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Prognostic Implications of Biomarker Assessments in Patients With Type 2 Diabetes at High Cardiovascular Risk
A Secondary Analysis of a Randomized Clinical Trial

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IMPORTANCE Cardiac biomarkers provide insights into pathophysiologic processes and offer an attractive strategy for the assessment of cardiovascular risk.

OBJECTIVE To assess the incremental prognostic value of biomarkers that reflect different pathophysiologic processes in patients with type 2 diabetes.

DESIGN, SETTING, AND PARTICIPANTS The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53 is a randomized, double-blind, placebo-controlled clinical trial that evaluated the safety of saxagliptin vs placebo in 16 492 outpatients with type 2 diabetes with overt cardiovascular disease (CVD) or multiple risk factors. In this secondary analysis, widely used biomarkers were evaluated to ascertain whether they would provide incremental prognostic value in the risk stratification. Median follow-up was 2.1 years (interquartile range, 1.8-2.3 years). The study was performed from May 10, 2010, to June 15, 2013.

INTERVENTIONS Randomization to saxagliptin vs placebo in addition to standard care.

MAIN OUTCOMES AND MEASURES Concentrations of high-sensitivity troponin T, N-terminal pro–B-type natriuretic peptide, and high-sensitivity C-reactive protein were analyzed continuously and by established cut points. Cardiovascular death, myocardial infarction, ischemic stroke, and hospitalization for heart failure (HF) were adjudicated by a blinded events committee.

RESULTS Of the 16 492 patients, 5455 (33.1%) were female and 11 037 (66.9%) were male. Mean (SD) age was 65.0 (8.5) years (range, 39-99 years). Baseline biomarkers were measured in 12 310 patients. Elevated levels of each biomarker were associated significantly with increased risk for all cardiovascular end points. When added to clinical variables, biomarkers significantly improved the discrimination and appropriate reclassification of risk. Elevated high-sensitivity troponin T was associated with an increased risk of cardiovascular death (adjusted hazard ratio [AHR], 3.07; 95% CI, 2.35-4.02; $P < .001$), myocardial infarction (AHR, 2.13; 95% CI, 1.69-2.67; $P < .001$), and hospitalization for HF (AHR, 3.85; 95% CI, 2.82-5.27; $P < .001$). Elevated N-terminal pro–B-type natriuretic peptide was also associated with an increased risk of cardiovascular death (AHR, 3.09; 95% CI, 2.46-3.89; $P < .001$), myocardial infarction (AHR, 1.95; 95% CI, 1.51-2.53; $P < .001$), and hospitalization for HF (AHR, 3.92; 95% CI, 3.11-4.92; $P < .001$). Elevated high-sensitivity C-reactive protein was more weakly associated with an increased risk of cardiovascular death (AHR, 1.49; 95% CI, 1.22-1.82; $P < .001$) and hospitalization for HF (AHR, 1.47; 95% CI, 1.20-1.81; $P < .001$). Consistent results were seen in patients with or without established CVD.

CONCLUSIONS AND RELEVANCE A substantial proportion of patients with stable type 2 diabetes with established CVD or multiple clinical risk factors have evidence of ongoing myocardial injury, hemodynamic stress, or systemic inflammation. Biomarker risk stratification thus challenges the traditional differentiation between primary and secondary prevention based simply on clinical history. Strategies to improve risk stratification in patients with type 2 diabetes, with or without CVD, should consider incorporation of biomarker data into standard risk algorithms.

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Supplemental content

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Type 2 diabetes accelerates atherogenesis, causes myocardial dysfunction, and significantly worsens outcomes in patients with and without established cardiovascular disease through a variety of mechanisms. As such, the presence of type 2 diabetes is commonly considered to be a risk factor for these adverse outcomes.[1-4] However, in patients with type 2 diabetes, assessing risk poses a particular challenge given the heterogeneity in the clinical and pathophysiologic characteristics in this condition and the overall higher rate of diabetes-related complications. This challenge is especially relevant when screening patients with type 2 diabetes without manifest cardiovascular disease, in whom the risk of ischemic complications varies widely based on age, duration of diabetes, and comorbidities. Because cardiac biomarkers provide insight into different pathophysiologic processes and improve risk stratification across the cardiovascular disease spectrum, we hypothesized that such biomarkers may aid in the risk stratification for the development of first or recurrent cardiovascular events in patients with type 2 diabetes.

The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)-Thrombolysis in Myocardial Infarction (TIMI) 53 trial evaluated the cardiovascular efficacy and safety of saxagliptin, a selective dipeptidyl peptidase 4 inhibitor, in patients with type 2 diabetes with overt cardiovascular disease or at risk for cardiovascular events.[5] During a median of 2.1 years of follow-up, saxagliptin reduced hemoglobin A_{1c} levels but did not alter the risk of the primary composite end point of cardiovascular death, myocardial infarction, or ischemic stroke or the secondary composite end point that added hospitalization for heart failure, unstable angina, and coronary revascularization to the primary end point, although there was a significant 27% increased relative risk of hospitalization for heart failure in patients randomized to receive saxagliptin.[6]

As part of a prespecified subgroup analysis, we evaluated biomarkers reflecting the pathophysiologic processes of myocardial injury with high-sensitivity troponin T (hsTnT), hemodynamic stress with N-terminal pro-B-type natriuretic peptide (NT-proBNP), and inflammation with high-sensitivity C-reactive protein (hsCRP) to ascertain whether these widely used biomarkers would provide incremental prognostic value in the risk stratification of patients with type 2 diabetes. We also wanted to determine whether there was any interaction among baseline levels of these 3 biomarkers and the effects of treatment with saxagliptin.

