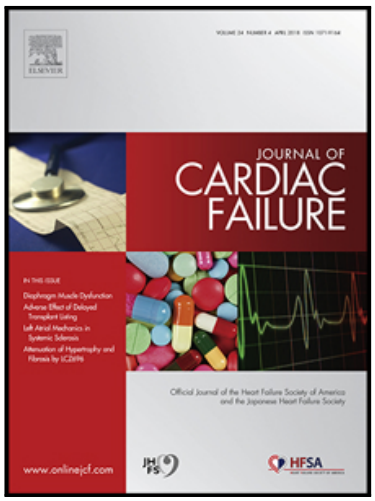


High sensitivity troponin T and incident heart failure in older men: British Regional Heart Study

Paul Welsh , Olia Papacosta , Sheena Ramsay , Peter Whincup , John McMurray , Goya Wannamethee , Naveed Sattar

PII: S1071-9164(18)30884-4
DOI: https://doi.org/10.1016/j.cardfail.2018.08.002
Reference: YJCAF 4185

To appear in: *Journal of Cardiac Failure*

Received date: 9 January 2018

Please cite this article as: Paul Welsh , Olia Papacosta , Sheena Ramsay , Peter Whincup , John McMurray , Goya Wannamethee , Naveed Sattar , High sensitivity troponin T and incident heart failure in older men: British Regional Heart Study, *Journal of Cardiac Failure* (2018), doi: https://doi.org/10.1016/j.cardfail.2018.08.002

High sensitivity troponin T and incident heart failure in older men: British Regional Heart Study

Paul Welsh [a] PhD, Olia Papacosta [b] MSc, Sheena Ramsay [b,c] MD PhD, Peter Whincup [b,d] PhD, MSc, MBBChir, BA, , John McMurray [a] MD, Goya Wannamethee [b] PhD *, Naveed Sattar [a] PhD, MBChB*

*Joint senior authors

[a] BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, UK

[b] Department of Primary Care and Population Health, University College London, London, UK

[c] Institute of Health & Society, Newcastle University, Newcastle upon Tyne, UK

[d] Population Health Research Institute, St George's, University of London, London UK

Short title: Troponin T and incident heart failure

Correspondence to:

Paul Welsh, BHF Glasgow Cardiovascular Research Centre, 126 University Place, Glasgow G12 8TA Tel: +441413302569 Fax: +441413306955 Email: paul.welsh@glasgow.ac.uk

Word count: 3039

ABSTRACT

Aim

To study the association of high sensitivity troponin T (hsTnT) with incident heart failure, and implications for its use in prediction models.

Methods and Results

The British Regional Heart Study of 3852 men aged 60-79 without baseline HF (3165 without baseline CHD) was followed up for a median of 12.6 years, during which 295 incident cases of HF occurred (7.7%). A 1 standard deviation increase in log-transformed hsTnT was associated with a higher risk of incident HF after adjusting for classical risk factors (HR 1.58 [95% CI 1.42, 1.77]) and after additional adjustment for NT-proBNP (HR 1.34 [95% CI 1.19, 1.52]). The strength of the association between hsTnT and incident HF did not differ by strata of other risk factors. A hsTnT concentration of <5ng/L had a sensitivity of 99.7% (95%CI 98.1-99.9%) and a specificity of 3.4% (95%CI 2.8%-4.0%). A risk prediction model including classic risk factors and NT-proBNP yielded a c-index of 0.791, but addition of hsTnT did not further improve prediction (p=0.28).

Conclusions

Elevated hsTnT is consistently associated with risk of HF in older men. HF rarely occurs over 12 years when baseline hsTnT is below the limit of detection. hsTnT measurement, however, does not improve HF prediction in a model already containing NT proBNP.

Key words: Risk prediction; heart failure; biomarkers; troponin T;

Introduction

The lifetime risk of developing heart failure (HF) of a person aged over 40 years in the general population is estimated at 20% and, although therapies for HF are improving, once diagnosed 14% of patients die in the first six months. [1,2] The etiology of HF varies from country to country, although the majority of cases are attributed to hypertension and coronary artery disease. [3] As such, it is well understood that onset of HF is a common occurrence after clinically diagnosed myocardial infarction. [4] However, it is possible that recurrent subclinical episodes of cardiac ischemia and cardiomyocyte necrosis lead to heart failure. [5]

Circulating cardiac troponin levels are excellent biomarkers of myocardial injury, including ischemia. [6,7] As such, several studies have used high sensitivity troponin T (hsTnT) or high sensitivity troponin I (hsTnI) assays as a proxy for subclinical myocardial damage in investigating causes of HF. [8–12] However, it is not clear from the existing literature what information troponin measurement adds to N-terminal pro B-type natriuretic peptide (NT proBNP). NT-proBNP integrates information about cardiac loading, structure and function, the heart rhythm, renal function and possibly other neurohumoral pathways. Since natriuretic peptides are increasingly part of the clinical definition of HF, [13] and are routinely measured during the diagnostic evaluation of patients with suspected HF, NT proBNP is a strong candidate biomarker for prediction models in people without HF. It is also possible that troponin will also be valuable in such predictive models. A key question is not only whether continuous troponin levels predict HF, but also whether low troponin levels, indicating an absence of myocardial injury, preclude occurrence of HF.

