JAMA Cardiology | Original Investigation

Cardiovascular Outcomes According to Urinary Albumin and Kidney Disease in Patients With Type 2 Diabetes at High Cardiovascular Risk

Observations From the SAVOR-TIMI 53 Trial

Benjamin M. Scirica, MD, MPH; Ofri Mosenzon, MD; Deepak L. Bhatt, MD, MPH; Jacob, A. Udell, MD, MPH; Ph Gabriel Steg, MD; Darren K. McGuire, MD, MHSc; KyungAh Im, PhD; Estella Kanevsky, MS; Christina Stahre, MD; Mikaela Sjöstrand, MD; Itamar Raz, MD; Eugene Braunwald, MD

IMPORTANCE An elevated level of urinary albumin to creatinine ratio (UACR) is a marker of renal dysfunction and predictor of kidney failure/death in patients with type 2 diabetes. The prognostic use of UACR in established cardiac biomarkers is not well described.

OBJECTIVE To evaluate whether UACR offers incremental prognostic benefit beyond risk factors and established plasma cardiovascular biomarkers.

DESIGN, SETTING, AND PARTICIPANTS The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus–Thrombolysis in Myocardial Infarction (SAVOR-TIMI) 53 study was performed from May 2010 to May 2013 and evaluated the safety of saxagliptin vs placebo in patients with type 2 diabetes with overt cardiovascular disease or multiple risk factors. Median follow-up was 2.1 years (interquartile range, 1.8-2.3 years).

INTERVENTIONS Patients were randomized to saxagliptin vs placebo plus standard care.

MAIN OUTCOMES AND MEASURES Baseline UACR was measured in 15 760 patients (95.6% of the trial population) and categorized into thresholds.

RESULTS Of 15 760 patients, 5205 were female (33.0%). The distribution of UARC categories were: 5805 patients (36.8%) less than 10 mg/g, 3891 patients (24.7%) at 10 to 30 mg/g, 4426 patients (28.1%) at 30 to 300 mg/g, and 1638 patients (10.4%) at more than 300 mg/g. When evaluated without cardiac biomarkers, there was a stepwise increase with each higher UACR category in the incidence of the primary composite end point (cardiovascular death, myocardial infarction, or ischemic stroke) (3.9%, 6.9%, 9.2%, and 14.3%); cardiovascular death (1.4%, 2.6%, 4.1%, and 6.9%); and hospitalization for heart failure (1.5%, 2.5%, 4.0%, and 8.3%) (adjusted $P < .001$ for trend). The net reclassification improvement at the event rate for each end point was 0.081 (95% CI, 0.025 to 0.161), 0.129 (95% CI, 0.029 to 0.202), and 0.056 (95% CI, −0.005 to 0.141), respectively. The stepwise increased cardiovascular risk associated with a UACR of more than 10 mg/g was also present within each chronic kidney disease category. The UACR was associated with outcomes after including cardiac biomarkers. However, the improvement in discrimination and reclassification was attenuated; net reclassification improvement at the event rate was 0.022 (95% CI, −0.022 to 0.067), −0.008 (−0.034 to 0.053), and 0.043 (−0.030 to 0.052) for the primary end point, cardiovascular death, and hospitalization for heart failure, respectively.

CONCLUSIONS AND RELEVANCE In patients with type 2 diabetes, UACR was independently associated with increased risk for a spectrum of adverse cardiovascular outcomes. However, the incremental cardiovascular prognostic value of UACR was minimal when evaluated together with contemporary cardiac biomarkers.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01107886

JAMA Cardiol. 2018;3(2):155-163. doi:10.1001/jamacardio.2017.4228
Published online December 6, 2017.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Chronic kidney disease is a well-recognized complication of type 2 diabetes (T2D) affecting 30% to 40% of patients.[1] Chronic kidney disease may be recognized by 2 distinct and complementary methods: estimated glomerular filtration rates (eGFR) and urinary albumin to creatinine ratio (UACR).[2-4] Elevated levels of urinary albumin, as assessed by UACR, reflect damage to the basement membrane and endothelium of glomerular capillaries and denote the presence of chronic kidney disease, even within different eGFR categories.[2,3] In patients with T2D, UACR often represents diabetic nephropathy, although other diseases, such as hypertension may also contribute. Urinary albumin to creatinine ratio levels between 30 mg/g to 300 mg/g, formerly termed *microalbuminuria*, represent moderately increased levels of albuminuria (Kidney Disease: Improving Global Outcomes category A2).[2,3,5] In healthy adults, UACR is typically less than 10 mg/g; however, even small elevations in urinary albumin between 10 mg/g and 29 mg/g have been associated with progression of renal disease and increased mortality.[6-10] The incremental value of UACR for the prediction of cardiovascular risk when combined with established cardiovascular biomarkers, such as high-sensitivity troponin T (hsTnT), natriuretic peptides, or high-sensitivity C-reactive protein (hsCRP), has not been well described, to our knowledge.

The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR-TIMI) 53 trial[11] evaluated the cardiovascular efficacy and safety of saxagliptin, a selective dipeptidyl peptidase-4 inhibitor, in 16 492 patients with T2D with overt atherosclerotic vascular disease or at risk for cardiovascular events. During a median follow-up of 2.1 years, saxagliptin did not alter the risk of the primary composite end point of cardiovascular death, myocardial infarction, or ischemic stroke, although there was a 27% increased relative risk of hospitalization for heart failure in patients assigned to receive saxagliptin.[12] In addition, saxagliptin improved UACR over time compared with placebo.[13,14] As part of a prespecified analysis, we evaluated the cardiovascular risk associated with baseline UACR and eGFR together with cardiac biomarkers.