Key Points

Question Do cardiac biomarkers provide incremental prognostic value in patients with type 2 diabetes?

Findings In this secondary analysis of a randomized clinical trial of 12 310 patients with overt cardiovascular disease or multiple risk factors, elevated levels of high-sensitivity troponin T, N-terminal pro–B-type natriuretic peptide, and high-sensitivity C-reactive protein significantly improved the discrimination and appropriate reclassification of risk, in particular for high-sensitivity troponin T and N-terminal pro–B-type natriuretic peptide.

Meaning Biomarkers appropriately risk stratify patients with diabetes in terms of future cardiovascular events and challenge the traditional differentiation between primary and secondary prevention based simply on clinical history.

Methods

Study Design and Oversight

As previously described,[5] SAVOR-TIMI 53 was a multicenter, randomized, double-blind, placebo-controlled clinical trial that randomized 16 492 patients with type 2 diabetes, hemoglobin A_{1c} levels between 6.5% and less than 12.0% within 6 months of randomization (to convert to proportion of total hemoglobin, multiply by 0.01), and a history of established cardiovascular disease or multiple clinical risk factors for vascular disease (dyslipidemia, hypertension, or smoking) to receive saxagliptin or matching placebo. The full eligibility criteria and analysis plan have been reported previously.[5,7] Written informed consent was obtained from all patients. All participating centers obtained approval from their local institutional review board. Biomarker analyses were performed with the approval of the Partners Human Research Committee.

End Points

The clinical end points in this analysis include (1) the primary composite end point of the trial (cardiovascular death, myocardial infarction, or ischemic stroke), (2) each individual component, and (3) hospitalizations for heart failure, a component of an expanded, prespecified secondary end point. A clinical events committee, unaware of the study group assignments, adjudicated all components of the primary and secondary composite efficacy end points,[5,7] using definitions based on draft guidelines for the standardization of end points in cardiovascular trials proposed by the US Food and Drug Administration.[8]

Biomarker Determinations

Concentrations of hsTnT, NT-proBNP, and hsCRP were measured in samples obtained at randomization in patients who consented to participate in the biomarker assessment. Serum was isolated and stored frozen in aliquots at −20° to −80°C at the enrolling site until shipped to the Biomarker Research/TIMI Clinical Trials Laboratory, Boston, Massachusetts, where they were maintained at −80°C or colder. Serum NT-proBNP concentrations were measured at the first thaw using a sandwich immunoassay (proBNP II; Roche Diagnostics). The analytic range extends from 5 to 35 000 pg/mL (to convert to nanograms per liter, multiply by 1). The reported within-run coefficient of variation was 4.2% at a level of 44 pg/mL and 2.7% at a level of 33 606 pg/mL. The cut points for elevated levels were defined as 450 pg/mL or higher for those younger than 50 years, 900 pg/mL or higher for those aged 50 to 75 years, and 1800 pg/mL or higher for those older than 75 years.[9] Concentrations of hsTnT were measured with an electrochemiluminescent immunoassay assay (Roche Diagnostics). The lower limit of detection of the assay is 3 pg/mL (to convert to nanograms per liter, multiply by 1).[10] Levels greater than 15.0 pg/mL

for men and greater than 10 pg/mL for women were used as the diagnostic cut points, or upper reference limit (URL), representing the 99th percentile in healthy individuals with a coefficient of variation less than 10%.[11] Concentrations of hsCRP were measured with an enhanced immunoturbidimetric assay (Roche Diagnostics) with a lower level of detection of 0.15 mg/L and a functional sensitivity of 0.3 mg/L (to convert to nanomoles per liter, multiply by 9.524). The cut point for an elevated level was defined as greater than 3 mg/L based on guidelines for cardiovascular risk stratification.[12]

Statistical Analysis

Categorical variables were compared using the χ^2 test and continuous variables with a 2-tailed, paired *t* test or Wilcoxon rank sum test, as appropriate. Events rates are presented as 2-year Kaplan-Meier estimates. Biomarkers were analyzed as continuous variables, categorized as sex-specific quartiles, and based on the prespecified cut points mentioned above. Multivariable clinical models that evaluated the association between biomarkers and clinical outcomes were stratified by established cardiovascular disease vs multiple risk factors and adjusted for the following clinical variables: age (continuous), sex, systolic blood pressure (continuous), history of heart failure, duration of diabetes, prior myocardial infarction, hypertension, hyperlipidemia, smoking, estimated glomerular filtration rate (continuous), and treatment allocation (saxagliptin vs placebo).