We therefore used the British Regional Heart study to test the hypothesis that hsTnT is associated with risk of incident HF in older men with and without clinical evidence of baseline CHD, adjusting for incident CHD during follow-up. We also examined whether the measurement of hsTnT usefully predicts risk of incident heart failure beyond NT-proBNP.

Materials and Methods

British Regional Heart Study

The British Regional Heart Study was a socioeconomically representative prospective study of 7735 men aged 40-59 years and of predominantly white European ethnicity (>99%), drawn from one general practice in each of 24 British towns, who were screened between 1978 and 1980. [14] In 1998-2000, surviving men aged 60-79 years were invited for a 20th year follow-up examination, on which these analyses are based. [15,16] Ethical approval was obtained from all relevant local research ethics committees, and informed consent has been obtained from the subjects. Follow-up was possible for 99% of the cohort. All men completed a mailed questionnaire providing information on their lifestyle and medical history, had a physical examination, and provided a fasting blood sample. Physical activity, alcohol consumption and an index of socioeconomic deprivation were derived and coded as detailed elsewhere. [17] Twelve-lead electrocardiograms were recorded using a Siemens Sicard 460 instrument and were analyzed using Minnesota Coding definitions at the University of Glasgow ECG core laboratory. Atrial fibrillation was defined according to Minnesota Codes 8.3.1 and 8.3.3 on baseline ECG. The men were asked whether a doctor had ever told them that they had MI, HF, or stroke; details of their medications including use of statins were recorded at the examination. Predicted glomerular filtration rate (eGFR) was estimated from serum creatinine; eGFR = 186 x $(\text{creatinine})^{-1.154}$ x $(\text{Age})^{-0.203}$.

In all, 4252 men (77% of survivors) attended the 1998 to 2000 examination; 130 men who experienced heart failure before the baseline examination were excluded; 79 men with missing information on history of MI or angina were also excluded; and an additional 191 with a missing hsTnT measurement were excluded, leaving 3852 men included in the analysis.

Baseline CHD was defined as previous self-reported, doctor-diagnosed, MI or angina, or MI identified during review of medical records as part of the prospective study; in this way, 687 men were defined as having evidence of CHD at baseline.

Evidence of HF was obtained by reports from GPs supplemented by biennial reviews of medical records (including correspondence). Incident HF was based on a confirmed doctor diagnosis of HF from primary care records and where possible, verified using details of available clinical information from primary and secondary care records, as well as from death certificates (ICD-9 code 428). [16]

Biomarker measurement

NT-proBNP and hsTnT were measured in plasma samples from both studies on an automated clinically validated immunoassay analyser (e411, Roche Diagnostics, Burgess Hill, UK) using the manufacturers calibrators and quality control reagents. The limit of detection was 5ng/L for NT-proBNP, and limit of blank was 3ng/L for hsTnT. We defined “low” hsTnT using the manufacturer’s limit of detection (5ng/L). Quality control materials over two levels for each biomarker ran between 4.4% and 7.7%.

Statistics

Eligible men were divided into equal tertiles based on the hsTnT distribution. Skewed continuous variables were log-transformed to approximate normality for parametric tests. Comparisons of baseline characteristics between the HF outcome groups (stratified by baseline CHD status) were performed using the χ^2 test for categorical variables and t-test for continuous variables. 95% confidence intervals for single proportions were derived using Jeffrey's method.

Kaplan –Meier curves and the log-rank test were used to evaluate differences in HF rates for the hsTnT tertiles. Multiple imputation using chained equations was used to generate 10 datasets with complete data [18]. The imputation model included hsTnT, age, CVD, diabetes, incident heart failure (none missing), smoking (4 missing), index of deprivation (6 missing), atrial fibrillation (9 missing), heart rate (10 missing), systolic blood pressure (17 missing), body mass index (17 missing), C-reactive protein (31 missing), eGFR (35 missing), total cholesterol (38 missing), glucose (39 missing), FEV1 (40 missing), blood pressure medications (49 missing), alcohol use (57 missing), HDL-cholesterol (61 missing), physical activity (138 missing), and NT-proBNP (272 missing). Cox proportional hazards models were generated using the *mi estimate* command in STATA. The hazard ratio (and 95% confidence intervals) of incident heart failure per a one standard deviation increase in log-transformed hsTnT was estimated using these models. Models adjusted for classical risk factors with the maximally adjusted model including the variables; age, smoking, total cholesterol, HDl-cholesterol, systolic blood pressure, index of multiple deprivation (IMD), BMI, any diabetes, eGFR, blood pressure medication, statin use, heart rate, physical activity, FEV1, alcohol

consumption, CRP and NT-proBNP. Models also included a time-varying term adjusting for non-fatal MI that occurred during the follow-up. Maximally adjusted models were also tested for evidence of interaction, stratified by baseline covariates of interest. The assumption of a linear relationship between hsTnT and risk of heart failure was supported by restricted cubic spline analysis.

