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

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OBJECTIVE

Current methods of risk stratification in patients with type 2 diabetes are suboptimal. The current study assesses the ability of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT) to improve the prediction of cardiovascular events and death in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

A nested case-cohort study was performed in 3,862 patients who participated in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial.

RESULTS

Seven hundred nine (18%) patients experienced a major cardiovascular event (composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) and 706 (18%) died during a median of 5 years of follow-up. In Cox regression models, adjusting for all established risk predictors, the hazard ratio for cardiovascular events for NT-proBNP was 1.95 per 1 SD increase (95% CI 1.72, 2.20) and the hazard ratio for hs-cTnT was 1.50 per 1 SD increase (95% CI 1.36, 1.65). The hazard ratios for death were 1.97 (95% CI 1.73, 2.24) and 1.52 (95% CI 1.37, 1.67), respectively. The addition of either marker improved 5-year risk classification for cardiovascular events (net reclassification index in continuous model, 39% for NT-proBNP and 46% for hs-cTnT). Likewise, both markers greatly improved the accuracy with which the 5-year risk of death was predicted. The combination of both markers provided optimal risk discrimination.

CONCLUSIONS

NT-proBNP and hs-cTnT appear to greatly improve the accuracy with which the risk of cardiovascular events or death can be estimated in patients with type 2 diabetes.

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The incidence of cardiovascular events is increased twofold to threefold in patients with type 2 diabetes (1–3), such that approximately two in every three patients with the condition will die due to cardiovascular disease (4). Despite this greatly increased likelihood of vascular complications, there remains a spectrum of risk (5). In addition, while intensive multifactorial interventions can reduce the complications of diabetes, the costs of such strategies can exceed the resources of the most affluent health care systems. There is, therefore, a need to identify those with type 2 diabetes who are at highest risk. Existing methods of risk prediction are imperfect, and classical cardiovascular risk factors are relatively poor predictors in patients with diabetes (6,7). Consequently, additional methods are required to improve risk stratification among those with type 2 diabetes.

The B-type natriuretic peptides BNP is used as an abbreviation for the active peptide—it is confusing to use the same abbreviation for the whole grouping of B-type natriuretic peptides are released in response to myocardial stretch (8). B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP; the split inactive metabolite) enhance risk prediction in several settings, including patients with stable coronary heart disease (9,10) and community populations (11–13). The prognostic information provided appears to be incremental to that derived from established risk factors. There are, however, relatively few data assessing the ability of BNP and NT-proBNP to predict cardiovascular outcomes in patients with type 2 diabetes (14,15) and no prior studies that assess the ability of these markers to reclassify the risk of individual patients.

Cardiac troponin I and cardiac troponin T are specific markers of myocardial cell damage. Elevated levels are integral to the diagnosis of acute myocardial infarction but are also found in other acute medical conditions (16,17). Almost universally, the degree of elevation is strongly associated with a worse cardiovascular outcome (17). Recently, highly sensitive assays, which can measure levels of troponin previously undetectable using "conventional" assays, have been developed (18,19). Using such sensitive assays, detectable levels of cardiac troponin T have been reported in patients with stable coronary heart disease (20) and in a sizeable proportion of the general population, including those with no known cardiovascular disease (21,22). However, the ability of these sensitive assays to enhance risk prediction in patients with type 2 diabetes remains unclear.

We hypothesized that both NT-proBNP and high-sensitivity cardiac troponin T (hs-cTnT) would predict major cardiovascular events and all-cause death in patients with type 2 diabetes and that these markers would provide prognostic information that was incremental to each other and to other widely accepted predictors of outcome.

RESEARCH DESIGN AND METHODS

We performed a nested case-cohort study assessing the association between circulating levels of NT-proBNP and hs-cTnT and all-cause mortality and major cardiovascular events (a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in patients with type 2 diabetes who participated in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study (ClinicalTrials.gov number NCT00145925). The ADVANCE study recruited 11,140 patients with type 2 diabetes from 215 centers in 20 countries between June 2001 and March 2003 (23,24). The study made two randomized comparisons: a double-blind assessment of the efficacy of perindopril/indapamide (2/0.625 mg for 3 months increasing, if tolerated, to 4/1.25 mg) versus placebo and an open-label evaluation of an intensive glucose-lowering regimen using modified-release gliclazide, with a target glycated hemoglobin (HbA_{1c}) of $\leq$6.5% (48 mmol/mol), versus standard, guideline-based glycemic control. The study was approved by the ethics committee for each participating center, and all participants provided written informed consent. Participants were $\geq$55 years of age and had been diagnosed with type 2 diabetes after the age of 30 years. In addition, they were required to have a history of cardiovascular disease or one or more additional cardiovascular risk factors (25). Detailed study methods (25) and the main results (23,24) of the ADVANCE study have been previously reported.