Key Points

Question What is the incremental prognostic value of urinary albumin excretion for cardiovascular risk assessment in patients with diabetes with and without the incorporation of cardiac biomarkers?

Findings In this secondary analysis of a randomized clinical trial population of 15 760 patients with type 2 diabetes and high cardiovascular risk, there was a stepwise increased risk of cardiovascular events according to baseline urinary albumin to creatinine ratio. The association with increased risk was present even at low-level elevations of urinary albumin to creatinine ratio, which are otherwise considered normal, although this relationship was attenuated when adjusted for cardiac biomarkers.

Meaning Low levels of albuminuria improve risk stratification for future cardiovascular risk in patients with type 2 diabetes; urinary albumin to creatinine ratio provides minimal incremental prognostic utility beyond cardiac biomarkers.

Methods

Study Design and Oversight

The SAVOR-TIMI 53 study[11] was a multicenter, randomized double-blind, placebo-controlled trial that randomized patients with T2D, hemoglobin A_{1C} level between 6.5% and 12.0% within 6 months of randomization, and either a history of established atherosclerotic vascular disease or multiple risk factors for vascular disease (ie, investigator-reported dyslipidemia, hypertension, or smoking) to receive either 5 mg of saxagliptin daily (or 2.5 mg daily in patients with an eGFR of ≤50 mL/min/1.73 m^2) or matching placebo.[11] The protocol specified the inclusion of at least 800 patients with at least moderate to severe kidney impairment (eGFR, <50 mL/min/1.73 m^2), of whom 300 patients were to have an eGFR less than 30 mL/min/1.73 m^2. Patients with a history of either end-stage renal disease receiving chronic dialysis, serum creatinine level of more than 6.0 mg/dL, or previous kidney transplant were excluded. The full eligibility criteria and analysis plan have been reported previously.[11,13] The trial protocol was reviewed and approved by all relevant ethics committees. Written informed consent was obtained from all patients.

End Points

The primary end point of the trial was a composite of the first occurrence of cardiovascular death, myocardial infarction, or ischemic stroke. The secondary composite end point included the elements of the primary end point and hospitalizations for heart failure, unstable angina, or coronary revascularization. A clinical events committee, unaware of the study group assignments, adjudicated all components of the primary and secondary composite efficacy end points[11,13] using definitions based on draft guidelines for the standardization of end points in cardiovascular trials proposed by the US Food and Drug Administration.[15]

Baseline Kidney Function Assessment

The eGFR was determined according to the Modification of Diet in Renal Disease formula based on serum creatinine and categorized as more than 60, 30 to 60, and less than 30 mL/min/1.73 m^2. Urinary albumin to creatinine ratio was measured from a single voided urine sample by a central laboratory (albumin, lower detection limit of 3 mg/L; creatinine, Jaffe reaction, lower detection limit of 4.0 mg/dL). The lowest reportable level of UACR was 1.0 mg/g. Urinary albumin to creatinine ratio was prospectively categorized as less than 10mg/g, 10 mg/g to 29 mg/g, 30 mg/g to 300 mg/g, and more than 300 mg/g.

Statistical Analysis

Categorical variables were compared using χ^2 test and continuous variables with a Kruskal-Wallis test. Event rates are presented as 2-year Kaplan-Meier estimates. Estimated glomerular filtration rates and UACR were analyzed as continuous variables (as restricted cubic splines) and then based on the

Table 1. Rates of Cardiovascular Events (2-Year Kaplan-Meier Estimates) by UACR Category

Characteristic	UACR Category, No. (%)[a]				
	<10 mg/g (n = 5805)	10 mg/g to 29 mg/g (n = 3891)	30 mg/g to 300 mg/g (n = 4426)	>300 mg/g (n = 1638)	*P* Value[a]
Primary composite end point	232 (3.9)	275 (6.9)	404 (9.2)	241 (14.3)	<.001
Secondary composite end point	515 (8.9)	458 (11.5)	648 (14.7)	365 (22.4)	<.001
Cardiovascular death	86 (1.4)	104 (2.6)	183 (4.1)	121 (6.9)	<.001
Any cause mortality	139 (2.3)	166 (4.0)	268 (5.8)	175 (9.7)	<.001
Fatal/nonfatal myocardial infarction	103 (1.8)	125 (3.1)	183 (4.2)	100 (6.2)	<.001
Ischemic stroke	66 (1.1)	71 (1.8)	98 (2.3)	49 (3.0)	<.001
Hospitalization for heart failure	85 (1.5)	97 (2.5)	177 (4.0)	134 (8.3)	<.001
Hospitalization for coronary revascularization	300 (5.2)	197 (5.0)	246 (5.7)	102 (6.5)	.034

Abbreviation: UACR, urinary albumin to creatinine ratio.

