Cardiac Stress and Inflammatory Markers as Predictors of Heart Failure in Patients With Type 2 Diabetes: The ADVANCE Trial

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OBJECTIVE

This study examined the individual and combined effect of N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin T (hs-cTnT), interleukin-6 (IL-6), and hs-CRP on the prediction of heart failure incidence or progression in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

A nested case-cohort study was conducted in 3,098 participants with type 2 diabetes in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial.

RESULTS

A higher value of each biomarker was significantly associated with a higher risk of heart failure incidence or progression, after adjustment for major risk factors. The hazard ratios per 1-SD increase were 3.06 (95% CI 2.37, 3.96) for NT-proBNP, 1.50 (1.27, 1.77) for hs-cTnT, 1.48 (1.27, 1.72) for IL-6, and 1.32 (1.12, 1.55) for hs-CRP. The addition of NT-proBNP to the model including conventional risk factors meaningfully improved 5-year risk-predictive performance (C statistic 0.8162 to 0.8800; continuous net reclassification improvement [NRI] 73.1%; categorical NRI [<5%, 5–10%, >10% 5-year risk] 24.2%). In contrast, the addition of hs-cTnT, IL-6, or hs-CRP did not improve the prediction metrics consistently in combination or when added to NT-proBNP.

CONCLUSIONS

Only NT-proBNP strongly and consistently improved the prediction of heart failure in patients with type 2 diabetes beyond a wide range of clinical risk factors and biomarkers.

The number of people with heart failure has been increasing, most likely the result of aging and the increasing prevalence of hypertension, diabetes, obesity, and atherosclerotic disease (1). Heart failure increases mortality and hospitalization, decreases health-related quality of life and functional status, and results in increasing medical costs (1). Therefore, the prevention and management of heart failure is an important global public health problem.

Diabetes is one of the major risk factors for heart failure, being associated with a more than 50% increase in risk (2), and has strong adverse effects on the prognosis of heart failure (3). Heart failure is also the second most common first presentation of

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cardiovascular disease (CVD) in patients with type 2 diabetes and more common than myocardial infarction (2). Yet, insufficient emphasis has been placed on the prevention and treatment of heart failure in the clinical management of diabetes (4).

Recently, several circulating biomarkers, such as C-reactive protein (CRP) (5), interleukin-6 (IL-6) (6), N-terminal pro-B-type natriuretic peptide (NT-proBNP) (7,8), and high-sensitivity (hs) cardiac troponin T (hs-cTnT) (9), have been shown to be associated with the incidence of CVD. That these biomarkers may be useful in predicting the risk of heart failure has also been suggested. However, few studies have examined the association between these biomarkers and the risk of heart failure in patients with diabetes, and how well these biomarkers can classify the risk of heart failure in such patients is uncertain. Given limited medical resources and costs, efficient identification of high-risk patients for subsequent precise evaluation and intervention is crucial.

The objective of the current study was thus to examine the association of circulating cardiac stress (NT-proBNP for myocardial stretch and volume overload and hs-cTnT for myocardial damage) and inflammatory (hs-CRP and IL-6) markers with the risk of heart failure and their additional risk-predictive ability beyond that from traditional clinical risk factors in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study Sample

We conducted a nested case-cohort study to examine the association between cardiac stress biomarkers and inflammatory markers and heart failure in patients with type 2 diabetes who participated in Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study. The design and results of ADVANCE have been published in detail previously (10–12). Briefly, 11,140 patients with type 2 diabetes at high risk of cardiovascular events were enrolled from 215 centers in 20 countries and randomly assigned to a gliclazide (modified release)-based intensive glucose control strategy (target hemoglobin A_{1c} [HbA_{1c}] $\leq$6.5%) or standard glucose control strategy based on local guidelines and to a fixed-dose combination of perindopril (4 mg) and indapamide (1.25 mg) or matching placebo after a 6-week active run-in period. Each center's institutional review board approved the study. All participants provided written informed consent.

Baseline data included demographic and clinical information. Weight, height, blood pressure, HbA_{1c}, fasting lipid levels, urinary albumin-to-creatinine ratio (ACR), and serum creatinine were measured. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (13). Twelve-lead electrocardiograms (ECGs) were obtained at baseline for the presence of atrial fibrillation, left ventricular hypertrophy, and pathological Q-waves. Atrial fibrillation was considered present when the investigator identified it on the baseline ECG or when atrial fibrillation confirmed by ECG had been previously diagnosed.