Estimates of the C statistic for the clinical model created from previously listed variables were calculated based on the Harrell method[13] and then compared to the models after the addition of the different biomarkers. The discriminative value of the biomarkers was further examined with the method described by Pencina and colleagues[14,15] to determine the continuous (categoryless) net reclassification improvement (NRI) (the probability that patients are appropriately assigned to a higher or lower risk) and integrated discrimination improvement (IDI) (a method to quantify mean predicted probabilities of events and nonevents based on the addition of the new biomarkers to the model). The NRI values above 0.6 are considered strong, those around 0.4 as intermediate, and those less than 0.2 as weak.[15] Comparisons between saxagliptin and placebo were examined using an unadjusted Cox proportional hazards regression model stratified by estimated glomerular filtration category and baseline cardiovascular risk group with assigned treatment as a model term. Statistical analyses were performed with SAS statistical software, version 9.4 (SAS Institute Inc).

Results

Serum and plasma biomarkers were collected in 12 310 of the 16 492 SAVOR-TIMI 53 patients, 74.6% of the entire trial population, from May 10, 2010, to June 15, 2013, and the biomarkers for this study were analyzed from September 1 to October 31, 2013. Baseline characteristics of the patients with (n = 12 310) and without (n = 4182) biomarkers are presented in eTable 1 in the Supplement. Of the 16 492 patients, 5455 (33.1%) were female and 11 037 (66.9%) were male. Mean (SD) age was 65.0 (8.5) years (range, 39-99 years). The proportions of patients with established cardiovascular disease (9619 [78.1%]) and risk factors alone (2691 [21.9%]) in the biomarker assessment were similar to the overall trial. Patients in the biomarker assessment group were more likely to be white or Hispanic and weigh more than patients without baseline biomarkers.

Outcomes by Biomarkers Quartile

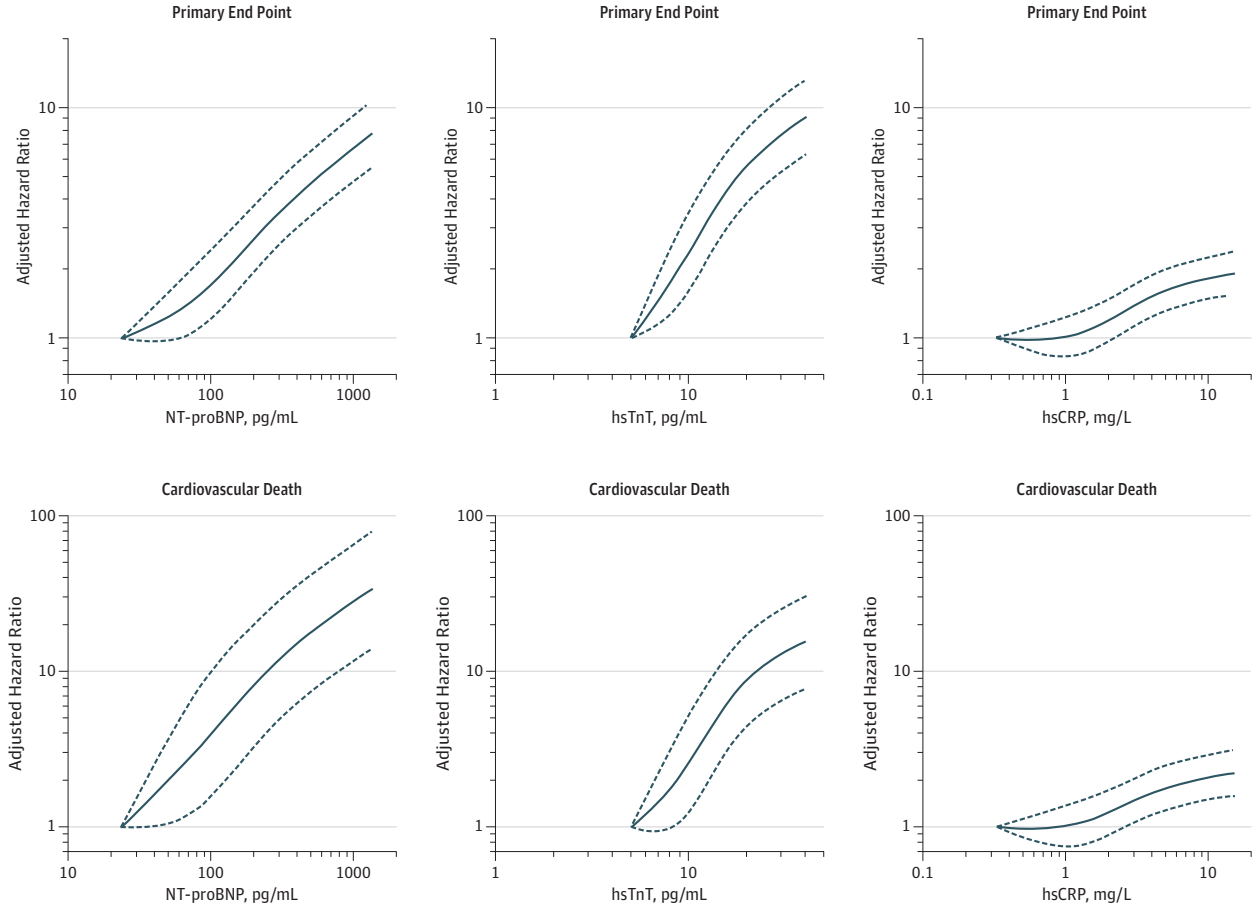
The median (interquartile ranges) of biomarkers were 12.0 pg/mL (8.1-18.4 pg/mL) for hsTnT, 141 pg/mL (64-332 pg/mL) for NT-proBNP, and 2.4 mg/L (1.1-5.0 mg/L) for hsCRP. In the overall population, there was a linear increase in the rates of the primary composite end point and the individual end points of cardiovascular death, myocardial infarction, ischemic stroke, and hospitalization for heart failure (**Figure 1** and **Table 1**). The association was most striking for hsTnT and NT-proBNP, with a weaker association with elevated levels of hsCRP. The association between biomarkers and outcomes was consistent in the 9619 patients with established cardiovascular disease and in the 2691 patients with multiple risk factors alone (eTable 2 in the Supplement).