[a] Using a 2-sided log-rank test for trend.

prespecified end points noted above. Multivariable models evaluating the association between UACR and clinical outcomes were adjusted for the following baseline variables: treatment arms (saxagliptin vs placebo), age (continuous), sex, race/ethnicity (white vs nonwhite), history of heart failure, duration of T2D (<5 years, 5-9 years, 10-14 years, 15-19 years, and ≥20 years), hemoglobin A_{1C} level (continuous), systolic blood pressure (continuous), prior myocardial infarction, history of hypertension, history of dyslipidemia, current smoker, and eGFR (continuous). The multivariable analyses were repeated with the inclusion of baseline N-terminal pro B-type natriuretic peptide (NT-proBNP), hsTnT, and hsCRP in the clinical model in analyses restricted to the 12 177 patients with data available on all 3 biomarkers. Biomarkers were examined as log-transformed as well as categorical variables using quartiles (NT-proBNP and hsTnT) and categories for hsCRP (<1 mg/l, 1-3 mg/l, >3 mg/l) when comparing categories of UACR. All models were calibrated using slight variations of variables in the Cox proportional hazards model with and without biomarker data. Calibration was evaluated by deciles of predicted probabilities.[16] Estimates of the C statistic for the clinical model created from previously listed variables were calculated based on the Harrell method[17] and then compared with 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[18] to determine the net reclassification improvement (NRI) at the event rate along with 95% CIs based on bootstrap resampling and integrated discrimination improvement.[19]

Results

Of 16 492 patients in the SAVOR-TIMI 53 trial, baseline UACR was available in 15 760 patients (95.6%). In total, 5205 patients were female (33.0%). The median UACR was 17.0 mg/g (interquartile range, 6.0-68.0 mg/g). Overall, 5805 patients had a UACR less than 10 mg/g (36.8%); 3891 (24.7%), 10 mg/g to 29 mg/g; 4426 (28.1%), 30 mg/g to 300 mg/g; and 1638 (10.4%), more than 300 mg/g. Patients with higher UACR were more likely not to be white, have higher baseline systolic blood pressures, longer duration of diabetes, a higher prevalence of dyslipidemia, hypertension, and established atherosclerotic disease, more elevated hemoglobin A_{1C} levels, and lower eGFR. In addition, patients with higher UACR had higher concentrations of hsTnT, NT-proBNP, and hsCRP (eTable 1 in the Supplement).

Baseline UACR and Cardiovascular Outcomes

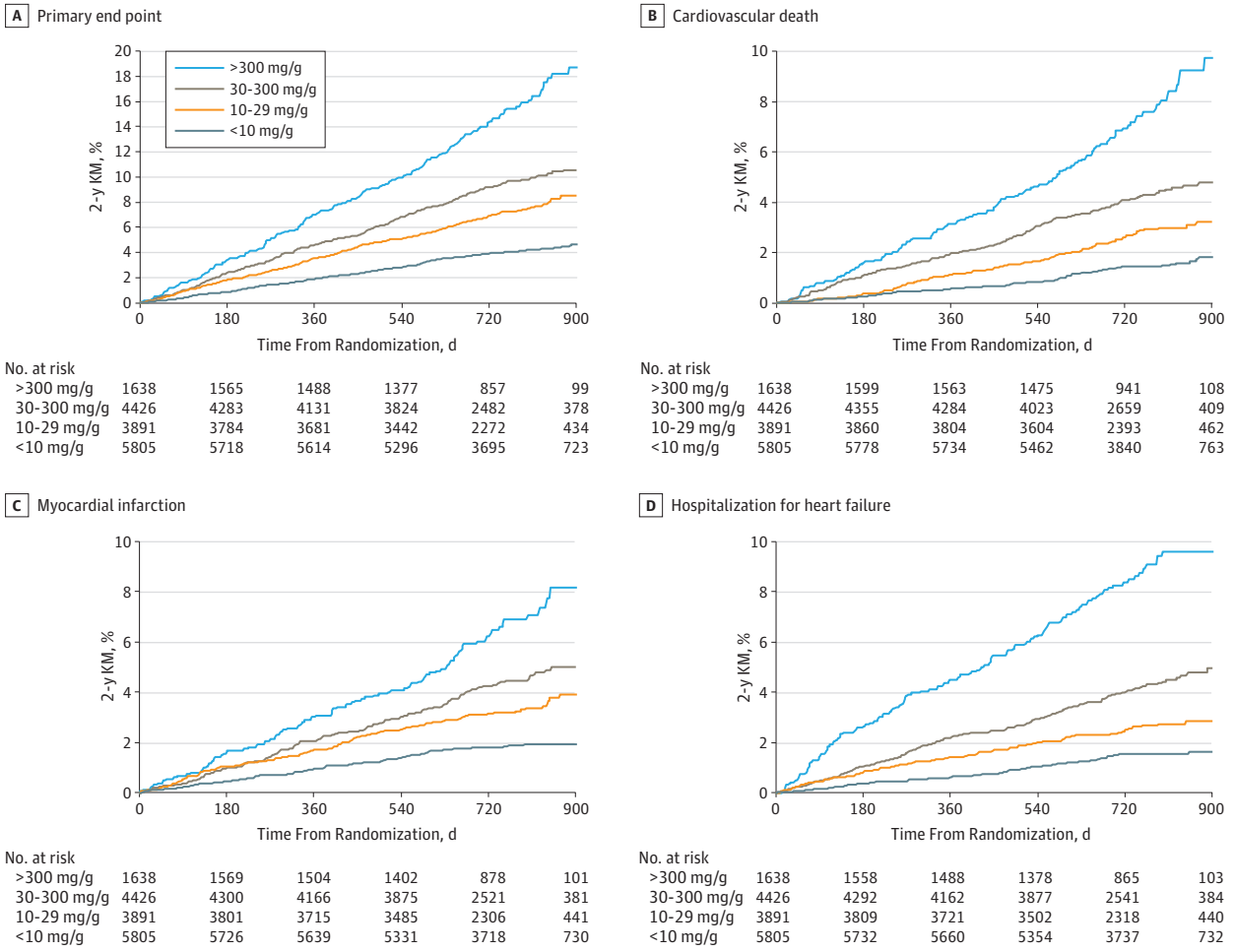
When evaluated without cardiac biomarkers, there was a stepwise increase in the incidence of all cardiovascular events according to baseline UACR categories (**Table 1** and **Figure 1**). When analyzed as a continuous variable in a multivariable model adjusted for baseline characteristics and eGFR, UACR was significantly associated with an increased risk of all-cause mortality, cardiovascular death, myocardial infarction, and hospitalization for heart failure (**Table 2** and **Figure 2**). When examining the associated risk according to the prespecified UACR categories, there was a consistent, stepwise pattern of increased cardiovascular risk with each level of UACR. Notably, the risk associated with UACR began to increase significantly even in patients with UACR concentrations between 10 mg/g and 29 mg/g (Table 2). The addition of UACR to the clinical model (without biomarkers) significantly improved discrimination and reclassification of risk for all end points with the exception of ischemic stroke and hospitalization for coronary revascularization (**Table 3**). The NRI at the event rate after the addition of UACR was improved for the primary end point (NRI, 0.081; 95% CI, 0.025 to 0.161), cardiovascular death (NRI, 0.129; 95% CI, 0.029 to 0.202), myocardial infarction (NRI, 0.082; 95% CI, −0.018 to 0.154), and hospitalization for heart failure (NRI, 0.056; 95% CI, −0.005 to 0.141).