Baseline data included demographic and clinical information. Weight, height, urinary albumin/creatinine ratio, serum creatinine, fasting lipid levels, and HbA_{1c} were also measured at baseline. 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 base population of 7,376. A random subcohort of 3,500 was selected from this base population for the case-cohort study, plus all additional individuals who had a cardiovascular event or died during follow-up (n = 697). All outcomes were validated by an independent adjudication committee.

NT-proBNP and hs-cTnT were measured using electrochemiluminescence immunoassays performed on a Roche Elecsys 2010 automated platform (Roche Diagnostics, Burgess Hill, U.K.). The NT-proBNP assay has an effective measuring range of 5–30,000 pg/mL (26). The hs-cTnT assay has a lower detection limit of 3 ng/L, and in a healthy population, the 99th percentile level is $\geq$14 ng/L (19). Assays were performed using the manufacturer's calibrators and quality controls. NT-proBNP and hs-cTnT had assay coefficients of variation of 6.5 and 4.5%, respectively, for the low control and 3.8 and 9.1%, respectively, for the high control.

Statistical Analyses

Categorical data are presented as number (percentage) and continuous data as mean (SD), where symmetrically distributed, or median (interquartile range), where skewed. Hazard ratios for a 1 SD increase in each of NT-proBNP and hs-cTnT, after log transformation to

remove effects of outliers, on cardiovascular events and death were obtained from weighted Cox regression models using the STSELPRE procedure for case-cohort analyses (StataCorp Ltd, College Station, TX). Nonlinearity was tested by comparing the deviances of linear and categorical models and by the inclusion of polynomial components (quadratic and cubic terms). Other analyses were performed using SAS v9.2 (SAS Institute, Cary, NC). All *P* values reported are two-sided, with the 5% threshold used to determine significance.

Three models, with different potential confounding variables, were fitted for each cardiac biomarker/outcome combination: model 1 with age, sex, and randomized treatment; model 2 with, additionally, a prior macrovascular complication of diabetes (myocardial infarction, stroke, hospital admission for a transient ischemic attack or for unstable angina, coronary or peripheral revascularization, or amputation secondary to peripheral vascular disease), duration of diabetes, current smoking, systolic blood pressure, BMI, albumin/creatinine ratio, estimated glomerular filtration rate, HbA_{1c}, plasma glucose, total and HDL cholesterol, triglycerides, aspirin or other antiplatelet agent, statin or other lipid-lowering agent, β-blocker, ACE inhibitor or angiotensin receptor blocker, history of heart failure, participation in moderate and/or vigorous exercise for >15 min at least once weekly, and high-sensitivity C-reactive protein; and model 3 with, additionally to model 2, the other biomarker (i.e., NT-proBNP or hs-cTnT). C-statistics for 5-year risk, accounting for censoring (27), were determined for the baseline clinical model (model 2 described above) and for this model plus each biomarker individually and in combination. In addition, the ability to discriminate and reclassify 5-year risk, using the integrated discrimination index (IDI) and the net reclassification improvement (NRI), were assessed by methods suitable for survival data, using bootstrapping (28,29). NRI was derived using a continuous model for changes in risk classification and from a categorical (or threshold) model based on 10, 10–15, and >15% risk.

RESULTS

The case-cohort study population comprised 4,197 patients. Blood samples for 335 (8%) participants were missing or unsuitable for analysis. Of the remaining 3,862 subjects, 709 (18%) experienced a major cardiovascular event during a median of 5 years of follow-up (382 cardiovascular deaths, 238 nonfatal myocardial infarctions, and 194 nonfatal strokes) and 706 (18%) died. The mean age of the study cohort was 67 years, and 61% were male (Table 1).