To test clinical prediction of incident HF, C-indices were calculated in the imputed datasets accounting for censoring, using a range of different prediction strategies (with or without hsTnT). Prediction models included: Model (A) age, baseline CHD, cholesterol, HDL cholesterol, systolic blood pressure, IMD, BMI, smoking, diabetes, eGFR, BP medication, statin use, heart rate, glucose, physical activity, FEV1, alcohol use, atrial fibrillation; Model (B) model A plus NT-proBNP; Model (C) model B plus hsTnT; Model (D) Age and NT-proBNP only. Increased concordance was tested comparing the C-index each model to every other.

The C statistic has been criticised for insensitivities to changes in clinical decisions across treatment thresholds defined by risk prediction. The categorical net reclassification index (NRI) estimates correct changes in clinical classification across risk thresholds. However, risk scores thresholds are currently not used to make treatment decisions to prevent heart failure. Therefore, we used a continuous net reclassification index (NRI), to compare model C compared to model B in one imputed dataset. NRI is based on improvements in classification across integer % risk thresholds, thus avoid making arbitrary decisions about defining clinically relevant risk categories. [19] We also calculated the integrated discrimination improvement index (IDI), a category free comparative measure of the clinical validity of a new risk score. [20]

All analyses were performed in STATA (version 14.2) and R (version 3.3.1, using the survIDINRI package and 5000 bootstrap samples to generate confidence intervals for the NRI and IDI).

Results

Classical risk factors

During a median follow-up period of 12.6 years (IQR 7.9-13.4 years), there were 295 incident cases of HF in the whole cohort (n=3852; incidence 7.7%), including 201 incident cases (6.4%) in those without baseline CHD (n=3165), and 94 incident cases (13.7%) in those with baseline CHD (n=687) (p<0.001). Those who experienced HF during follow-up were also generally older, had higher BMI and waist circumference and were more likely to have diabetes, had lower FEV1 and eGFR, had a higher heart rate, were more likely to be on blood pressure lowering medication and to have atrial fibrillation and a higher CRP (Table 1). hsTnT was slightly higher in those with baseline CHD compared to those without (median and interquartile range: 12.9 (9.9-18.2) vs. 11.4ng/L (8.6-15.6) , p<0.001). NT-proBNP was also higher in those with clinical evidence of baseline CHD compared to those without (median and interquartile range: 180ng/L (88-416) vs.79ng/L (41-158), p<0.001).

hsTnT and incident HF

Kaplan-Meier curves show that over the follow-up time, baseline hsTnT concentration (as thirds of the distribution) was strongly associated with risk of incident HF in both those with and without baseline CHD (log rank p<0.001 for both) (Fig 1).

In adjusted models, the association of log transformed hsTnT with heart failure was linear (graphical abstract uses 10ng/L, approximately the median hsTnT, as the referent). In all participants, a 1 standard deviation higher log hsTnT was associated with a 58% (95% CI 42%, 77%) higher risk of HF after adjusting for classical risk factors (model 3, Table 2), and this was attenuated to a 34% higher risk (95% CI 19%, 52%) after adjusting for NT-proBNP as well (model 4). A test for interaction between the risk of HF associated with baseline hsTnT concentration and baseline CHD status was not significant p=0.32, Fig 2). Indeed, there was no evidence that level of any risk factor modified the association between hsTnT and risk of HF (Fig 2).

Prediction of HF

Of the 121 people with a baseline hsTnT <5ng/L (the assay limit of detection), only 1 developed new onset HF (0.8%; 95%CI 0%-3.8%), compared with 294 of the 3731 with a detectable hsTnT (7.9%; 95%CI 7.1-8.8%). This corresponds to a sensitivity of 99.7% (95%CI 98.1-99.9%) anda specificity of 3.4% (95%CI 2.8%-4.0%). Only 35 participants had an NT-proBNP below the limit of detection (5pg/ml), and none developed heart failure during follow-up.

A HF risk score based on classical risk factors (without sex or race) yielded a c-index of 0.730 (model A, Table 3). Addition of NT-proBNP improved the c-index substantially to 0.791 (model B). However, further addition of hsTnT (Model C) did not further improve prediction (c-index 0.794). A model based on age and NT-proBNP only (model D) yielded a c-index of 0.757 and was almost as good at discriminating HF events as any of the other more complex models.

Using other prediction metrics, adding hsTnT to a model containing NT-proBNP (Model C vs. B) did not improve the continuous net reclassification index (+6.7%; 95%CI -4.9, 16.0%; p=0.26) although there was a slight improvement in the integrated discrimination index (+0.013; 95%CI; 0.003, 0.026; p=0.006). Data were similar when stratified by baseline CHD (data not shown).

Discussion

In this cohort of older British men, hsTnT was consistently strongly associated with incident HF, suggesting that subclinical myocardial damage may be an important risk factor for HF, even in individuals without diagnosed CHD. HF rarely occurred during 12.6 years of follow-up (0.8% incidence; 95%CI 0%-3.8%) in men who had a baseline hsTnT below the limit of detection (5ng/L). As such, these data raise mechanistic questions regarding the source of troponin elevation in apparently healthy men, and as to how pathologies that raise troponin might be associated with increased HF risk. Although useful in predicting HF when added to conventional risk factors, TnT did not improve HF prediction when added to NT-proBNP.