After adjusting for baseline levels of NT-proBNP, hsTnT, and hsCRP, levels of UACR remained significantly associated with cardiovascular outcomes; however, the relationship was attenuated (Table 2). With the inclusion of cardiac biomarkers, the improvements in C statistics, the NRI at the event rate, and integrated discrimination improvement, while present, were relatively small (Table 3).

Baseline UACR and eGFR

The incidence of cardiovascular events increased with higher concentrations of UACR and lower eGFR, regardless of whether UACR was analyzed as a categorical or continuous variable. Even

Figure 1. Kaplan-Meier (KM) Estimates According to Baseline Urinary Albumin to Creatinine Ratio Levels



within each of the 3 different categories of eGFR, a higher UACR was associated with an increased risk of cardiovascular events and therefore identified differential risk within each eGFR category. For example, in patients with normal kidney function or mild kidney insufficiency (eGFR >60 mL/min/1.73 m^2), the incidence of the primary end point increased progressively from 3.5% with a UACR of less than 10 mg/g to 12.3% in patients with a UACR of more than 300 mg/g (eTable 2 in the Supplement). This excess risk remained significant after adjusting for other baseline characteristics (eFigure and eTable 3 in the Supplement) and for cardiac biomarkers (eTable 4 in the Supplement).

The association between UACR and outcomes was consistent in patients treated with saxagliptin or placebo (*P* values for interactions were all >.05, except for ischemic stroke [*P* = .033]) (eTable 5 in the Supplement) and irrespective of baseline use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (eTable 6 in the Supplement).

Discussion

In this study of 15 760 patients with T2D at high cardiovascular risk, we found that when evaluated together with standard clinical markers including eGFR, baseline UACR was independently associated with total mortality as well as cardiovascular events, such as cardiovascular death, myocardial infarction, ischemic stroke, and hospitalization for heart failure, thus expanding prior observations and supporting the hypothesis that UACR provides complementary insight into the association between diabetic kidney disease and cardiovascular risk. Currently, urinary albumin testing is already recommended for all patients with T2D to assess for chronic kidney disease. Urinary albumin to creatinine ratio could therefore readily be used as a more formal tool for cardiovascular risk prognostication without any additional testing or costs above standard therapy.

In contrast, when evaluated simultaneously with 3 frequently used cardiac plasma biomarkers (hsTnT, NT-proBNP, and hsCRP), the incremental prognostic value of UACR was minimal. This is not unexpected given the strong association between cardiac biomarkers and cardiovascular outcomes in patients with T2D.[20,21] To our knowledge, no practice guidelines, however, currently recommend their use in stable patients with diabetes. Consequently, hsTnT, NT-proBNP, and hsCRP are rarely used in this clinical setting, and UACR may therefore still offer additional incremental prognostic infor-