Outcomes by Biomarker Cut Points

Nearly all patients (99.7%) had a detectable baseline level of hsTnT (≥3 pg/mL). Overall, 5239 patients (43.0%) had a level above the 99th percentile URL (>15 pg/mL for men and >10 pg/mL for women); this proportion was higher in patients with established cardiovascular disease (4394 [46.2%]) than in patients with cardiovascular risk factors only (845 [31.6%]) ($P < .001$). Overall, a level of hsTnT greater than 99th percentile URL was associated with an increased risk of the primary end point (12.3% vs 4.1%; adjusted hazard ratio [AHR], 2.19; 95% CI, 1.87-2.56; $P < .001$), cardiovascular death (5.9% vs 1.2%; AHR, 3.07; 95% CI, 2.35-4.02; $P < .001$), myocardial infarction (5.7% vs 1.9%; AHR, 2.13; 95% CI, 1.69-2.67; $P < .001$), ischemic stroke (2.6% vs 1.2%; AHR, 1.64; 95% CI, 1.21-2.22; $P = .001$), or hospitalization for heart failure (6.2% vs 0.8%; AHR, 3.85; 95% CI, 2.82-5.27; $P < .001$) (Table 1). Of note, in patients with clinical risk factors only, an elevated level of hsTnT identified individuals with a higher risk of the primary end point, cardiovascular death, myocardial infarction, and hospitalization for heart failure, but not ischemic stroke (**Figure 2** and eTable 2 in the Supplement). Conversely, in patients with clinical risk factors only and hsTnT levels in the less than the 99th percentile URL, the rate of each of these clinical end points was individually less than 0.5% per year. Patients with established cardiovascular disease but an hsTnT level in the less than 99th percentile URL had a risk lower than those patients with risk factors alone and elevated levels of hsTnT. A similar pattern of risk was seen when categorizing patients according to the presence or absence of a history of myocardial infarction (eFigure 1 in the Supplement).

A large proportion of patients also had biomarker levels above a priori cut points for NT-proBNP (≥450 pg/mL for those younger than 50 years, ≥900 pg/mL for those 50-75 years old, and ≥1800 pg/mL for those older than 75 years;

Figure 1. Risk of Primary End Point and Cardiovascular Death by N-terminal Pro–B-Type Natriuretic Peptide (NT-proBNP), High-Sensitivity Troponin T (hsTnT), and High-Sensitivity C-Reactive Protein (hsCRP)



Hazard ratios (solid lines) were adjusted for treatment arms, age (continuous), systolic blood pressure (continuous), sex, history of heart failure, duration of diabetes, prior myocardial infarction, history of hypertension, history of hyperlipidemia, smoking, estimated glomerular filtration rate (continuous), and established cardiovascular disease vs multiple risk factors. Dashed lines indicate 95% CI.

964 patients [7.8%]) and hsCRP (>3 mg/L; 5086 [41.3%]). A level above these established cut points for each biomarker was significantly associated with cardiovascular death, myocardial infarction, ischemic stroke, and hospitalization for heart failure (Table 1). The pattern of risk was similar when biomarkers were analyzed as quartiles (eFigure 2 and eTable 3 in the Supplement).

The addition of the biomarkers, as a continuous variable or by cut points, significantly improved metrics of discrimination (C statistic and IDI) and net reclassification (NRI) when compared with the multivariable clinical model alone (see the Methods section) (**Table 2** and eTable 4 in the Supplement). The improvement with NT-proBNP and hsTnT was most striking with a continuous NRI and relative IDI of greater than 0.60 for cardiovascular death and hospitalization for heart failure compared with less than 0.20 with hsCRP. A similar pattern was seen in patients with established cardiovascular disease and patients with clinical risk factors only, although hsCRP did not improve the discrimination or reclassification in patients with risk factors only (eTable 5 in the Supplement).

Multimarker Approach

When compared with patients without any elevated biomarkers, there was a stepwise increase in the risk of cardiovascular events in patients who had 1, 2, or 3 elevated biomarkers by cut point. In the 481 patients (3.9%) with 3 elevated biomarkers, the 2-year rates were 17.3% for cardiovascular death, 11.7% for myocardial infarction, 4.7% for ischemic stroke, and 21.7% for hospitalization for heart failure, whereas the corresponding rates in the patients without any elevated biomarkers (4266 patients [34.7%]) were 1.0%, 1.9%, 1.0%, and 0.7%, respectively (**Table 3**). This stepwise increase in risk was apparent in patients with established cardiovascular disease or multiple risk factors alone (eFigure 3 in the Supplement).