Heart failure prediction

One of the reasons NT-proBNP is such an attractive and powerful biomarker in CVD prediction in general [17,21,22] is that it integrates information from several important pathophysiological pathways. As well as reflecting cardiac overload, NT-proBNP is also a marker of myocardial ischemia, therefore overlapping with troponin. [23,24] Circulating levels of both NT-proBNP and hsTnT probably also reflect renal function. [25] Despite this, we still found a moderate association between hsTnT and HF, even after adjusting for classic

risk factors and NT-proBNP. However, once NT-proBNP is included in a model for HF prediction, the baseline C-statistic is already high (0.79), and it is therefore difficult to improve upon. Data from the ARIC study showed that when TnT was added to a range of classical risk factors plus NT-proBNP, the c-index for HF prediction was improved statistically significantly, but only clinically modestly (by +0.014 in men and +0.012 in women). [9] Although the present study is smaller in size, our data broadly agree with those of ARIC: if hsTnT does predict HF beyond NT-proBNP, the discrimination gained is very moderate. Our data also advance findings from studies from patients with established acute and chronic heart failure. For instance, in chronic heart failure patients in the Reduction of Events by Darbepoetin Alfa in Heart Failure (RED-HF) trial, among a range of cardiac biomarkers only hsTnT added to NT-proBNP in the prediction of adverse outcome [26]. In the Multicentre Australian Risk Algorithm To predict Heart failure readmission (MARATHON) study, comprising patients hospitalized with preserved or reduced ejection fraction heart failure, elevated troponin I predicted 30-day readmission to hospital or death, individually and as part of a panel of variables [27]. Therefore, elevated troponin appears to be a predictor of adverse outcomes in the pre-symptomatic, chronic and acute phases of heart failure.

Mechanisms linking troponin and heart failure

In line with these being older men, the median baseline hsTnT level in this cohort was approximately 12ng/L (the 99th percentile in the healthy population is 14ng/L), and was only slightly higher in those with clinically identified baseline CHD. CHD is the most obvious cause of elevated troponin, although only a minority of our participants had diagnosed CHD at baseline. However, even in the absence of a diagnosis of CHD, the prevalence of subclinical coronary disease was probably high in the older British men we studied. However, even in

the absence of a diagnosis of CHD, the prevalence of subclinical coronary disease was probably high in the older British men we studied. In addition, other potentially undiagnosed cardiac conditions such as left ventricular hypertrophy and atrial fibrillation may cause myocardial ischemia. Hypertension, diabetes and chronic kidney disease (which frequently coexist) lead to the development of left ventricular hypertrophy and atrial fibrillation, as well as coronary microvascular dysfunction which may also raise troponin. Hypertension, diabetes and chronic kidney disease, left ventricular hypertrophy, atrial fibrillation and coronary microvascular dysfunction are also predictors (and those measured in this study) precursors of heart failure. Moreover, those developing HF had a higher baseline NT-proBNP concentration, suggesting pre-existing myocardial and/or renal dysfunction. Other non-cardiac pathologies including chronic inflammatory disorders are also associated with myocardial injury and the higher baseline CRP in individuals experiencing incident HF is consistent with this pathophysiological connection as well. [28] Thus, there are mechanisms that might explain why troponin is not only associated with incident heart failure in those with diagnosed CHD. Many of these factors were taken into account in our statistical analysis. Future studies should investigate specifically the ability of troponin measurements to predict onset of non-ischaemic dilated cardiomyopathy.

It may be possible to detect subclinical myocardial injury early and intervene to reduce the risk of heart failure. This might be achieved using measurement of troponin, NT-proBNP or both to diagnose such patients and thereby target therapy to those at highest risk of HF. Interventions that might be effective include antihypertensive therapies, anti-ischemic therapies, lipid-lowering treatments, anti-thrombotic therapy and, possibly, drugs improving metabolic status (e.g. treatments for diabetes and obesity). The small but statistically

significant effect of statins in reducing the risk of incident heart failure, independently of myocardial infarction, is consistent with this hypothesis. [29] A recent example of a hypotensive agent which also lowers troponin is sacubitril/valsartan (formerly LCZ696).[30] Prevention of myocardial injury to reduce risk of heart failure in later life is therefore an important public health aim, in the same way that reduction in acute myocardial infarction and stroke is.