The associations between categories of NT-proBNP and hs-cTnT and cardiovascular risk factors and known disease at baseline are shown in Supplementary Tables 1 and 2. Levels of NT-proBNP and hs-cTnT were moderately correlated (Spearman coefficient 0.40; $P < 0.001$). Sixty-two percent of ADVANCE study participants in the random subcohort had detectable (≥3 ng/L) levels of hs-cTnT, including 58% of patients with no prior history of macrovascular disease.

There was a log-linear association between both biomarkers and both outcomes ($P < 0.001$), with no evidence of nonlinearity ($P > 0.05$ for both markers and outcomes). After adjustment for age, sex, and randomized treatment in the ADVANCE trial, both NT-proBNP and hs-cTnT were strong predictors of cardiovascular events and death (Table 2). These associations were only mildly attenuated after further adjustment for key clinical risk factors and other potential confounders. Even after additional adjustment for the other biomarker, each remained a strong predictor of both outcomes (Table 2). These results were similar regardless of the age of the patient (≤ or >67 years, the median for the cohort), their sex, or whether they did or did not have known macrovascular disease (Fig. 1).

Both NT-proBNP and hs-cTnT significantly increased the C-statistic for the prediction of cardiovascular events and for death when compared with the baseline clinical model (Table 3). In addition, a range of prediction metrics confirm that, even when all these clinical factors were taken into account, both markers greatly improved the ability to predict a cardiovascular event or death (Table 3).

The increase in the C-statistic and improvements in the reclassification of risk were similar regardless of whether NT-proBNP or hs-cTnT was added to the baseline clinical model, while the combination of both provided better prognostic information (Table 3). The addition of NT-proBNP significantly improved the C-statistic, IDI, and NRI of a model that included all recognized clinical predictors of outcome plus hs-cTnT (Table 4). However, when hs-cTnT was added to a similar model plus NT-proBNP, the improvements were smaller and not uniformly significant (Table 4). In comparison, the addition of total cholesterol resulted in minimal increases in the C-statistic or reclassification statistics (Supplementary Table 3), while the addition of high-sensitivity C-reactive protein led to only modest improvements in the reclassification of the risk of death (Supplementary Table 4).

CONCLUSIONS

This study demonstrates that, in patients with type 2 diabetes, levels of both NT-proBNP and hs-cTnT are strongly associated with an increased risk of cardiovascular events and death over the subsequent 5 years. These associations persist after extensive adjustment for established and emerging clinical predictors of outcome in type 2 diabetes and for several other potential confounding factors. Likewise, a comprehensive range of prediction metrics suggest that both NT-proBNP and hs-cTnT considerably improve the prediction of future cardiovascular events and death in patients with type 2 diabetes, even after accounting for conventional clinical risk factors. By contrast, levels of total cholesterol or high-sensitivity C-reactive protein provide minimal additional prognostic information. Combining both NT-proBNP and hs-cTnT in a model with clinical variables provides maximal prognostic information, although much of the discriminative information is contributed by NT-proBNP alone.

