and Houston Methodist DeBakey Heart and Vascular Center, Houston, TX, USA); Christopher DeFilippi (University of Maryland School of Medicine, Baltimore, MD, USA); Paul M Ridker (Brigham and Women’s Hospital and Harvard Medical School, Boston, MA, USA); Mary Cushman (University of Vermont, Burlington, VT, USA); Wayne D Rosamond (University of North Carolina at Chapel Hill, Chapel Hill, NC, USA); Simon G Thompson (University of Cambridge, Cambridge, UK);
VilmunordGudnason† (Icelandic Heart Association, Kopavogur, Iceland and University of Iceland, Reykjavik, Iceland); NaveedSattar† (University of Glasgow, Glasgow, UK); JohnDanesh† (University of Cambridge, Cambridge, UK).

*Contributed equally. †Contributed equally.

NatriureticPeptidesStudiesCollaboration

ARI:C VijayNambi, ChristieMBallantyne, RonCHoogeveen, SunilRGaragwal; ATTICA: DemosthenesBPanagiotakos; BRH: StefanKiechl, SunilKAgarwal; BRHS: NatriureticPeptidesStudiesCollaboration

Cambridge, UK).

of Glasgow, Glasgow, UK); John Danesh† (University of Cambridge, and University of Iceland, Reykjavik, Iceland); Naveed Sattar† (University

Vilmunord Gudnason† (Icelandic Heart Association, Kopavogur, Iceland and University of Iceland, Reykjavik, Iceland); Naveed Sattar† (University of Cambridge, Cambridge, UK).

Declaration of interests

AngelaMWood, JohnDanesh.

For CHS see http://www.chs-nhhs.org

For MESA see http://www.mesa-nhhs.org

For the list of funders see http://www.phc.cam.ac.uk/ceu/research/npcs/studies/

References