Study strengths and limitations

Strengths of the study include the prospective nature of the data and the relatively large size of the study with a long follow-up period. We used a high quality validated clinical assay in routine use in clinical biochemistry departments to measure both NT-proBNP and hsTnT. Weaknesses include that current findings are based on doctor-diagnosed HF, and although diagnoses were usually supported by evidence from hospital investigations, there is likely to be some outcome misclassification, including under-reporting of incident heart failure. Because we did not have echocardiographic data, we were unable to differentiate incident HF with reduced ejection fraction from HF with preserved ejection fraction. Similarly, routine coronary angiography was not performed in common with most cohort studies. These limitations mean that we cannot be sure to what extent information gained from measuring hsTnT overlaps with information that have might been available had other diagnostic investigations been performed. However, a potential use of cardiac biomarkers is to select the most appropriate patients in which to carry out these investigations. [31,32] Finally, we studied older male survivors from a socioeconomically representative general cohort study, but participants were a predominantly white population of European origin, so that the results cannot be generalised directly to women, or to younger individuals or other

ethnic groups. However, additional studies such as ARIC (aged 45-64 at baseline) [9] also demonstrate an association of hsTnT with incident heart failure in both men and women in an ethnically diverse cohort, providing external validity.

Conclusion

Although NT-proBNP is the most powerful predictor of HF, even low grade elevation in hsTnT is consistently associated with a higher risk of HF in older men, and HF rarely occurs when hsTnT is near the limit of detection. Interventions to prevent myocardial injury may mitigate risk of HF in later life.

Acknowledgements

We thank Elaine Butler (University of Glasgow) for technical support.

Sources of funding

This work was supported by a BHF Programme grant (RG/08/013/25942) which funds the British Regional Heart Study. PW was supported by BHF fellowship FS/12/62/29889 which funded biomarker work. None of the funding bodies were involved in the study design or the collection, analysis, and interpretation of data for this paper or in the writing of the report.

Disclosure

PW has received grant support from Roche Diagnostics. NS reports consulting, speaking, and/or honoraria from Amgen, Roche Diagnostics, Sanofi/Regeneron, Astrazeneca, Boehringer Ingelheim, NovoNordisk and Janssen. JMc reports consulting fees from

cytokinetics/ Amgen. All other authors report no conflict of interest. All authors have approved the final article for publication.

References

1. The National Institute for Health and Care Excellence. Chronic heart failure in adults: management. NICE; https://www.nice.org.uk/guidance/cg108 (11 May 2018)
2. Mehta PA, Dubrey SW, McIntyre HF, et al. Improving survival in the 6 months after diagnosis of heart failure in the past decade: population-based data from the UK. *Heart* 2009;95:1851–1856.
3. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. *Nat Rev Cardiol* 2016;13:368–378.
4. Jhund PS, McMurray JJ V. Heart failure after acute myocardial infarction: a lost battle in the war on heart failure? *Circulation* 2008;118:2019–2021.
5. Yusuf S, Pepine CJ, Garces C, et al. Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. *Lancet* 1992;340:1173–1178.
6. Higgins JP, Higgins JA. Elevation of cardiac troponin I indicates more than myocardial ischemia. *Clin Investig Med Médecine Clin Exp* 2003;26:133–147.
7. Katus HA, Remppis A, Scheffold T, et al. Intracellular compartmentation of cardiac troponin T and its release kinetics in patients with reperfused and nonreperfused myocardial infarction. *Am J Cardiol* 1991;67:1360–1367.
8. Bansal N, Hyre Anderson A, Yang W, et al. High-sensitivity troponin T and N-terminal pro-B-type natriuretic peptide (NT-proBNP) and risk of incident heart failure in patients with CKD: the Chronic Renal Insufficiency Cohort (CRIC) Study. *J Am Soc Nephrol* 2015;26:946–956.
9. Nambi V, Liu X, Chambless LE, Lemos JA De, et al. Troponin T and N-Terminal Pro-B-type natriuretic peptide: A biomarker approach to predict heart failure risk-the

atherosclerosis risk in communities study. *Clin Chem* 2013;59:1802–1810.

10. Ndumele CE, Coresh J, Lazo M, et al. Obesity, Subclinical Myocardial Injury, and Incident Heart Failure. *JACC Hear Fail* 2014;2:600–607.

11. Silverman MG, Patel B, Blankstein R, et al. Impact of Race, Ethnicity, and Multimodality Biomarkers on the Incidence of New-Onset Heart Failure With Preserved Ejection Fraction (from the Multi-Ethnic Study of Atherosclerosis). *Am J Cardiol* 2016;117:1474–1481.

12 Sundström J, Ingelsson E, Berglund L, et al. Cardiac troponin-I and risk of heart failure: a community-based cohort study. Eur Heart J. 2009;30:773-81.

13. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology. *Eur Heart J*. 2016;37:2129-200.

14. Shaper AG, Pocock SJ, Walker M, et al. British Regional Heart Study: cardiovascular risk factors in middle-aged men in 24 towns. *Br Med J (Clin Res Ed)* 1981;283:179–186.

15. Wannamethee SG, Welsh P, Papacosta O, et al. Elevated Parathyroid Hormone, But Not Vitamin D Deficiency, Is Associated With Increased Risk of Heart Failure in Older Men With and Without Cardiovascular Disease. *Circ Heart Fail* 2014;732–740.

16. Wannamethee SG, Whincup PH, Lennon L, et al. Alcohol consumption and risk of incident heart failure in older men: a prospective cohort study. *Open Heart* 2015;2:e000266.