Plasma samples were obtained from all study participants at baseline and stored at −80°C for a median of 7.8 years. Samples were available from all countries involved in ADVANCE, except China and India, giving a total population of 7,376. For the nested case-cohort study (14), a random subcohort of 3,500 participants was selected from this base population plus 131 additional participants who had experienced a heart failure event during 5-year follow-up (Supplementary Fig. 1).

Levels of hs-IL-6 were assayed by ELISA (R&D Systems, Oxford, U.K.) and hs-CRP by immunonephelometry (ProSpec; Dade Behring, Milton Keynes, U.K.) (15). NT-proBNP and hs-cTnT were assayed by electrochemiluminescence immunoassays performed on a Roche Elecsys 2010 automated platform (Roche Diagnostics, Burgess Hill, U.K.) (16,17). A detailed description of the measurement of stored samples was published previously (15–17).

Study Outcome

The study outcome in this project was the incidence or progression of heart failure (death due to heart failure, hospitalization due to heart failure, or worsening New York Heart Association Functional Classification).

Statistical Analysis

Categorical data are presented as number (percentage) and continuous data as mean (SD) where approximately symmetrically distributed, or median (interquartile range) where skewed. Differences in the mean values or proportions of the baseline characteristics of the patients according to outcome status were tested by χ^2 test, unpaired *t* test, or Wilcoxon test, as appropriate. Hazard ratios (HRs) for incidence or progression of heart failure were calculated by weighted Cox regression models for case-cohort analyses using groups defined by the fifths and for a 1-SD increase in each of IL-6, hs-CRP, hs-cTnT, and NT-proBNP after log transformation. Three models, with different potential confounding variables, were fitted for each biomarker–heart failure combination: model 1 with age, sex, randomized blood pressure–lowering intervention, and randomized glucose-control intervention; model 2 with, additionally, duration of diabetes, current smoking, history of myocardial infarction, history of hospitalization for heart failure, BMI, systolic blood pressure, heart rate, current or previous atrial fibrillation, pathological Q-wave on ECG, left ventricular hypertrophy on ECG, aspirin or other antiplatelet agent use, β-blocker use, calcium channel blocker use, diuretic use, ACE inhibitor or angiotensin II receptor blocker use, total cholesterol, HDL cholesterol, triglyceride, statin or other lipid-lowering agent, HbA_{1c}, thiazolidinedione use, insulin use, urinary ACR and eGFR; and model 3 with, additionally to model 2, the other three biomarkers. Predefined subgroup analyses, using model 2, were performed by baseline history of heart failure, history of myocardial infarction, sex, age (split at its median), and duration of diabetes (also split at its median).

Prediction metrics for heart failure were calculated in the random subcohort. Discrimination was evaluated by C statistics for 5-year risk, accounting for censoring (18), and compared between model 2 and model 2 plus each biomarker individually and in combination. In addition, the ability of each biomarker to better classify the 5-year risk for incidence or progression of heart failure, compared with model 2, was evaluated by the integrated discrimination index (IDI) and the net reclassification improvement (NRI), using methods suitable for survival data (14). NRI was calculated by a continuous model for changes in risk classification and a categorical model based on <5%, 5–10%, and >10% 5-year risk.

In addition, sensitivity analyses were conducted after excluding *1*) patients with a history of hospitalization for heart failure (*n* = 136) and *2*) patients with

NT-proBNP levels >400 pg/mL (n = 391). All analyses were performed using SAS Enterprise Guide 7.11 (SAS Institute Inc., Cary, NC) or Stata 13 software (StataCorp, College Station, TX). A two-sided $P < 0.05$ was considered statistically significant in all analyses.

RESULTS

The entire case-cohort study comprised 3,631 patients. After a number of exclusions, shown in Supplementary Fig. 1 (283 patients with insufficient stored plasma for measurement of biomarkers and 250 with missing values for covariates), the remaining 3,098 patients were included in the present analysis. During a median follow-up of 5.0 years, 237 experienced a heart failure event. Table 1 lists the baseline characteristics of study participants. Women comprised 40% of the cohort, and the mean age was 67 years. IL-6, hs-CRP, hs-cTnT, and NT-proBNP levels were significantly higher in patients who experienced a heart failure event.