Saxagliptin vs Placebo According to Baseline Biomarker Levels

Compared with placebo, patients randomized to receive saxagliptin had a similar risk of the primary and secondary end points of the trial, including the individual components of cardiovascular death and myocardial infarction, regardless

Table 1. Cardiovascular Risk According to Baseline Biomarkers as Continuous Variables and by Cut Points

End Point or Biomarker[a]	2-y Kaplan-Meier Estimate, %		Adjusted HR (95% CI)[b]	Continuous HR per 1 SD (95% CI)[c]
	Below or Equal to the Cut Point	Greater Than the Cut Point		
Primary composite end point				
hsTnT	4.1	12.3	2.19 (1.87-2.56)	1.41 (1.32-1.51)
NT-proBNP	6.2	24.1	2.44 (2.07-2.88)	1.62 (1.50-1.74)
hsCRP	6.4	9.3	1.37 (1.20-1.56)	1.10 (1.03-1.17)
Cardiovascular death				
hsTnT	1.2	5.9	3.07 (2.35-4.02)	1.41 (1.27-1.55)
NT-proBNP	2.3	14.4	3.09 (2.46-3.89)	2.09 (1.87-2.33)
hsCRP	2.5	4.3	1.49 (1.22-1.82)	1.09 (1.00-1.20)
Myocardial infarction				
hsTnT	1.9	5.7	2.13 (1.69-2.67)	1.43 (1.29-1.59)
NT-proBNP	3.0	9.8	1.95 (1.51-2.53)	1.40 (1.25-1.57)
hsCRP	3.2	4.0	1.18 (0.97-1.44)	1.08 (0.98-1.18)
Ischemic stroke				
hsTnT	1.2	2.6	1.64 (1.21-2.22)	1.39 (1.21-1.60)
NT-proBNP	1.6	5.1	2.52 (1.75-3.63)	1.33 (1.13-1.56)
hsCRP	1.5	2.2	1.36 (1.04-1.79)	1.12 (0.99-1.28)
Hospitalization for heart failure				
hsTnT	0.8	6.2	3.85 (2.82-5.27)	1.39 (1.26-1.55)
NT-proBNP	1.9	17.9	3.92 (3.11-4.92)	2.28 (2.03-2.56)
hsCRP	2.3	4.3	1.47 (1.20-1.81)	1.15 (1.05-1.27)

Abbreviations: HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; hsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

[a] The cut points for elevated biomarkers levels were defined as 450 pg/mL or higher for those younger than 50 years, 900 pg/mL or higher for those aged 50 to 75 years, and 1800 pg/mL or higher for those older than 75 years for NT-proBNP (to convert to nanograms per liter, multiply by 1); greater than 15.0 pg/mL for men and greater than 10 pg/mL for women for hsTNT (to convert to micrograms per liter, multiply by 1); and greater than 3 mg/L for hsCRP (to convert to nanomoles per liter, multiply by 9.524).

[b] The HRs were adjusted for treatment arms, age (continuous), systolic blood pressure (continuous), sex, history of heart failure, duration of diabetes, prior myocardial infarction, history of hypertension, history of hyperlipidemia, smoking, estimated glomerular filtration rate (continuous), and all 3 biomarkers (as binary variables) and stratified by established cardiovascular disease vs multiple risk factors.

[c] For continuous biomarker data, the HRs are reported per 1 SD of log-transformed biomarker.

of baseline biomarker level, whether analyzed as continuous variables or by cut points. The previously reported overall increased risk of hospitalization for heart failure observed in patients randomized to receive saxagliptin was also consistent across different baseline biomarkers levels (eTable 6 in the Supplement).