Table 1—Baseline characteristics classified by outcome status

	Cardiovascular events*				Death				Overall	
	Yes *n* = 709		No *n* = 3,153		Yes *n* = 706		No *n* = 3,156		*n* = 3,862	
Males, *n* (%)	491	69.3%	1,865	59.2%	492	69.7%	1,864	59.1%	2,356	61.0%
Current smokers, *n* (%)	105	14.8%	476	15.1%	119	16.9%	462	14.6%	581	15.0%
History of macrovascular event, *n* (%)	347	48.9%	998	31.6%	312	44.2%	1,033	32.7%	1,345	34.8%
Age (years), mean (SD)	69.01	6.55	66.41	6.53	69.96	6.65	66.20	6.41	66.89	6.61
Duration of diabetes (years), mean (SD)	9.00	6.99	7.60	6.25	9.04	7.48	7.60	6.12	7.86	6.41
BMI (kg/m^2), mean (SD)	29.65	5.00	30.15	5.32	29.58	5.13	30.17	5.29	30.06	5.26
History of heart failure, *n* (%)	63	8.9%	118	3.7%	68	9.6%	113	3.6%	181	4.7%
Participation in moderate or vigorous activity†, *n* (%)	292	41.2%	1,579	50.1%	298	42.2%	1,573	49.8%	1,871	48.4%
Aspirin or other antiplatelet agent, *n* (%)	416	58.7%	1,495	47.4%	390	55.2%	1,521	48.2%	1,911	49.5%
Statin or other lipid-lowering agent, *n* (%)	304	42.9%	1,411	44.8%	288	40.8%	1,427	45.2%	1,715	44.4%
β-Blocker, *n* (%)	228	32.2%	946	30.0%	216	30.6%	958	30.4%	1,174	30.4%
ACE inhibitor or angiotensin receptor blocker, *n* (%)	458	64.6%	1,821	57.8%	443	62.8%	1,836	58.2%	2,279	59.0%
Blood pressure (mmHg), mean (SD)										
Systolic	150.94	22.99	146.80	21.29	149.84	23.63	147.05	21.18	147.56	21.67
Diastolic	81.61	11.43	81.61	10.75	80.77	11.81	81.80	10.65	81.61	10.88
Cholesterol (mmol/L), mean (SD)										
Total	5.10	1.18	5.14	1.17	5.05	1.14	5.15	1.18	5.14	1.17
HDL	1.17	0.31	1.24	0.33	1.18	0.31	1.23	0.34	1.22	0.33
Triglycerides (mmol/L), median (Q1, Q3)	1.61	(1.20, 2.30)	1.70	(1.20, 2.36)	1.60	(1.20, 2.30)	1.7	(1.20, 2.37)	1.70	(1.20, 2.35)
HbA_{1c} (%), mean (SD)	7.60	1.58	7.37	1.39	7.60	1.56	7.37	1.40	7.41	1.43
HbA_{1c} (mmol/mol), mean (SD)	60	17.3	57	15.2	60	17.1	57	15.3	57	15.6
Urinary ACR (μ/mg), median (Q1, Q3)	21.22	(8.84, 70.72)	13.26	(6.19, 37.13)	21.22	(8.57, 65.42)	13.61	(6.19, 37.13)	15.03	(6.54, 41.46)
Glucose (mmol/L), mean (SD)	8.59	2.83	8.46	2.70	8.56	2.93	8.46	2.68	8.48	2.72
eGFR, mean (SD)	67.45	17.83	72.39	16.50	66.43	17.79	72.60	16.44	71.48	16.86
hs-CRP (mg/L), median (Q1, Q3)	2.01	(0.93, 4.35)	1.77	(0.86, 4.00)	2.05	(1.01, 4.67)	1.78	(0.85, 3.92)	1.81	(0.88, 4.06)
hs-cTnT (ng/L), median (Q1, Q3)	9.0	(4.0, 18.0)	5.0	(1.5, 10.0)	11.0	(4.0, 18.0)	5.0	(1.5, 9.0)	5.0	(1.5, 11.0)
NT-proBNP (pg/mL), median (Q1, Q3)	204.0	(75.0, 499.0)	76.0	(31.0, 175.0)	205.0	(84.0, 535.0)	75.0	(30.0, 175.0)	90.0	(35.0, 223.0)

ACR, albumin/creatinine ratio; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; Q, quartile. *Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. †Participation in moderate and/or vigorous exercise for >15 min at least once weekly.

Table 2—Hazard ratios (95% CIs) for a 1 SD increment in cardiac biomarkers

	Cardiovascular events*	Death
NT-proBNP (log scale) (1 SD = 1.58)		
Model 1	2.23 (2.00, 2.48)	2.16 (1.93, 2.41)
Model 2	1.95 (1.72, 2.20)	1.97 (1.73, 2.24)
Model 3	1.77 (1.56, 2.01)	1.78 (1.57, 2.03)
hs-cTnT (log scale) (1 SD = 1.05)		
Model 1	1.69 (1.55, 1.84)	1.70 (1.55, 1.86)
Model 2	1.50 (1.36, 1.65)	1.52 (1.37, 1.67)
Model 3	1.29 (1.17, 1.42)	1.30 (1.18, 1.44)

Model 1 is adjusted for age, sex, and randomized treatment allocations. Model 2 is additionally adjusted for duration of diabetes, current smoking, prior macrovascular complication of diabetes (see text for details), systolic blood pressure, BMI, albumin/creatinine ratio, estimated glomerular filtration rate, HbA_{1c}, glucose, total and HDL cholesterol, triglycerides, high-sensitivity C-reactive protein, aspirin or other antiplatelet agent, statin or other lipid-lowering agent, β-blocker, ACE inhibitor or angiotensin receptor blocker, history of heart failure, and participation in moderate and/or vigorous exercise for >15 min at least once weekly. Model 3 is additionally adjusted for the other biomarker. $P < 0.001$ for all models in cardiovascular events and death. *Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