Table 2. Risk of Cardiovascular Events per Levels of UACR

	Log of UACR as Continuous[a,b]		UACR as Categorical Adjusted HR (95% CI)[b]				
End Points	Adjusted HR (95% CI)	*P* Value	<10 mg/g	10 mg/g to 29 mg/g	30 mg/g to 300 mg/g	>300 mg/g	*P* Value
Without biomarkers (n = 15 688)							
Primary composite end point[c]	1.39 (1.32-1.47)	<.001	1 [Reference]	1.65 (1.39-1.97)	2.01 (1.70-2.38)	3.11 (2.55-3.80)	<.001
Secondary composite end point[d]	1.33 (1.27-1.39)	<.001	1 [Reference]	1.28 (1.13-1.46)	1.56 (1.38-1.76)	2.35 (2.02-2.72)	<.001
Cardiovascular death	1.55 (1.42-1.70)	<.001	1 [Reference]	1.65 (1.24-2.21)	2.40 (1.84-3.14)	4.10 (3.02-5.57)	<.001
Any cause mortality[e]	1.51 (1.40-1.62)	<.001	1 [Reference]	1.66 (1.32-2.09)	2.25 (1.82-2.79)	3.65 (2.85-4.68)	<.001
Myocardial infarction[e]	1.40 (1.28-1.52)	<.001	1 [Reference]	1.73 (1.33-2.24)	2.10 (1.64-2.69)	2.97 (2.19-4.01)	<.001
Ischemic stroke	1.22 (1.09-1.38)	<.001	1 [Reference]	1.43 (1.02-2.01)	1.56 (1.13-2.16)	1.94 (1.29-2.91)	.001
Hospitalization for heart failure[f]	1.77 (1.62-1.93)	<.001	1 [Reference]	1.65 (1.22-2.21)	2.68 (2.05-3.51)	5.49 (4.05-7.44)	<.001
Hospitalization for coronary revascularization	1.08 (1.00-1.16)	.045	1 [Reference]	0.98 (0.82-1.18)	1.07 (0.90-1.27)	1.21 (0.94-1.54)	.099
With biomarkers (n = 11 685)							
Primary composite end point	1.15 (1.07-1.23)	<.001	1 [Reference]	1.36 (1.12-1.66)	1.33 (1.10-1.62)	1.65 (1.31-2.09)	<.001
Secondary composite end point	1.12 (1.06-1.19)	<.001	1 [Reference]	1.10 (0.95-1.27)	1.11 (0.96-1.28)	1.42 (1.19-1.70)	<.001
Cardiovascular death	1.20 (1.08-1.33)	<.001	1 [Reference]	1.12 (0.81-1.54)	1.30 (0.96-1.76)	1.81 (1.27-2.57)	<.001
Any cause mortality	1.24 (1.14-1.35)	<.001	1 [Reference]	1.18 (0.91-1.54)	1.32 (1.03-1.69)	1.91 (1.43-2.55)	<.001
Myocardial infarction[e]	1.18 (1.07-1.31)	.001	1 [Reference]	1.60 (1.19-2.16)	1.62 (1.21-2.17)	1.88 (1.31-2.68)	<.001
Ischemic stroke	0.99 (0.86-1.15)	.917	1 [Reference]	1.20 (0.82-1.75)	1.15 (0.79-1.67)	0.99 (0.60-1.63)	.931
Hospitalization for heart failure	1.30 (1.17-1.44)	<.001	1 [Reference]	0.94 (0.67-1.32)	1.28 (0.94-1.75)	1.99 (1.40-2.84)	<.001
Hospitalization for coronary revascularization[g]	0.98 (0.90-1.07)	.636	1 [Reference]	0.94 (0.77-1.16)	0.89 (0.72-1.09)	0.93 (0.70-1.25)	.582

Abbreviations: HR, hazard ratio; UACR, urinary albumin to creatinine ratio.

[a] Per log (SD) is 1 (1.76).

[b] Hazard ratio is adjusted for treatment arms (saxagliptin vs placebo), age (years), sex, race (white vs nonwhite), history of heart failure, duration of diabetes (<5 years, 5-9 years, 10-14 years, 15-19 years, and ≥20 years), hemoglobin A_{1C} (percentage), systolic blood pressure, prior myocardial infarction, history of hypertension, history of dyslipidemia, current smoker, and estimated glomerular filtration rates (millimeters per minute), and for the models with biomarkers, high-sensitivity troponin T quartiles, pro B-type natriuretic peptide quartiles, and C-reactive protein (<1, 1-3, >3 mg/L).

[c] Used a shortened model for when UACR is continuous: age (<65 years vs ≥65 years), race (white vs nonwhite), history of heart failure, hemoglobin A_{1C}, prior myocardial infarction, hypertension, current smoking, estimated glomerular filtration rates (<30, 30-60, >60 mL/min/1.73 m^2).

[d] Age (<65 vs ≥65 years), systolic blood pressure (<120, 120-<130, 130-<140, ≥140 mm Hg), and estimated glomerular filtration rates (<30, 30-60, >60 mL/min/1.73 m^2) are categorical.

[e] Age is binary (<65 vs ≥65 years).

[f] Age is binary (<65 vs ≥65 years) only when UACR is categorical. Duration of diabetes was dropped from the model when UACR is continuous.