17. Welsh P, Hart C, Papacosta O, et al. Prediction of Cardiovascular Disease Risk by Cardiac Biomarkers in 2 United Kingdom Cohort Studies: Does Utility Depend on Risk

Thresholds For Treatment? *Hypertension* 2016;67:309–315.

18. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res* 2007;16:219–242

19. Pencina MJ, D'Agostino RB, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med* 2011;30:11–21.

20. Kerr KF, McClelland RL, Brown ER, et al. Evaluating the incremental value of new biomarkers with integrated discrimination improvement. *Am J Epidemiol* 2011;174:364–374.

21. Welsh P, Poulter NR, Chang CL, et al. The value of N-terminal pro-B-type natriuretic peptide in determining antihypertensive benefit: observations from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT). *Hypertension* 2014;63:507–513.

22. Welsh P, Doolin O, Willeit P, et al. N-terminal pro-B-type natriuretic peptide and the prediction of primary cardiovascular events: results from 15-year follow-up of WOSCOPS. *Eur Heart J* 2013;34:443–450.

23. Nadir MA, Dow E, Davidson J, et al. Myocardial ischaemia is associated with an elevated brain natriuretic pepide level even in the presence of left ventricular systolic dysfunction. *Eur J Heart Fail* 2014;16:56–67.

24. Nadir MA, Witham MD, Szwejkowski BR, et al. Meta-analysis of B-type natriuretic peptide's ability to identify stress induced myocardial ischemia. *Am J Cardiol* 2011;107:662–667.

25. Kim Y, Matsushita K, Sang Y, et al. Association of high-sensitivity cardiac troponin T and natriuretic peptide with incident ESRD: the Atherosclerosis Risk in Communities (ARIC) study. *Am J Kidney Dis* 2015;65:550–558.

26. Welsh P, Kou L, Yu C, et al. Prognostic importance of emerging cardiac, inflammatory, and renal biomarkers in chronic heart failure patients with reduced ejection fraction and anaemia: RED-HF study. Eur J Heart Fail. 2018;20:268-277.

27. Huynh QL, Saito M, Blizzard CL, et al. Roles of nonclinical and clinical data in prediction of 30-day rehospitalization or death among heart failure patients. J Card Fail. 2015;21:374-81.

28. Tanindi A, Cemri M. Troponin elevation in conditions other than acute coronary syndromes. *Vasc Health Risk Manag* 2011;7:597–603.

29. Preiss D, Campbell RT, Murray HM, et al. The effect of statin therapy on heart failure events: a collaborative meta-analysis of unpublished data from major randomized trials. *Eur Heart J* 2015;36:1536–1546.

30. Jhund PS, Claggett BL, Voors AA, et al. Elevation in high-sensitivity troponin T in heart failure and preserved ejection fraction and influence of treatment with the angiotensin receptor neprilysin inhibitor LCZ696. *Circ Heart Fail* 2014;7:953–959.

31. Willeit P, Welsh P, Evans JDW, et al. High-Sensitivity Cardiac Troponin Concentrationm and Risk of First-Ever Cardiovascular Outcomes in 154,052 Participants. J Am Coll Cardiol. 2017;70:558-568.

32. Natriuretic Peptides Studies Collaboration, Willeit P, Kaptoge S, et al. Natriuretic peptides and integrated risk assessment for cardiovascular disease: an individual-participant-data meta-analysis. Lancet Diabetes Endocrinol. 2016;4:840-9.

Figure legends

Figure 1

Kaplan Meier curves illustrating event free survival from HF by tertiles of hsTnT in a) those without baseline CHD b) those with baseline CHD. Blue curves are the lowest tertile(≤9.7ng/L), red the middle tertile (9.8-14.2ng/L), and green the top tertile (≥14.3ng/L). Cutoffs are defined from the whole cohort.