Prior Studies

The prognostic utility of NT-proBNP and BNP has been reported in patients with an acute coronary syndrome and those with heart failure. These markers also predict outcome in other settings, including community populations (11,13). In general populations and patients with stable cardiovascular disease, the improvement in risk discrimination, as assessed by the increase in the C-statistic, has generally been in keeping with those observed in the current study (approximately 0.05) (30). Two recent studies, both using data from relatively homogeneous samples of middle-aged men, have reported the ability of NT-proBNP to more correctly reclassify cardiovascular events (12,31). In the West of Scotland Coronary Prevention Study (WOSCOPS), the addition of NT-proBNP to traditional risk factors improved the continuous NRI by 19.8% (31). In the British Regional Heart Study (BRHS), the categorical NRI was improved by 8.8% in patients without known cardiovascular disease and 8.2% in those with preexisting cardiovascular disease, after the addition of NT-proBNP to clinical models (12). While the risk models and reclassification thresholds considered in ADVANCE were (by necessity) different to those used in WOSCOPS or BRHS, it appears that NT-proBNP levels are at least as good in improving risk classification for cardiovascular events in individuals with type 2 diabetes as in the general population, and most likely better.

In patients with diabetes, higher BNP levels have been associated with abnormal left ventricular systolic and diastolic function and silent ischemia (32,33). Both BNP and NT-proBNP have also been associated with higher cardiovascular and all-cause mortality in patients with type 2 diabetes (14,15). Our study extends these findings, confirming the powerful prognostic role of NT-proBNP in a larger cohort with much more comprehensive adjustment for potential confounding factors, including both high-sensitivity C reactive protein and hs-cTnT. More important, we have confirmed, to our knowledge for the first time, that levels of NT-pro-BNP can considerably improve risk discrimination in patients with type 2 diabetes, suggesting that they may be of clinical value in this role.

Low levels of hs-cTnT, well below the threshold where they could be detected using a conventional assay, are commonly found in patients with stable coronary heart disease and/or heart failure and, in both settings, are strong predictors of adverse outcomes (20,34,35). Even in community-based middle-aged and elderly cohorts, the prevalence of detectable hs-cTnT is significant (21,22,36). For example, in randomly selected inhabitants of Dallas County, aged between 30 and 65 years, 25% had hs-cTnT levels ≥3 ng/L and 2% had levels ≥14 ng/L (21). Commensurate with these reports, we found that 62% of our random subcohort of participants in ADVANCE had detectable (≥3 ng/L) levels of hs-cTnT.

Only one prior study (37) has previously assessed the prognostic utility of hs-cTnT in patients with diabetes. In 512 women with diabetes and a mean age of 56 years, after adjustment for a range of clinical factors plus high-sensitivity C-reactive protein and NT-proBNP, the presence of detectable hs-cTnT was associated with a 76% increase in the hazard of the composite end point of cardiovascular death, myocardial infarction, or stroke (37). The confidence interval for the increased hazard was, however, wide (ranging from 0 to 308%), and the limited number of events preclude any more detailed assessment of the relationship between hs-cTnT elevation and outcome (37). Likewise, the investigators were unable to assess the ability of hs-cTnT to reclassify risk. The ADVANCE data extend these findings; confirming that hs-cTnT is a strong and independent predictor of major cardiovascular events and death in both men and women with type 2 diabetes and that, like NT-proBNP, it can be used in combination with clinical factors to more accurately discriminate the risk of an individual.

Clinical Implications of the Current Findings

Patients with type 2 diabetes are at considerable risk of vascular complications and have a high prevalence of, often asymptomatic, cardiovascular disease. Nevertheless, the risk of any individual may vary considerably, and current methods to determine this have limitations. Patients with type 2 diabetes are, therefore, a population where simple screening tests that could better detect those at highest risk would be of particular value. Our data suggest that levels of NT-proBNP and hs-cTnT may be useful adjuncts to clinical assessment and that both provide much more prognostic information than total cholesterol or high-sensitivity C-reactive protein levels in this cohort. In addition, they have a complimentary prognostic