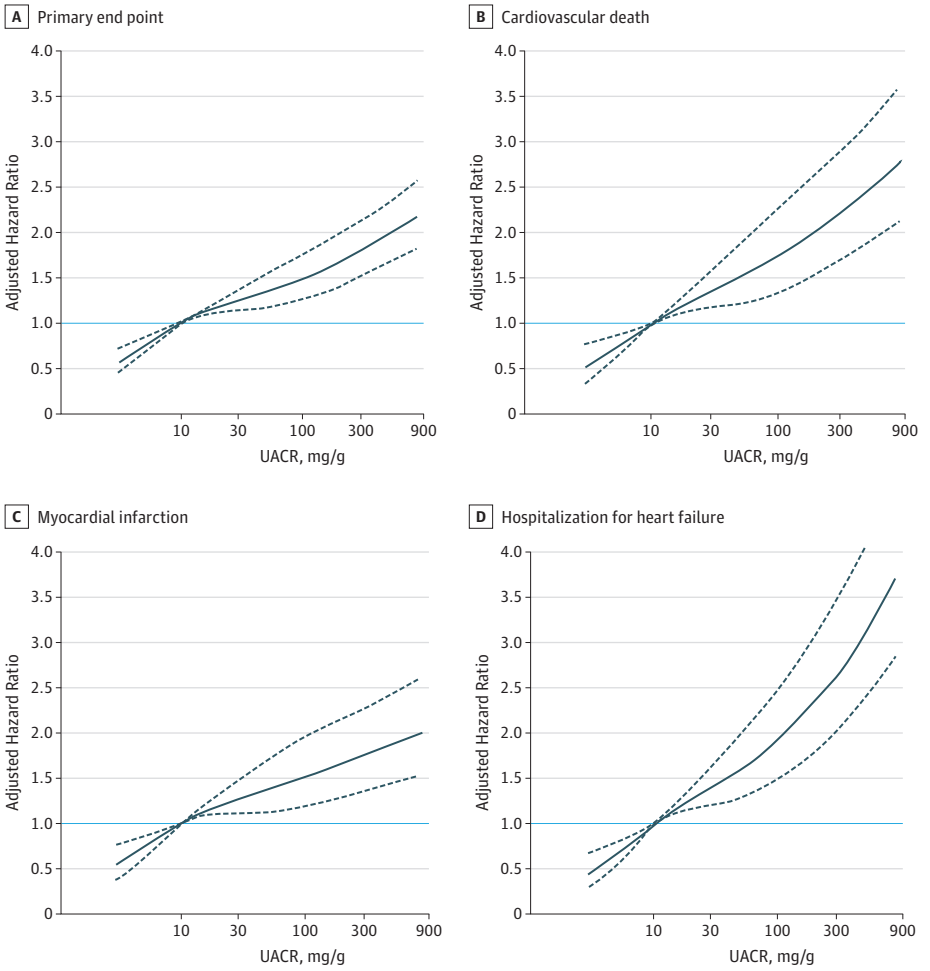
[g] Prior heart failure was dropped from the model.

mation. Eventual integration of cardiac biomarkers into risk stratification algorithms in T2D would provide additional clinical value, although at increased cost, through a more nuanced risk assessment.

In patients with T2D, increased levels of urinary albumin are likely an early signal of microvascular disease and indicate some degree of kidney damage.[4] Historically, a cut point of 30 mg/g has been used in the diagnosis of albuminuria and thereby labeling a patient with kidney disease, which is diabetic nephropathy in most patients with T2D.[2,22] Our data indicate that from a prognostic stand point, even low-level elevations in UACR (10-30 mg/L), which would not be classified by contemporary clinical standards as elevated levels of albuminuria,[5] are associated with increased all-cause mortality as well as cardiovascular risk when compared with patients with UACR of less than 10 mg/g and are therefore clinically relevant and successfully identify high-risk patients.

The association between UACR and heart failure has been reported previously in a general population of patients with prevalent heart failure[6,23-25] and in patients with T2D.[6,26,27] Without the inclusion of cardiac biomarkers, the risk of heart failure hospitalization in SAVOR-TIMI 53 began to rise with a UACR of more than 10 mg/g, even after adjusting for many baseline characteristics and regardless of baseline eGFR. We have previously demonstrated that in the SAVOR-TIMI 53 population, baseline eGFR is associated with an increased cardiovascular risk, including heart failure[28]; however, that analysis did not include UACR. Levels of NT-proBNP and hsTnT are strongly associated with worsening heart failure in stable populations, so the attenuation of the association between UACR and hospitalization for heart

Figure 2. Risk of Primary End Point, Cardiovascular Death, Myocardial Infarction, and Hospitalization for Heart Failure, by Urinary Albumin to Creatinine Ratio (UACR) as Continuous Variable



The solid dark blue line indicates the adjusted hazard ratio; dotted dark blue line, 95% CI; and the solid light blue line, a reference when the adjusted hazard ratio for UACR is 1.

failure when these cardiac biomarkers were added to the model is not surprising.

The association between albuminuria and cardiovascular mortality and end-stage kidney disease are well described in patients with T2D and in the general population.[6,7,9,29-31] Other studies, many including patients without T2D, found an association between UACR and heart failure,[25,32] coronary heart disease[32] and incident hypertension. None of these studies included cardiac biomarkers, which have been described as some of the most robust predictors of risk in primary and secondary prevention populations of patients with T2D.[20,21] Other studies in patients with and without diabetes that also found an association between UACR and cardiovascular events lacked a sufficient number of patients to evaluate the different cardiac events individually[33] or did not simultaneously assess both natriuretic peptides and high-sensitivity troponin.[34-36]

In addition to inhibitors of the renin-angiotensin-aldosterone system, several glucose-lowering drugs, including dipeptidyl peptidase 4 inhibitors,[37] sodium-glucose cotransporter 2 inhibitors,[38] and glucagon-like peptide 1 agonist,[39] improve UACR. In SAVOR-TIMI 53, saxagliptin improved UACR compared with placebo, regardless of baseline eGFR and UACR.[13,14] The apparent discordance between the minor reductions in UACR with saxagliptin without any corresponding benefit in major adverse cardiovascular events with saxagliptin may be because of a median follow-up of 2 years that may have been sufficient to improve UACR but not sufficient to observe any cardiovascular benefit. Moreover, it is not known whether UACR is a causal vs bystander marker of cardiovascular risk such that lower UACR per se would result in improved outcomes.