The HRs and 95% CIs for heart failure according to fifths of each biomarker are depicted in Fig. 1. The risk of heart failure increased significantly with increasing levels of all of the biomarkers after adjustment for age, sex, randomized blood pressure–lowering, and glucose-control interventions, and clinical risk factors (all P for trend <0.01 in model 2). Multivariable-adjusted HRs (95% CIs) for the highest fifths compared with the lowest fifths were 2.62 (1.48, 4.63) for IL-6, 2.22 (1.33, 3.72) for hs-CRP, 2.70 (1.68, 4.34) for hs-cTnT, and 12.53 (5.41, 29.02) for NT-proBNP. Figure 2 shows the HRs and 95% CIs for heart failure according to a 1-SD increment in each biomarker. Higher values of all four biomarkers were significantly associated with a higher risk of

Table 1—Baseline characteristics according to outcome status

	Heart failure event		Overall
Variables	Yes, n = 237	No, n = 2,861	n = 3,098
Female (%)	83 (35)	1,162 (41)	1,245 (40)
Age (years)	70 (7)*	66 (7)	67 (7)
Duration of diabetes (years)	10.0 (7.6)*	7.5 (6.2)	7.7 (6.3)
Current smoking (%)	30 (13)	426 (15)	456 (15)
History of myocardial infarction (%)	61 (26)*	98 (3)	159 (5)
History of hospitalization for heart failure (%)	38 (16)*	98 (3)	136 (4)
BMI (kg/m^2)	30.7 (5.6)	30.0 (5.2)	30.0 (5.2)
Blood pressure (mmHg)			
Systolic	149 (23)	147 (21)	147 (21)
Diastolic	80 (12)*	82 (11)	82 (11)
Heart rate (bpm)	74 (13)	73 (12)	73 (12)
Current or previous atrial fibrillation (%)	49 (21)*	275 (10)	324 (10)
Pathological Q-wave on ECG (%)	51 (22)*	307 (11)	358 (12)
LVH on ECG (%)	37 (16)*	222 (8)	259 (8)
Aspirin or other antiplatelet agent (%)	143 (60)*	1,378 (48)	1,521 (49)
β-Blocker (%)	71 (30)	856 (30)	927 (30)
Calcium channel blocker (%)	106 (45)*	815 (28)	921 (30)
Diuretics¶ (%)	119 (50)*	823 (29)	942 (30)
ACE inhibitors¶ or ARB (%)	175 (74)*	1,628 (57)	1,803 (58)
Total cholesterol (mmol/L)	5.03 (1.13)	5.16 (1.17)	5.15 (1.17)
HDL cholesterol (mmol/L)	1.17 (0.28)*	1.23 (0.33)	1.23 (0.33)
Triglyceride (mmol/L)	1.60 (1.22, 2.30)	1.70 (1.20, 2.34)	1.70 (1.20, 2.33)
Statin or other cholesterol-lowering agent (%)	101 (43)	1,265 (44)	1,366 (44)
HbA_{1c} (%)	7.8 (1.5)*	7.4 (1.4)	7.4 (1.4)
HbA_{1c} (mmol/mol)	61.3 (16.0)*	56.9 (15.1)	57.2 (15.2)
Thiazolidinedione (%)	7 (3)	126 (4)	133 (4)
Other oral antidiabetic agents (%)	219 (92)	2,562 (90)	2,781 (90)
Insulin (%)	4 (2)	37 (1)	41 (1.3)
Urinary ACR (μg/mg)	30.9 (10.4, 91.1)*	12.9 (6.2, 32.7)	13.5 (6.2, 36.2)
eGFR (mL/min/1.73 m^2)	63 (18)*	73 (16)	72 (17)
IL-6 (pg/mL)	3.05 (2.13, 4.49)*	2.19 (1.57, 3.21)	2.26 (1.61, 3.33)
hs-CRP (mg/L)	2.35 (1.19, 5.89)*	1.75 (0.84, 3.91)	1.80 (0.86, 4.03)
hs-cTnT (ng/L)	12.0 (6.0, 20.0)*	5.0 (1.5, 10.0)	5.0 (1.5, 10.0)
NT-proBNP (pg/mL)	353.0 (131.0, 819.0)*	75.0 (31.0, 172.0)	84.0 (33.0, 203.0)

Values are mean (SD) or median (interquartile range) for continuous variables and number (%) for categorical variables. ARB, angiotensin II receptor blocker; LVH, left ventricular hypertrophy. *$P < 0.05$ vs. patients without heart failure event. ¶Randomized blood pressure–lowering treatment with perindopril-indapamide was not included.