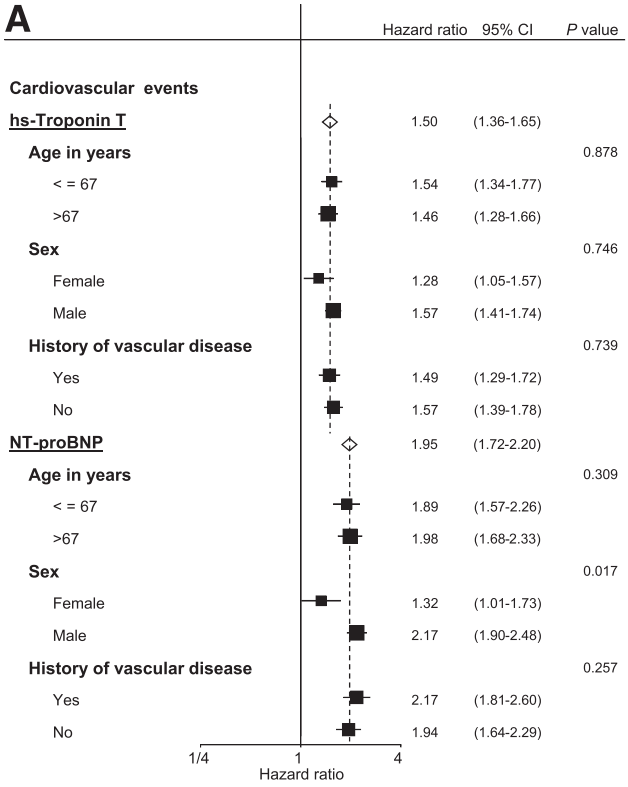

Figure 1—The predictive value of hs-cTnT and NT-proBNP for (*A*) cardiovascular events and (*B*) death, stratified by age (> or ≤67 years), sex, and a prior history of vascular disease. *P* value for interaction.

role, such that the combination of both markers, along with clinical variables, maximizes their predictive utility. It appears, however, that levels of NT-proBNP better capture the risk of cardiovascular events and death than levels of hs-cTnT.

Accurate risk stratification allows treatments to be targeted to individuals who may derive particular benefit from interventions such as more intensive blood pressure lowering or statin therapy. Biomarkers might also identify a subgroup of patients who have the most to gain from antiplatelet therapy. These potential uses remain, however, untested.

Levels of hs-cTnT and NT-proBNP might also identify patients with type 2 diabetes who may benefit from further investigation. Both of these proteins are nonspecific markers of cardiac disease. They may be increased due to systolic and/or diastolic dysfunction, left ventricular hypertrophy, valvular heart disease, ischemia, or a combination of these factors (38). The ability of both hs-cTnT and NT-proBNP to integrate the effects of multiple pathogenic pathways on the myocardium underpins their ability to predict "global" cardiovascular risk. It means, however, that an elevated level of either or both does not explain the underlying cause(s). A strategy that selects patients with type 2 diabetes who are at elevated risk, based on these markers, for further investigation such as echocardiography and stress testing is attractive but once again untested. Recent data (39) do, however, support this approach. In a cohort of 300 randomly selected members of the community, Nadir et al. (39) explored the ability of cardiovascular biomarkers to identify individuals who had undiagnosed cardiac disease. They confirmed that a combination of BNP and hs-cTnT provided the optimal screening tests to identify patients for further investigation, though BNP alone was almost as useful (39).

Strengths and Limitations

The current study describes a cohort derived from a large population with diverse ethnic backgrounds, which was well characterized and followed up