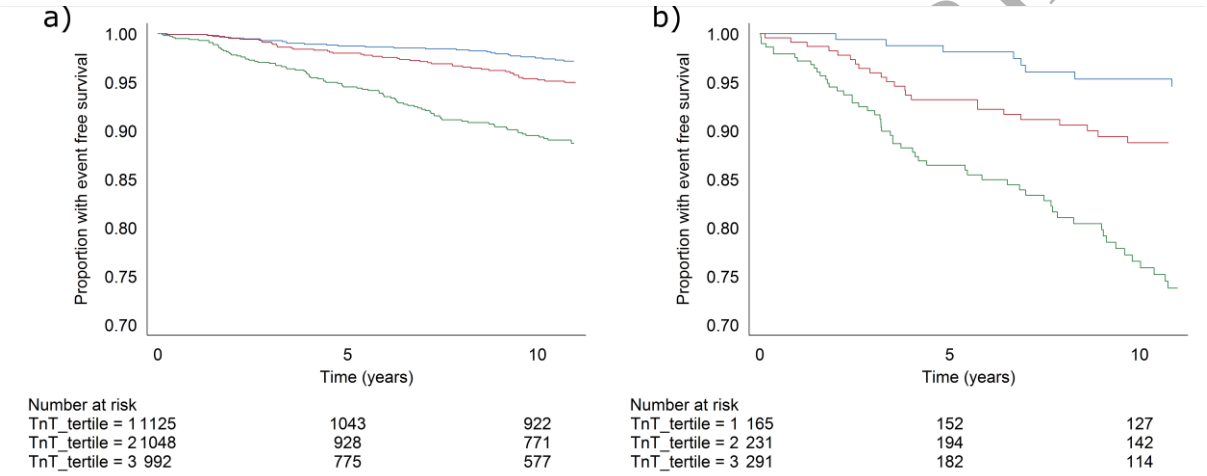
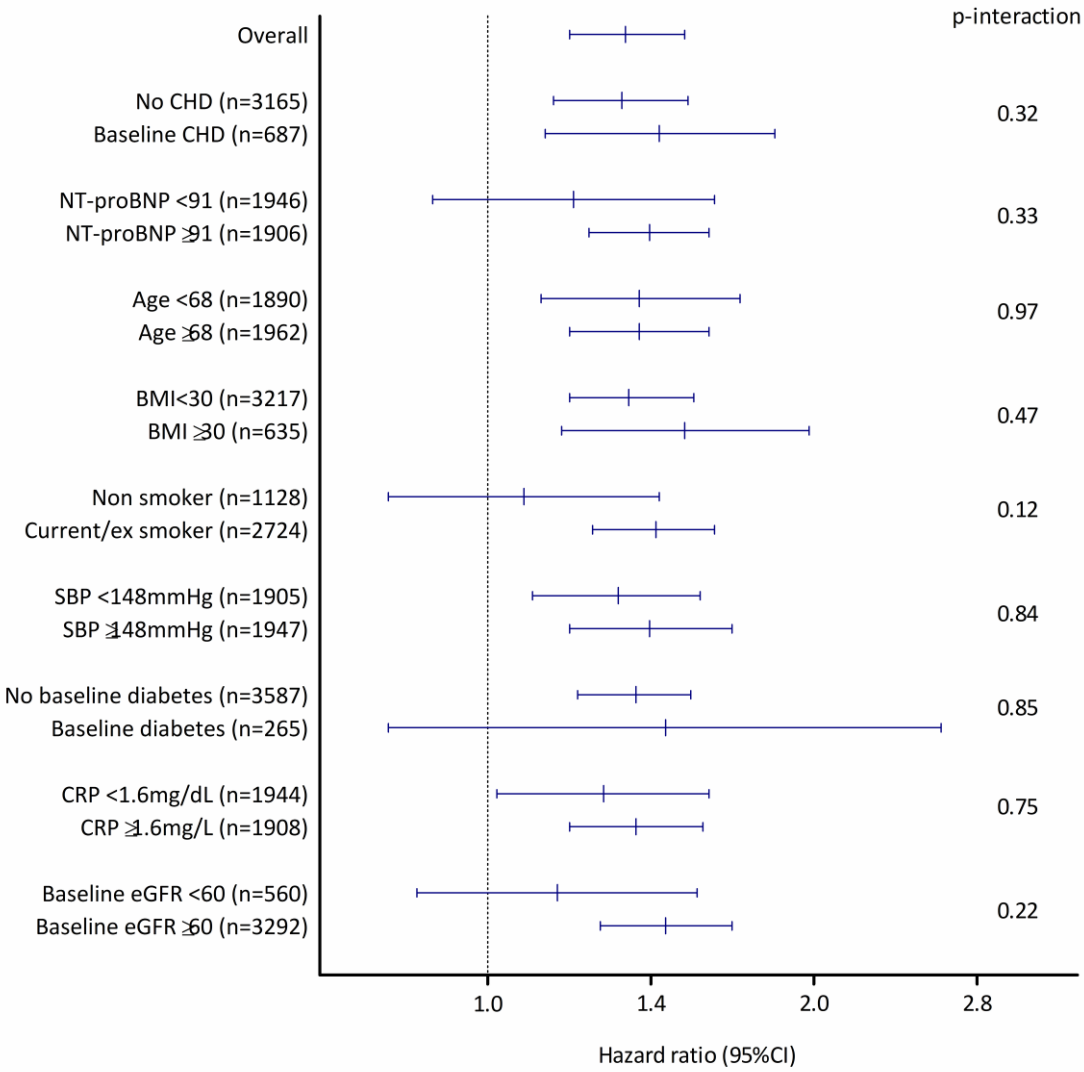


Figure 2

Hazard ratio for heart failure per 1 SD increase in hsTnT, stratified by a range of other risk factors. P-values are tests for interaction comparing the effect of hsTnT in stratified groups


p-interaction
Overall
No CHD (n=3165)
Baseline CHD (n=687)
0.32
NT-proBNP <91 (n=1946)
NT-proBNP ≥91 (n=1906)
0.33
Age <68 (n=1890)
Age ≥68 (n=1962)
0.97
BMI<30 (n=3217)
BMI ≥30 (n=635)
0.47
Non smoker (n=1128)
Current/ex smoker (n=2724)
0.12
SBP <148mmHg (n=1905)
SBP ≥148mmHg (n=1947)
0.84
No baseline diabetes (n=3587)
Baseline diabetes (n=265)
0.85
CRP <1.6mg/dL (n=1944)
CRP ≥1.6mg/L (n=1908)
0.75
Baseline eGFR <60 (n=560)
Baseline eGFR ≥60 (n=3292)
0.22
1.0
1.4
2.0
2.8
Hazard ratio (95%CI)

.