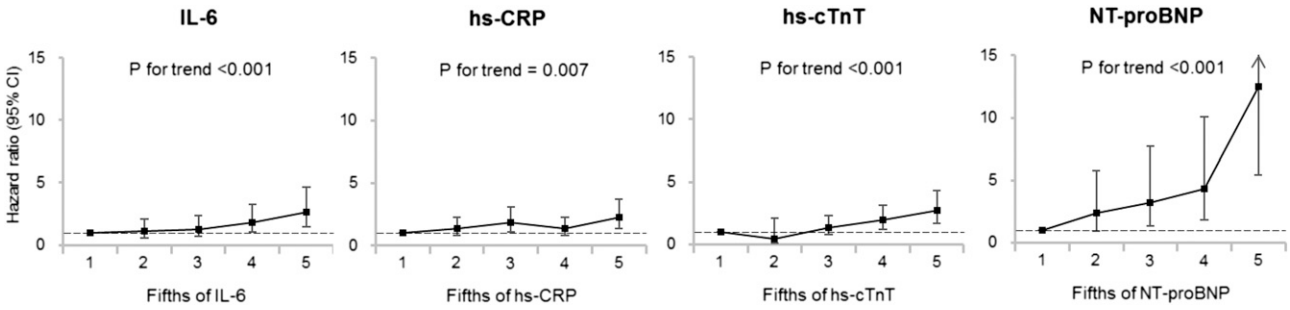

Figure 1—Adjusted HRs and 95% CIs for heart failure according to fifths of the biomarker. Each biomarker was categorized into five groups according to the fifths. The ranges of IL-6 were 0.19–1.48, 1.49–1.95, 1.96–2.58, 2.59–3.68, and 3.69–16.13 pg/mL. The ranges of hs-CRP were 0.08–0.73, 0.74–1.33, 1.34–2.45, 2.46–4.75, and 4.78–130.00 mg/L. The ranges of hs-cTnT were 1.5–3.0, 4.0–6.0, 7.0–12.0, and 13.0–751.0 ng/L. The ranges of NT-proBNP were 2.5–24.0, 25.0–59.0, 60.0–116.0, 117.0–255.0, and 256.0–35,000.0 pg/mL. HRs were adjusted for age, sex, randomized blood pressure–lowering intervention, randomized glucose-control intervention, duration of diabetes, current smoking, history of myocardial infarction, history of hospitalization for heart failure, BMI, systolic blood pressure, heart rate, current or previous atrial fibrillation, pathological Q-wave on ECG, left ventricular hypertrophy on ECG, aspirin or other antiplatelet agent use, β-blocker use, calcium channel blocker use, diuretic use, ACE enzyme inhibitor or angiotensin II receptor blocker use, total cholesterol, HDL cholesterol, triglyceride, statin or other lipid-lowering agent, HbA_{1c}, thiazolidinedione use, insulin use, urinary ACR, and eGFR.

heart failure after adjusting for clinical risk factors (model 2, all $P < 0.001$). After further adjustment for the other biomarkers (model 3), associations were attenuated and became nonsignificant for hs-CRP and hs-cTnT. In all adjustment sets, NT-proBNP showed the strongest association with heart failure (HR 2.77 [95% CI 2.12, 3.63] in model 3). Broadly similar findings were observed in the sensitivity analyses after excluding patients with a history of hospitalization for heart failure (Supplementary Fig. 2) or those with NT-proBNP levels >400 pg/mL (Supplementary Fig. 3), although the associations were slightly attenuated when patients with NT-proBNP levels >400 pg/mL were excluded. There was no evidence of effect modification in the association between heart failure and NT-proBNP by sex, age, duration of diabetes, or history of hospitalization for heart failure (model 2, Supplementary Fig. 4). Although significant heterogeneity (P = 0.004) was observed in the association in those with (HR 2.28 [95% CI 1.08, 4.81]) and without (HR 3.52 [95% CI 2.66, 4.66]) a history of myocardial infarction, the direction of the association was the same in both groups.