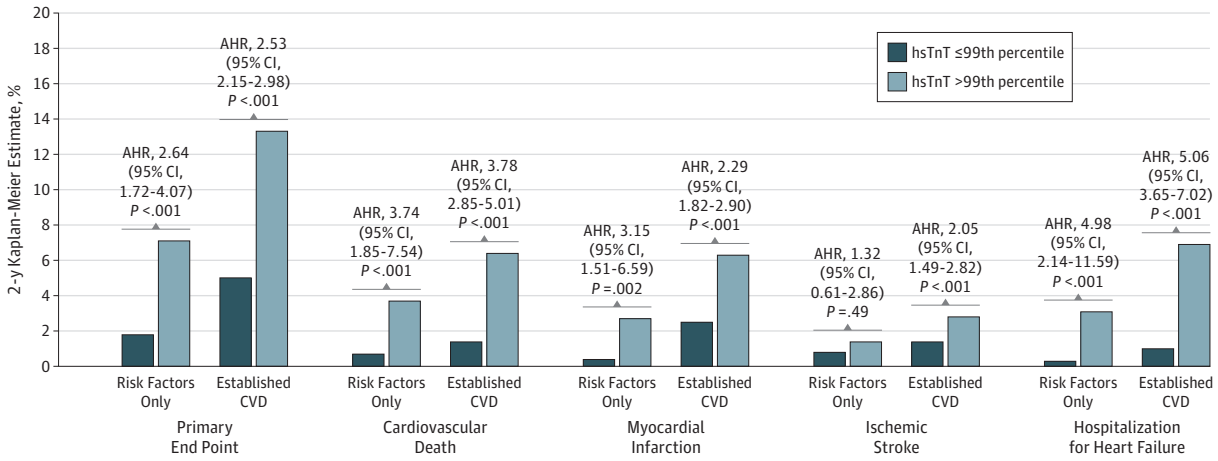
Discussion

In patients with type 2 diabetes and established cardiovascular disease or multiple cardiovascular risk factors, 3 cardiovascular biomarkers were associated with adverse cardiovascular outcomes, independent of baseline clinical features. They significantly improved the discrimination and reclassification of the risk for the primary end point (cardiovascular death, myocardial infarction, or ischemic stroke) and the individual end points, in addition to hospitalization for heart failure. Moreover, even small elevations of hsTnT and NT-proBNP carried significant prognostic implications in patients with or without manifest cardiovascular disease. Biomarker risk stratification thus challenges the traditional differentiation between primary and secondary prevention that is based simply on a history of a clinically recognized cardiovascular event. For example, the risk of cardiovascular death in a patient with clinical risk factors alone but with an elevated hsTnT level is higher (3.7%) than in a patient with established cardiovascular disease and a low hsTnT level (1.4%). Integration of these biomarkers into routine screening and risk stratification algorithms of patients with type 2 diabetes can more accurately assess risk and thereby target patients in whom modification or intensification of diagnostic and treatment strategies, as well as the frequency of follow-up, might reduce future complications.

Despite enrollment criteria that excluded patients with recent cardiovascular events, a large proportion of patients in this cohort had levels of hsTnT, NT-proBNP, and hsCRP that would be considered elevated. Nearly half of patients with established cardiovascular disease and one-quarter of patients with risk factors alone had hsTNT levels above the 99th percentile of a healthy population, a level that if dynamic, and in the appropriate clinical context, would be consistent with a myocardial infarction according to current consensus guidelines.[16]

Compared with other studies[17-19] in patients with stable type 2 diabetes, the proportion of patients in SAVOR-TIMI 53

Figure 2. Risk of Various End Points According to Baseline High-Sensitivity Troponin T (hsTnT) Levels Above and Below the 99th Percentile in Patients With Established Cardiovascular Disease (CVD) and Patients With Only Cardiovascular Risk Factors



Hazard ratios were adjusted for treatment arms, age (continuous), sex, systolic blood pressure (continuous), history of heart failure, duration of diabetes, prior myocardial infarction, hypertension, hyperlipidemia, smoking, and estimated glomerular filtration rate (continuous) (multiple risk factor subgroup is not adjusted for prior myocardial infarction). Sex-specific 99th percentiles are greater than 15 pg/mL for men and greater than 10 pg/mL for women (to convert to micrograms per liter, multiply by 1). Rates of end points according to low vs high levels of hsTnT are as follows: primary end point: 1.8% vs 7.1% for risk factors and 5.0% vs 13.3% for established CVD; cardiovascular death: 0.7% vs 3.7% for risk factors and 1.4% vs 6.4% for established CVD; myocardial infarction: 0.4% vs 2.7% for risk factors and 2.5% vs 6.3% for established CVD; ischemic stroke: 0.8% vs 1.4% for risk factors and 1.4% vs 2.8% for established CVD; and hospitalization for heart failure: 0.3% vs 3.1% for risk factors and 1.0% vs 6.9% for established CVD. AHR indicates adjusted hazard ratio.

with detectable levels of hsTnT above the 99th percentile URL was in general higher, likely because of a combination of factors, including the older age of our patients, their longer duration of diabetes, and the requirement that patients have established cardiovascular disease or documented cardiovascular risk factors for inclusion. The proportion of patients with established cardiovascular disease in SAVOR-TIMI 53 who had an elevated hsTnT level was similar to the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) cohort.[20]

These findings have several implications. Even in asymptomatic patients with diabetes without any recent acute ischemic event, we observed evidence of myocardial injury as identified by elevated levels of hsTnT. In fact, patients without established cardiovascular disease or a history of myocardial infarction but with elevated levels of hsTnT are at equal or higher subsequent risk than patients with documented atherothrombotic disease and lower levels of hsTnT. This finding may be related to persistent myocardial injury from glycemic dysregulation, leading to endothelial and microvascular dysfunction, myocardial cell death, and subsequent fibrosis.[21] Moreover, because heart failure is now recognized to be one of the first manifestations of cardiovascular disease in patients with type 2 diabetes,[22] better screening tools, such as hsTnT or natriuretic peptides, may improve earlier identification of patients at risk. Current treatment recommendations do not incorporate these biomarkers.[23]

The strong association between increased concentrations of hsTnT and the risk of a first or recurrent myocardial infarction in this large and diverse population of patients with diabetes and various levels of atherothrombotic risk is noteworthy and consistent with what has been described in patients with coronary artery disease in other cohorts of patients with type 2 diabetes.[20] Moreover, because a large proportion of asymptomatic patients with type 2 diabetes have circulating levels of hsTnT above the myocardial infarction cut point, the evaluation of patients with type 2 diabetes presenting with a suspected acute coronary syndrome must integrate the rise and fall of hsTnT levels rather than the absolute concentration into the diagnostic algorithm to avoid inappropriate diagnoses of acute coronary syndromes.[16] Consistent with prior studies[24-27] of natriuretic peptides in patients with type 2 diabetes, elevated levels of NT-proBNP were strongly associated with the risk of cardiovascular death and hospitalization with heart failure.