Limitations

Urinary albumin to creatinine ratio was only measured once at baseline in this study; thus, we cannot exclude intrapatient sampling variability. However, this imprecision would likely bias toward a weaker association between UACR and outcomes. We did not measure cystatin C in this population and therefore cannot correlate outcomes with this kidney biomarker. Changes after baseline in medications and subsequent changes in glycemic indices or blood pressure were not

Table 3. Improvements in Discrimination and Reclassification of Risk With the Addition of UACR to Clinical Model[a]

End Points	C Statistic Clinical Model Without UACR	C Statistic With UACR as Categorical	Change in C Statistic (95% CI)	LR *P* Value	Absolute IDI Adding UACR as Categorical	Relative IDI Adding UACR as Categorical	NRI at the Event Rate (95% CI)[b]
Without biomarkers							
Primary composite end point	0.666 (0.650 to 0.682)	0.690 (0.675 to 0.705)	−0.024 (−0.033 to −0.015)	<.001	0.0083 (0.0063 to 0.0103)	0.297	0.081 (0.025 to 0.161)
Secondary composite end point[c]	0.655 (0.642 to 0.667)	0.668 (0.656 to 0.681)	−0.014 (−0.020 to −0.008)	<.001	0.0094 (0.0074 to 0.0114)	0.220	0.054 (0.014 to 0.096)
Cardiovascular death	0.718 (0.694 to 0.743)	0.751 (0.728 to 0.773)	−0.033 (−0.046 to −0.019)	<.001	0.0068 (0.0042 to 0.0095)	0.241	0.129 (0.029 to 0.202)
Any cause mortality[d]	0.688 (0.668 to 0.709)	0.716 (0.697 to 0.736)	−0.028 (−0.039 to −0.017)	<.001	0.0082 (0.0060 to 0.0104)	0.306	0.127 (0.035 to 0.190)
Myocardial infarction[d]	0.676 (0.652 to 0.699)	0.695 (0.672 to 0.718)	−0.020 (−0.031 to −0.008)	<.001	0.0037 (0.0024 to 0.0050)	0.244	0.082 (−0.018 to 0.154)
Ischemic stroke	0.664 (0.631 to 0.696)	0.673 (0.642 to 0.705)	−0.010 (−0.024 to 0.004)	.003	0.0009 (0.0002 to 0.0015)	0.129	−0.014 (−0.080 to 0.138)
Hospitalization for heart failure[d]	0.781 (0.759 to 0.803)	0.807 (0.787 to 0.827)	−0.026 (−0.038 to −0.014)	<.001	0.0159 (0.0110 to 0.0209)	0.284	0.056 (−0.005 to 0.141)
Hospitalization for coronary revascularization	0.629 (0.610 to 0.648)	0.630 (0.611 to 0.649)	−0.001 (−0.004 to 0.001)	.440	0.0002 (−0.0001 to 0.0005)	0.015	0.012 (−0.036 to 0.054)
With biomarkers							
Primary composite end point	0.740 (0.724 to 0.756)	0.743 (0.727 to 0.759)	−0.003 (−0.006 to −0.0001)	.001	0.0015 (0.0003 to 0.0028)	0.024	0.022 (−0.022 to 0.067)
Secondary composite end point	0.707 (0.694 to 0.720)	0.708 (0.695 to 0.721)	−0.001 (−0.003 to 0.001)	.006	0.0017 (0.0006 to 0.0028)	0.020	−0.009 (−0.021 to 0.031)
Cardiovascular death	0.815 (0.794 to 0.836)	0.817 (0.797 to 0.838)	−0.003 (−0.006 to 0.0001)	.030	0.0014 (−0.0005 to 0.0033)	0.023	−0.008 (−0.034 to 0.053)
Any cause mortality	0.787 (0.768 to 0.806)	0.790 (0.771 to 0.809)	−0.004 (−0.007 to −0.001)	.003	0.0020 (0.0001 to 0.0039)	0.030	0.015 (−0.034 to 0.049)
Myocardial infarction[d]	0.735 (0.711 to 0.759)	0.741 (0.717 to 0.764)	−0.006 (−0.011 to 0.0002)	.005	0.0014 (0.0003 to 0.0024)	0.045	0.051(−0.035 to 0.103)
Ischemic stroke	0.708 (0.674 to 0.742)	0.710 (0.677 to 0.743)	−0.002 (−0.008 to 0.004)	.447	0.0002 (−0.0003 to 0.0007)	0.015	−0.026 (−0.069 to 0.105)
Hospitalization for heart failure	0.875 (0.860 to 0.891)	0.879 (0.863 to 0.894)	−0.003 (−0.006 to −0.001)	<.001	0.0053 (0.0015 to 0.0090)	0.051	0.043 (−0.030 to 0.052)
Hospitalization for coronary revascularization[e]	0.655 (0.634 to 0.675)	0.655 (0.635 to 0.676)	−0.0002 (−0.002 to 0.002)	.669	0.0002 (−0.0001 to 0.0005)	0.012	−0.016 (−0.044 to 0.052)

Abbreviations: IDI, integrated discrimination improvement; LR, likelihood ratio; NRI, net reclassification improvement; UACR, urinary albumin to creatinine ratio.

[a] The clinical model includes treatment arms (saxagliptin vs placebo), age (years), sex, race (white vs nonwhite), history of heart failure, duration of diabetes (<5 years, 5-9 years, 10-14 years, 15-19 years, and ≥20 years), hemoglobin A_{1C} (percentage), systolic blood pressure, prior myocardial infarction, history of hypertension, history of dyslipidemia, current smoker, estimated glomerular filtration rates (milliliters per minute), high-sensitivity troponin T quartiles, pro B-type natriuretic peptide quartiles, and C-reactive protein (<1, 1-3, >3 mg/L) for the models with biomarkers.

[b] 95% CIs based on bootstrap resampling.

[c] Age (<65 vs ≥65 years), systolic blood pressure (<120g, 120-129, 130-139, ≥140 mm Hg) and estimated glomerular filtration rates (<30, 30-60, >60 mL/min/1.73 m^2) are categorical.