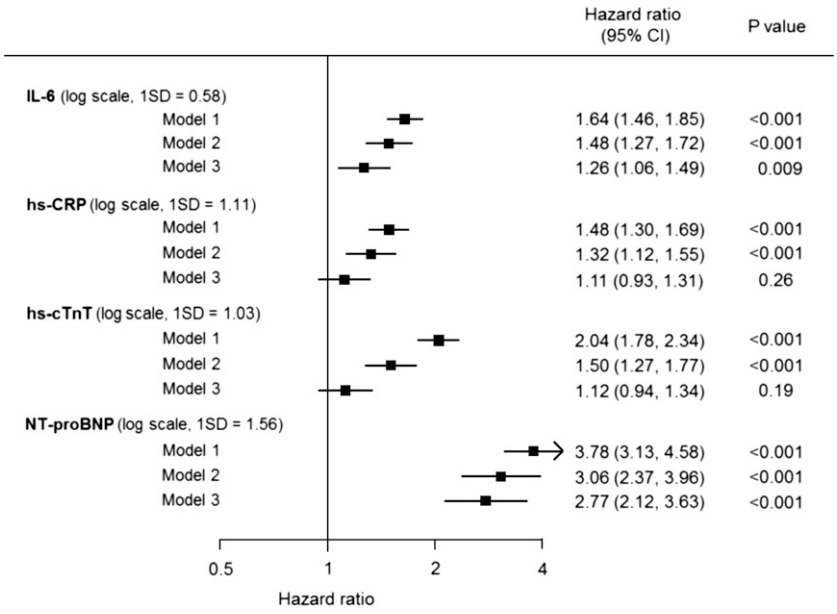

Figure 2—Adjusted HRs and 95% CIs for heart failure according to a 1-SD increment in the biomarker. Model 1 was adjusted for age, sex, randomized blood pressure–lowering intervention, and randomized glucose-control intervention. Model 2 was additionally adjusted for duration of diabetes, current smoking, history of myocardial infarction, history of hospitalization for heart failure, BMI, systolic blood pressure, heart rate, current or previous atrial fibrillation, pathological Q-wave on ECG, left ventricular hypertrophy on ECG, aspirin or other antiplatelet agent use, β-blocker use, calcium channel blocker use, diuretic use, ACE inhibitor or angiotensin II receptor blocker use, total cholesterol, HDL cholesterol, triglyceride, statin or other lipid-lowering agent, HbA_{1c}, thiazolidinedione use, insulin use, urinary ACR, and eGFR. Model 3 was additionally adjusted for the other biomarkers.

The addition of NT-proBNP to a model including conventional risk factors (model 2) greatly improved discrimination and classification of the 5-year risk of heart failure (C statistic: 0.8162 to 0.8800, $P < 0.001$; IDI: 0.107, $P < 0.001$; continuous NRI: 0.731, $P < 0.001$; categorical NRI: 0.242, $P < 0.001$) (Table 2). However, the improvements were not uniformly significant when adding any of IL-6, hs-CRP, or hs-cTnT to model 2. NT-proBNP alone showed comparable predictive ability compared with a comprehensive set of conventional risk factors (C statistic: 0.8239 vs. 0.8162, P = 0.74).

On the one hand, addition of NT-proBNP to model 2 plus IL-6, hs-CRP, and hs-cTnT significantly improved the C statistic (0.8384 to 0.8816, $P < 0.001$) and classification of outcomes (IDI: 0.081, $P < 0.001$; continuous NRI: 0.664, $P < 0.001$; categorical NRI: 0.191, $P < 0.001$). On the other hand, addition of a combination of IL-6, hs-CRP, and hs-cTnT to model 2 plus NT-proBNP improved classification (IDI: 0.029, P = 0.002; continuous NRI: 0.304, P = 0.002; categorical NRI: 0.010, P = 0.56) but did not improve discrimination (C statistic: 0.8800 to 0.8816, P = 0.65). Almost identical results were obtained when patients with a history of hospitalization for

heart failure or those with NT-proBNP levels >400 pg/mL were excluded (Supplementary Tables 1 and 2).