Simultaneous assessment of all 3 biomarkers identified particularly low- and high-risk populations. In patients with 3 elevated biomarkers, the 2-year rates of cardiovascular death approached 20%, more than 10-fold the risk of a similarly sized cohort of patients who had no elevated levels. A multimarker approach, reported to be useful in acute coronary syndromes,[28,29] may also provide an approach to discriminate risk in patients with stable type 2 diabetes more fully.

To become fully integrated into clinical care, a biomarker must fulfill several criteria.[30,31] The assay should ideally be high throughput and demonstrate adequate precision and reproducibility. Clinically, the biomarker must provide incremental prognostic information to standard risk tools, in particular through improved discrimination and reclassification as tested with contemporary statistical methods.[14] On the basis of the continuous NRI and relative IDI, NT-proBNP and hsTnT provide at least moderate improvement in risk stratification (relative IDI and NRI >0.4) for all cardiovascular end points, with a particularly strong improvement in reclassification with

Table 2. Improvement in Discrimination and Reclassification With the Addition of Biomarkers[a]

End Point or Biomarker	C Index for Model (95% CI)		Change in C Index (95% CI)	IDI (95% CI)		Continuous NRI (95% CI)
	Without Biomarker	With Biomarker[b]		Absolute	Relative	
Primary End Point						
hsTnT	0.65 (0.63 to 0.67)					
Cut points		0.69 (0.68 to 0.71)	−0.04 (−0.06 to −0.03)	0.0123 (0.0100 to 0.0145)	0.48	0.52 (0.46 to 0.59)
Continuous		0.72 (0.70 to 0.73)	−0.07 (−0.08 to −0.05)	0.0285 (0.0233 to 0.0336)	1.12	0.44 (0.38 to 0.51)
NT-proBNP						
Cut points		0.69 (0.67 to 0.70)	−0.04 (−0.05 to −0.03)	0.0202 (0.0158 to 0.0246)	0.80	0.19 (0.13 to 0.26)
Continuous		0.72 (0.71 to 0.74)	−0.07 (−0.09 to −0.06)	0.0379 (0.0321 to 0.0438)	1.50	0.48 (0.41 to 0.55)
hsCRP						
Cut points		0.66 (0.64 to 0.68)	−0.01 (−0.02 to −0.004)	0.0036 (0.0022 to 0.0051)	0.14	0.19 (0.12 to 0.26)
Continuous		0.66 (0.65 to 0.68)	−0.01 (−0.02 to −0.01)	0.0038 (0.0022 to 0.0053)	0.15	0.17 (0.10 to 0.24)
All 3 biomarkers						
Cut points		0.71 (0.70 to 0.73)	−0.06 (−0.08 to −0.05)	0.0303 (0.0253 to 0.0352)	1.20	0.40 (0.33 to 0.47)
Continuous		0.74 (0.73 to 0.76)	−0.09 (−0.11 to −0.07)	0.0490 (0.0422 to 0.0558)	1.94	0.56 (0.49 to 0.62)
Cardiovascular Death						
hsTnT	0.70 (0.67 to 0.73)					
Cut points		0.75 (0.73 to 0.77)	−0.05 (−0.07 to −0.03)	0.0089 (0.0068 to 0.0109)	0.36	0.65 (0.56 to 0.75)
Continuous		0.77 (0.75 to 0.79)	−0.07 (−0.09 to −0.05)	0.0217 (0.0155 to 0.0278)	0.88	0.54 (0.44 to 0.64)
NT-proBNP						
Cut points		0.75 (0.72 to 0.77)	−0.05 (−0.06 to −0.03)	0.0227 (0.0167 to 0.0288)	0.92	0.33 (0.23 to 0.43)
Continuous		0.80 (0.78 to 0.82)	−0.10 (−0.13 to −0.08)	0.0484 (0.0380 to 0.0589)	1.96	0.71 (0.62 to 0.81)
hsCRP						
Cut points		0.71 (0.69 to 0.74)	−0.01 (−0.02 to −0.004)	0.0035 (0.0016 to 0.0054)	0.14	0.27 (0.16 to 0.37)
Continuous		0.71 (0.69 to 0.74)	−0.01 (−0.02 to −0.004)	0.0032 (0.0013 to 0.0050)	0.13	0.20 (0.10 to 0.30)
All 3 biomarkers						
Cut points		0.78 (0.76 to 0.80)	−0.08 (−0.10 to −0.06)	0.0302 (0.0238 to 0.0366)	1.22	0.54 (0.44 to 0.64)
Continuous		0.82 (0.79 to 0.84)	−0.12 (−0.14 to −0.09)	0.0539 (0.0433 to 0.0645)	2.18	0.74 (0.65 to 0.84)

Abbreviations: hsCRP, high-sensitivity C-reactive protein; hsTnT, high-sensitivity troponin T; IDI, integrated discrimination improvement; NRI, net reclassification improvement; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

[a] Models were adjusted for treatment arms, age (continuous), systolic blood pressure (continuous), sex, history of heart failure, duration of diabetes, prior myocardial infarction, history of hypertension, history of hyperlipidemia, smoking, and estimated glomerular filtration rate (continuous) and stratified by established cardiovascular disease vs multiple risk factors with and without biomarker(s) listed.