Table 3—Reclassification and discrimination statistics (95% CIs) for 5-year risk

				NRI	
	C-statistic	IDI	Relative IDI (%)	Continuous	Categorical
Cardiovascular events*					
Base model†	0.704 (0.673, 0.734)				
Base model plus NT-proBNP	0.744 (0.715, 0.773) $P < 0.001$‡	0.061 (0.048, 0.074) $P < 0.001$	71.2 (55.4, 86.9)	0.386 (0.273, 0.508) $P < 0.001$	0.112 (0.047, 0.182) $P < 0.001$
Base model plus hs-cTnT	0.728 (0.698, 0.757) $P = 0.001$‡	0.032 (0.024, 0.041) $P < 0.001$	37.9 (27.6, 48.6)	0.465 (0.348, 0.584) $P < 0.001$	0.130 (0.072, 0.187) $P < 0.001$
Base model plus NT-proBNP and hs-cTnT	0.751 (0.722, 0.779) $P < 0.001$‡	0.071 (0.058, 0.086) $P < 0.001$	83.4 (65.8, 100.9)	0.411 (0.297, 0.527) $P < 0.001$	0.169 (0.102, 0.236) $P < 0.001$
Death					
Base model†	0.713 (0.682, 0.744)				
Base model plus NT-proBNP	0.757 (0.729, 0.785) $P < 0.001$‡	0.062 (0.050, 0.076) $P < 0.001$	70.0 (55.0, 86.0)	0.412 (0.304, 0.525) $P < 0.001$	0.117 (0.055, 0.179) $P = 0.006$
Base model plus hs-cTnT	0.734 (0.704, 0.764) $P = 0.004$‡	0.029 (0.022, 0.037) $P < 0.001$	32.6 (24.2, 41.1)	0.449 (0.330, 0.566) $P < 0.001$	0.080 (0.015, 0.142) $P = 0.018$
Base model plus NT-proBNP and hs-cTnT	0.762 (0.734, 0.790) $P < 0.001$‡	0.074 (0.060, 0.089) $P < 0.001$	82.9 (65.7, 101.4)	0.461 (0.345, 0.579) $P < 0.001$	0.126 (0.057, 0.196) $P < 0.001$

Both NT-proBNP and hs-cTnT were log transformed, and results were derived from the random subcohort ($n = 3,500$). NRI categories were <10, 10–15, and >15% 5-year risk. *Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. †Using model 2, described in Table 2. ‡Compared with base model.

closely. All end points were independently adjudicated according to predefined criteria. Nevertheless, it has the limitations inherent in any post hoc analysis. The study population comprises participants in a clinical trial who were eligible for this on the basis of having preexisting cardiovascular disease or at least one cardiovascular risk factor in addition to diabetes. The results of the current study need, therefore, to be validated in an unselected community cohort.

Although the large study population and case-cohort design ensures considerable statistical power and allows reliable correction for many potential confounding factors, other possible confounders may be present. Levels of hs-cTnT and NT-proBNP were measured only once, and the effects of serial changes in levels cannot be assessed. Likewise, we have no data on cardiac structure, function, or perfusion, so we cannot determine the mechanisms of the elevations observed.

In summary, our data suggest that, in patients with type 2 diabetes, levels of hs-cTnT and NT-proBNP greatly improve the accuracy with which the risk of cardiovascular events or death can be estimated and may be clinically useful in this role.

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Table 4—Reclassification and discrimination statistics (95% CIs) for 5-year risk after addition of NT-proBNP or hs-cTnT to a model containing the other marker

				NRI	
	C-statistic	IDI	Relative IDI (%)	Continuous	Categorical
Cardiovascular events*					
Addition of NT-proBNP to baseline clinical model† plus hs-cTnT	0.751 (0.722, 0.779) $P = 0.001$ vs. base model plus hs-cTnT‡	0.039 (0.028, 0.050) $P < 0.001$	32.9 (24.1, 42.4)	0.334 (0.223, 0.445) $P < 0.001$	0.077 (0.024, 0.133) $P = 0.01$
Addition of hs-cTnT to baseline clinical model† plus NT-proBNP	0.751 (0.722, 0.779) $P = 0.061$ vs. base model plus NT-proBNP‡	0.010 (0.005, 0.016) $P < 0.001$	7.1 (3.3, 11.1)	0.308 (0.188, 0.432) $P < 0.001$	0.066 (0.021, 0.111) $P = 0.004$
Death					
Addition of NT-proBNP to baseline clinical model† plus hs-cTnT	0.762 (0.734, 0.790) $P < 0.001$ vs. base model plus hs-cTnT‡	0.045 (0.034, 0.057) $P < 0.001$	38.0 (28.0, 48.6)	0.332 (0.215, 0.442) $P < 0.001$	0.055 (−0.004, 0.112) $P = 0.06$
Addition of hs-cTnT to baseline clinical model† plus NT-proBNP	0.762 (0.734, 0.790) $P = 0.168$ vs. base model plus NT-proBNP‡	0.012 (0.006, 0.017) $P < 0.001$	7.6 (3.9, 11.6)	0.279 (0.157, 0.401) $P < 0.001$	0.016 (−0.030, 0.062) $P = 0.444$

*Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. †Using model 2, described in Table 2. ‡See Table 3.

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