CONCLUSIONS

To the best of our knowledge, this is the first study to use a comprehensive set of prediction metrics to examine the improvement in the risk-predictive ability for future heart failure by adding biomarkers to conventional risk factors in patients with type 2 diabetes. Higher values of IL-6, hs-CRP, hs-cTnT, and NT-proBNP were significantly associated with a higher risk of incidence or progression of heart failure in patients with type 2 diabetes. These associations persisted after adjusting for a comprehensive set of conventional CVD risk factors. In addition, incorporation of NT-proBNP into a prediction model greatly improved discrimination and classification of the 5-year risk of heart failure beyond conventional use of risk factors. In contrast, IL-6, hs-CRP, and hs-cTnT did not provide clinically useful incremental information. These data were broadly similar in those with no history of heart failure hospitalization and when those with NT-proBNP levels >400 pg/mL were excluded.

A number of studies have reported the usefulness of newly identified biomarkers, such as NT-proBNP, hs-cTnT, hs-CRP, and IL-6, to predict incident heart failure (19,20). However, few studies have investigated the prognostic ability for heart failure in patients with diabetes. A subanalysis of the Intensified Multifactorial Intervention in Patients With Type 2 Diabetes and Microalbuminuria (Steno-2) study found that NT-proBNP levels above the median of the study population were associated with an increased risk of a composite of cardiovascular mortality and hospitalization for congestive heart failure in 160 patients with microalbuminuria and type 2 diabetes (21). Another observational study from the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) randomized trial, among 12,301 patients with type 2 diabetes, also showed a stepwise increased risk of hospitalization for heart failure with increasing levels of NT-proBNP, with no evidence of heterogeneity among those taking saxagliptin treatment or placebo (22). The addition of NT-proBNP to the model with clinical

Table 2—Discrimination and reclassification statistics (95% CIs) for 5-year risk of heart failure after addition of biomarkers to a model containing clinical risk factors

				NRI	
	C statistic	IDI	Relative IDI (%)	Continuous	Categorical†
Base model*	0.8162 (0.7785, 0.8540)				
Base model plus IL-6	0.8264 (0.7904, 0.8624)	0.029 (0.008, 0.050)	8.73 (2.38, 15.98)	0.393 (0.210, 0.569)	0.030 (−0.053, 0.108)
P	0.052	0.006		<0.001	0.45
Base model plus hs-CRP	0.8261 (0.7900, 0.8621)	0.018 (0.003, 0.034)	5.50 (0.91, 10.45)	0.215 (0.036, 0.387)	0.092 (0.024, 0.160)
P	0.11	0.02		0.03	0.008
Base model plus hs-cTnT	0.8253 (0.7888, 0.8618)	0.020 (0.004, 0.038)	6.08 (1.19, 11.70)	0.403 (0.223, 0.583)	0.065 (−0.008, 0.140)
P	0.22	0.01		<0.001	0.07
Base model plus NT-proBNP	0.8800 (0.8529, 0.9072)	0.107 (0.064, 0.154)	32.2 (18.2, 49.3)	0.731 (0.564, 0.892)	0.242 (0.145, 0.342)
P	<0.001	<0.001		<0.001	<0.001
Base model plus IL-6, hs-CRP, and hs-cTnT	0.8384 (0.8040, 0.8729)				
Addition of NT-proBNP	0.8816 (0.8546, 0.9085)	0.081 (0.043, 0.123)	20.8 (10.4, 32.6)	0.664 (0.492, 0.828)	0.191 (0.105, 0.287)
P	<0.001	<0.001		<0.001	<0.001
Base model plus NT-proBNP	0.8800 (0.8529, 0.9072)				
Addition of IL-6, hs-CRP, and hs-cTnT	0.8816 (0.8546, 0.9085)	0.029 (0.010, 0.049)	6.57 (2.21, 11.2)	0.304 (0.117, 0.497)	0.010 (−0.040, 0.059)
P	0.65	0.002		0.002	0.56