[b] *P* value (likelihood ratio) comparing C index for the models with and without biomarkers are all <.001.

NT-proBNP and hsTnT for cardiovascular death (NRI and relative IDI >0.60 for hsTnT and >1.9 for NT-proBNP) and hospitalization for heart failure (NRI and relative IDI >0.60 for hsTnT and >1.0 for NTproBNP).[15] The incremental improvement with hsCRP was less marked (relative IDI and NRI ≤0.15 for cardiovascular death), highlighting that a general marker of inflammation, such as hsCRP, may not provide similar discrimination of risk in patients with the ongoing low-level chronic inflammatory processes associated with diabetes.

Ideally, a biomarker should also provide actionable diagnostic and treatment implications. Of the cardiovascular biomarkers, only hsTnT in the setting of acute coronary syndromes has clearly met this last hurdle. In other scenarios, hsTnT and NT-proBNP are excellent discriminators of risk but to date have not been found to definitively change treatment decisions.[32] The proof-of-principle NT-proBNP Guided Primary Prevention of CV Events in Diabetic Patients (PONTIAC) study[33] found a significant reduction in cardiovascular death and hospitalization in patients with elevated levels of natriuretic peptides randomized to more aggressive up-titration of inhibitors of the renin-angiotensin-aldosterone system and β-blockers, but additional studies on larger populations with more extended observation will be required to validate these findings.

Table 3. Risk of Cardiovascular Events According to the Number of Elevated Biomarkers Based on Cut Points[a]

No. of Elevated Biomarkers per End Point	No. of Events	2-y Kaplan-Meier Estimate, %	Adjusted HR (95% CI)[b]
Primary composite end point			
0	4266	3.6	1 [Reference]
1	5085	6.7	1.80 (1.49-2.19)
2	2345	12.6	3.14 (2.56-3.85)
3	481	28.3	7.09 (5.53-9.08)
Cardiovascular death			
0	4266	1.0	1 [Reference]
1	5085	2.5	2.54 (1.78-3.63)
2	2345	6.1	5.28 (3.67-7.59)
3	481	17.3	13.63 (9.10-20.43)
Myocardial infarction			
0	4266	1.9	1 [Reference]
1	5085	3.3	1.61 (1.23-2.10)
2	2345	5.5	2.46 (1.83-3.29)
3	481	11.7	4.84 (3.33-7.02)
Ischemic stroke			
0	4266	1.0	1 [Reference]
1	5085	1.6	1.59 (1.11-2.29)
2	2345	3.2	2.90 (1.97-4.28)
3	481	4.7	4.64 (2.69-8.03)
Hospitalization for heart failure			
0	4266	0.7	1 [Reference]
1	5085	1.9	2.44 (1.61-3.71)
2	2345	6.6	6.84 (4.53-10.32)
3	481	21.7	17.97 (11.52-28.04)

Abbreviations: HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; hsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

[a] The cut points for elevated biomarkers levels were defined as 450 pg/mL or higher for those younger than 50 years, 900 pg/mL or higher for those aged 50 to 75 years, and 1800 pg/mL or higher for those older than 75 years for NT-proBNP (to convert to nanograms per liter, multiply by 1); greater than 15.0 pg/mL for men and greater than 10 pg/mL for women for hsTNT (to convert to micrograms per liter, multiply by 1); and greater than 3 mg/L for hsCRP (to convert to nanomoles per liter, multiply by 9.524).

[b] The HRs were adjusted for treatment arms, age (continuous), systolic blood pressure (continuous), sex, history of heart failure, duration of diabetes, prior myocardial infarction, history of hypertension, history of hyperlipidemia, smoking, estimated glomerular filtration rate (continuous), and all 3 biomarkers (as binary variables) and stratified by established cardiovascular disease vs multiple risk factors.

Although biomarkers clearly identified patients at increased cardiovascular risk, no biomarker identified a particular patient population that benefited or was harmed by treatment with saxagliptin. Now that several different classes of diabetes drugs have been reported to improve cardiovascular outcomes,[34,35] biomarkers may provide additional insight into the mechanism of action and identification of patients most likely to benefit from therapy.

This study has some limitations. We did not assess left ventricular function. Baseline lipid levels were not measured, although most patients were undergoing lipid-lowering therapy in this trial.

Conclusions

Elevated levels of hsTnT, NT-proBNP, and hsCRP improved risk stratification in more than 12 000 patients with type 2 diabetes and established cardiovascular disease or multiple cardiovascular risk factors. Strategies to improve risk stratification in type 2 diabetes, with or without manifest cardiovascular disease, should consider incorporation of biomarker data into standard risk algorithms because they provide more accurate risk stratification than clinical variables alone.

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