Table 1 Distribution of risk factors at baseline comparing those who experience HF during follow-up to those who do not

Risk factor	**No incident heart failure (n=3557)**	**Incident heart failure (n=295)**	
Age (years)	68.5 (5.5)	70.5 (5.4)	p<0.001
BMI	26.8 (3.6)	27.8 (3.9)	p<0.001
Waist Circ (cm)	96.7 (10.4)	99.7 (11.2)	p<0.001
Smoking			p=0.42
Never	1048 (29.5%)	79 (26.8%)	
Ex	2039 (57.4%)	181 (61.4%)	
Current	466 (13.1%)	35 (11.9%)	
FEV1	2.62 (0.65)	2.40 (0.68)	p<0.001
SBP	149.1 (24.0)	152.2 (25.2)	p=0.04
DBP	85.4 (11.1)	84.8 (11.0)	p=0.43
Heart rate	65.5 (12.5)	67.6 (13.7)	p=0.006
Total Chol	6.02 (1.07)	5.90 (1.12)	p=0.08
HDL Chol	1.32 (0.34)	1.29 (0.34)	p=0.14
Glucose	5.99 (1.79)	6.30 (2.55)	p=0.006
Physical activity			p=0.03

Inactive	360 (10.5%)	35 (12.3%)	
Occasional-light	1424 (41.5%)	127 (44.6%)	
Moderate-vigorous	1645 (48.0%)	123 (43.2%)	
Alcohol			p=0.79
None	347 (9.9%)	32 (11.2%)	
Occasional/light	2469 (70.5%)	205 (69.7%)	
Moderate-Heavy	688 (19.6%)	54 (19.1%)	
Diabetes	232 (6.5%)	33 (11.2%)	p=0.002
Atrial fibrillation	105 (3.0%)	30 (10.2%)	p<0.001
Statin	212 (6.0%)	25 (8.5%)	p=0.084
Blood pressure med	1056 (30.1%)	139 (47.8%)	p<0.001
Index of multiple deprivation (IMD)	20.2 (14.7)	20.6 (14.7)	p=0.66
eGFR	72.8 (12.6)	70.1 (13.4)	p<0.001
CRP	1.54 [0.81, 3.33]	2.16 [1.04, 4.18]	p<0.001
NT-proBNP	85 [44, 173]	231 [102, 577]	p<0.001
hsTnT	11.5 [8.7, 15.6]	15.5 [11.0, 20.1]	p<0.001

Table 2 Associations of hsTnT (per SD increase on log scale) with HF

Study/events	N (n events)	**Model 1**		**Model 2**		**Model 3**		**Model 4**	
		HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
All participants	3852 (295)	1.81 (1.66, 1.97)	<0.001	1.64 (1.47, 1.82)	<0.001	1.58 (1.42, 1.77)	<0.001	1.34 (1.19, 1.52)	<0.001
Participants without baseline CHD	3165 (201)	1.76 (1.57, 1.96)	<0.001	1.59 (1.40, 1.81)	<0.001	1.51 (1.32, 1.74)	<0.001	1.33 (1.15, 1.53)	<0.001
Participants with baseline CHD	687 (94)	1.82 (1.55, 2.12)	<0.001	1.79 (1.47, 2.18)	<0.001	1.83 (1.48, 2.26)	<0.001	1.44 (1.13, 1.84)	0.001

Model 1 unadjusted
Model 2 adjusted for: age, total cholesterol, HDL cholesterol, systolic blood pressure, IMD, BMI, smoking, diabetes, eGFR, BP medication use, statin use, and MI that occurred during follow-up
Model 3 additionally adjusted for: heart rate, glucose, physical activity, FEV1, alcohol use, atrial fibrillation, CRP
Model 4: additionally adjusted for: NT-proBNP

Table 3 Prediction of heart failure in those without baseline CHD: C-statistics matrix comparing various models with and without hsTnT (n=3852)

Model	C-index	Vs Model A	Vs Model B	Vs Model C
Model A Classical risk factors*	0.730 (0.701, 0.759)			
Model B Classical risk factors plus NT-proBNP	0.791 (0.766, 0.816)	+0.061 (0.039, 0.082) p<0.001		
Model C Classical risk factors plus NT-proBNP and hsTnT	0.794 (0.769, 0.819)	+0.064 (0.043, 0.086) p<0.001	+0.004 (-0.003, 0.010) p=0.28	
Model D Age and NT-proBNP	0.757 (0.729, 0.785)	+0.027 (-0.004, 0.058) p=0.09	-0.034 (-0.050, -0.018) p<0.001	-0.037 (-0.055, -0.020) p<0.001

* age, total cholesterol, HDL cholesterol, systolic blood pressure, IMD, BMI, smoking, diabetes, eGFR, BP medication use, statin use, heart rate, glucose, physical activity, FEV1, alcohol use, atrial fibrillation, and baseline CVD