Results were derived from the random subcohort (n = 2,989). Biomarkers were log transformed. *Base model included age, sex, randomized blood pressure–lowering intervention, randomized glucose-control intervention, duration of diabetes, current smoking, history of myocardial infarction, history of hospitalization for heart failure, BMI, systolic blood pressure, heart rate, current or previous atrial fibrillation, pathological Q-wave on ECG, left ventricular hypertrophy on ECG, aspirin or other antiplatelet agent use, β-blocker use, calcium channel blocker use, diuretic use, ACE inhibitor or angiotensin II receptor blocker use, total cholesterol, HDL cholesterol, triglyceride, statin or other lipid-lowering agent, HbA_{1c}, thiazolidinedione use, insulin use, urinary ACR, and eGFR. †Using cutoff points of 5% and 10% 5-year risk.

variables increased the C statistic from 0.81 to 0.85 (22). The current study, by using a comprehensive set of discrimination and reclassification metrics, adds to these prior studies by providing evidence that NT-proBNP considerably improved risk prediction for heart failure beyond that derived from a wide range of clinical risk factors. The addition of NT-proBNP to the model with clinical risk factors increased the C statistic and improved IDI, continuous NRI, and categorical NRI. These findings suggest that assessment of NT-proBNP will help to identify those at high risk who should go on to further investigation, such as an echocardiogram, and intervention.

Only one prior study has examined the association between CRP and heart failure in patients with diabetes, and no study has examined associations for IL-6 and hs-cTnT. In a subgroup analysis from the Strong Heart Study, elevated CRP levels were associated with incident heart failure in American Indians with diabetes (23). Our findings are consistent and extend to patients with diabetes from a range of countries across Australasia, Europe, and North America. In addition, our study adds new information on the relationship between the risk of heart failure and IL-6 and hs-cTnT levels, with findings showing an elevated risk of heart failure with increasing levels in these markers but no improvements in prediction metrics when added to a model with traditional clinical risk factors.

Only the addition of NT-proBNP to the model with clinical risk factors and the other three biomarkers strongly improved prognostic ability. However, the addition of a combination of IL-6, hs-CRP, and hs-cTnT to the model with clinical risk factors and NT-proBNP had no such benefit. This suggests that NT-proBNP adds to the predictive capacity for the incidence of heart failure and could be added to the routine assessment of the risk.

Recently, the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPAREG-REG OUTCOME) trial reported that patients with type 2 diabetes who received empagliflozin, an inhibitor of sodium–glucose cotransporter 2, had a significantly lower risk of hospitalization for heart failure than those in the placebo group (24). This association may be partly driven by osmotic diuresis and changes in plasma volume and sodium excretion with modulation of the cardiorenal axis mediated by empagliflozin (25,26). NT-proBNP is a cardiac hormone secreted by cardiac myocytes in response to ventricular wall stresses secondary to volume and pressure overload (27). Thus, risk prediction for heart failure using NT-proBNP could more accurately identify those patients who may benefit most from this kind of drug. Future interventional studies are required to ascertain the utility of this possible strategy.

The strengths of the current study include its large sample size, international recruitment in a well-characterized trial population, which was monitored closely and treated uniformly, completeness of follow-up, and adjustment for a variety of risk factors. In addition, this is the first study to examine the additional predictive ability of biomarkers beyond conventional risk factors, using a comprehensive range of prediction statistics, in patients with type 2 diabetes.

Some limitations of our study should be discussed. First, a single measurement of levels of biomarkers may not accurately represent the true status of the participants. However, this would bias our results toward the null hypothesis of no association. The true association may therefore be stronger than that observed in the current study. Second, the participants in this study were those eligible for the clinical trial. Therefore, applicability of the present findings to the general populations of patients with diabetes may not be justified, although the characteristics of the ADVANCE cohort of baseline were similar to those reported by a number of community-based epidemiological studies (28). Finally, there may be other possible confounders besides those used in the current study, leading to bias by residual confounding.

In conclusion, we found that IL-6, hs-CRP, hs-cTnT, and NT-proBNP were independent predictors of the incidence of heart failure in patients with type 2 diabetes. However, only the addition of NT-proBNP materially improved the predictive performance for heart failure beyond that from conventional clinical risk factors. Further studies are needed to validate our findings.

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References

1. Yancy CW, Jessup M, Bozkurt B, et al.; Writing Committee Members; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013;128:e240–e327

2. Shah AD, Langenberg C, Rapsomaniki E, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1·9 million people. Lancet Diabetes Endocrinol 2015;3:105–113

3. Pocock SJ, Wang D, Pfeffer MA, et al. Predictors of mortality and morbidity in patients with chronic heart failure. Eur Heart J 2006;27:65–75

4. McMurray JJ, Gerstein HC, Holman RR, Pfeffer MA. Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored. Lancet Diabetes Endocrinol 2014;2:843–851

5. Kaptoge S, Di Angelantonio E, Lowe G, et al.; Emerging Risk Factors Collaboration. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 2010;375:132–140

6. Danesh J, Kaptoge S, Mann AG, et al. Long-term interleukin-6 levels and subsequent risk of coronary heart disease: two new prospective studies and a systematic review. PLoS Med 2008;5:e78

7. Wannamethee SG, Welsh P, Lowe GD, et al. N-terminal pro-brain natriuretic peptide is a more useful predictor of cardiovascular disease risk than C-reactive protein in older men with and without pre-existing cardiovascular disease. J Am Coll Cardiol 2011;58:56–64
8. 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
9. Wang TJ, Wollert KC, Larson MG, et al. Prognostic utility of novel biomarkers of cardiovascular stress: the Framingham Heart Study. Circulation 2012;126:1596–1604
10. ADVANCE Management Committee. Study rationale and design of ADVANCE: action in diabetes and vascular disease–preterax and Diamicron MR controlled evaluation. Diabetologia 2001;44: 1118–1120
11. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007; 370:829–840
12. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572
13. Levey AS, Stevens LA, Schmid CH, et al.; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–612
14. Woodward M. *Epidemiology: Study Design and Data Analysis*. Boca Raton, Chapman & Hall/CRC, 2014
15. Lowe G, Woodward M, Hillis G, et al. Circulating inflammatory markers and the risk of vascular complications and mortality in people with type 2 diabetes and cardiovascular disease or risk factors: the ADVANCE study. Diabetes 2014;63: 1115–1123
16. Hillis GS, Welsh P, Chalmers J, et al. The relative and combined ability of high-sensitivity cardiac troponin T and N-terminal pro-B-type natriuretic peptide to predict cardiovascular events and death in patients with type 2 diabetes. Diabetes Care 2014;37:295–303
17. Welsh P, Woodward M, Hillis GS, et al. Do cardiac biomarkers NT-proBNP and hsTnT predict microvascular events in patients with type 2 diabetes? Results from the ADVANCE trial. Diabetes Care 2014;37:2202–2210
18. Newson R. Comparing the predictive power of survival models using Harrell's C or Somers' D. Stata J 2010;10:339–358
19. Echouffo-Tcheugui JB, Greene SJ, Papadimitriou L, et al. Population risk prediction models for incident heart failure: a systematic review. Circ Heart Fail 2015;8:438–447
20. Rahimi K, Bennett D, Conrad N, et al. Risk prediction in patients with heart failure: a systematic review and analysis. JACC Heart Fail 2014;2: 440–446
21. Gaede P, Hildebrandt P, Hess G, Parving HH, Pedersen O. Plasma N-terminal pro-brain natriuretic peptide as a major risk marker for cardiovascular disease in patients with type 2 diabetes and microalbuminuria. Diabetologia 2005;48: 156–163
22. Scirica BM, Braunwald E, Raz I, et al.; SAVOR-TIMI 53 Steering Committee and Investigators. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation 2014;130:1579–1588
23. Barac A, Wang H, Shara NM, et al. Markers of inflammation, metabolic risk factors, and incident heart failure in American Indians: the Strong Heart Study. J Clin Hypertens (Greenwich) 2012;14:13–19
24. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128
25. Fitchett D, Zinman B, Wanner C, et al.; EMPA-REG OUTCOME® trial investigators. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. Eur Heart J 2016;37:1526–1534
26. Sattar N, McLaren J, Kristensen SL, Preiss D, McMurray JJ. SGLT2 inhibition and cardiovascular events: why did EMPA-REG outcomes surprise and what were the likely mechanisms? Diabetologia 2016;59:1333–1339
27. Ghashghaei R, Arbit B, Maisel AS. Current and novel biomarkers in heart failure: bench to bedside. Curr Opin Cardiol 2016;31:191–195
28. Chalmers J, Arima H. Importance of blood pressure lowering in type 2 diabetes: focus on ADVANCE. J Cardiovasc Pharmacol 2010;55:340–347