[d] Age is binary (<65 vs ≥65 years).

[e] Prior heart failure was dropped from the model.

evaluated in this analysis and therefore cannot account for any differences that might influence the association between UACR and outcomes.

Conclusions

Elevated levels of UACR, even within what has been considered to be in the normal range, are independently associated with increased risk of all-cause mortality as well as across a spectrum of cardiovascular end points, even after adjusting for known cardiovascular risk factors and eGFR. In contrast, the prognostic value of UACR when evaluated in the context of cardiac biomarkers such as natriuretic peptides and high-sensitivity troponin was minimal. Thus the utility of using UACR as a tool for cardiovascular risk assessment in patients with T2D is dependent on whether established cardiac biomarkers are also being assessed simultaneously.

ARTICLE INFORMATION

Accepted for Publication: September 21, 2017.

Published Online: December 6, 2017. doi:10.1001/jamacardio.2017.4228

Author Affiliations: Thrombolysis in Myocardial Infarction Study Group, Cardiovascular Division, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (Scirica, Bhatt, Im, Kanevsky, Braunwald); Diabetes Unit, Division of Internal Medicine, Hadassah Hebrew University Hospital, Jerusalem, Israel (Mosenzon, Raz); Women's College Research Institute and Cardiovascular Division, Department of Medicine, Women's College Hospital, Toronto, Ontario, Canada (Udell); Peter Munk Cardiac Centre, University Health Network, University of Toronto, Toronto, Ontario, Canada (Udell); Département Hospitalo-Universitaire Fibrosis, Inflammation and REmodeling, INSERM U-1148, Université Paris-Diderot, Hôpital Bichat, Assistance Publique–Hôpitaux de Paris, Paris, France (Steg); National Heart and Lung Institute, Imperial College, Institute of Cardiovascular Medicine and Sciences, Royal Brompton Hospital, London, United Kingdom (Steg); Division of Cardiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas (McGuire); AstraZeneca R&D, Gothenburg, Sweden (Stahre, Sjöstrand).

Corresponding Author: Benjamin M. Scirica, MD, MPH, Thrombolysis in Myocardial Infarction Study Group, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115 (bscirica@partners.org).

Author Contributions: Dr Scirica had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Scirica and Mosenzon served as co-first authors and contributed equally to the work.
Study concept and design: Scirica, Mosenzon, Bhatt, Udell, Steg, McGuire, Bruanwald.
Acquisition, analysis, or interpretation of data: Scirica, Mosenzon, Bhatt, Udell, Steg, McGuire, Im, Kanevsky, Stahre, Sjostrand, Raz.
Drafting of the manuscript: Scirica.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Im, Kanevsky.
Obtained funding: Bhatt, Bruanwald.
Administrative, technical, or material support: Scirica, Stahre, Sjostrand, Bruanwald.
Study supervision: Scirica, Bhatt, Im, Sjostrand, Raz, Bruanwald.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Scirica reports research grants from AstraZeneca, Eisai, Merck, and Poxel; consulting fees from AstraZeneca, Biogen Idec, Boehringer Ingelheim, Covance, Dr Reddy's Laboratory, Elsevier Practice Update Cardiology, GlaxoSmithKline, Lexicon, Merck, NovoNordisk, Sanofi, St. Jude's Medical; and equity in Health[at]Scale. Dr Mosenzon is on the advisory board of Novo Nordisk, Eli Lilly, Sanofi, Merck Sharp & Dohme, Boehringer Ingelheim, Jansen and Jansen, Novartis, and AstraZeneca; receives grants paid to institution as study physician by AstraZeneca and Bristol-Myers Squibb; receives research grant support through Hadassah Hebrew University Hospital and Novo Nordisk; and is on the speaker's bureau for AstraZeneca, Bristol-Myers Squibb, Novo Nordisk, Eli Lilly, Sanofi, Novartis, Merck, Sharp & Dohme, and Boehringer Ingelheim. Dr Bhatt is on the advisory board for Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences; is on the board of directors for Boston VA Research Institute and the Society of Cardiovascular Patient Care; is a chair for the American Heart Association Quality Oversight Committee; is on the data monitoring committees for Cleveland Clinic, Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine, and Population Health Research Institute; receives honoraria from the American College of Cardiology (senior associate editor), Clinical Trials and News, ACC.org, Belvoir Publications (editor, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (editor, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (guest editor; associate editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (chief medical editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (secretary/treasurer), and WebMD (continuing medical education steering committees); is deputy editor of *Clinical Cardiology*; chair of National Cardiovascular Data Registry-ACTION Registry Steering Committee and VA CART Research and Publications Committee (Chair); has received research funding from Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Ironwood, Ischemix, Lilly, Medtronic, Pfizer, Roche, Sanofi Aventis, and The Medicines Company; receives royalties from Elsevier (editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); is a site co-investigator at Biotronik, Boston Scientific, and St. Jude Medical (now Abbott); is a trustee at American College of Cardiology; and has unfunded research with FlowCo, Merck, PLx Pharma, and Takeda. Dr Udell reports grants from AstraZeneca and Bristol-Myers Squibb; personal fees/honoraria for advisory board participation from Janssen, Merck, Sanofi Pasteur, and Novartis outside the submitted work; and grants from Novartis for participation as a site investigator in a clinical trial. Dr Steg reports grants from Merck, Sanofi, and Servier; personal fees from Amarin, AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers-Squibb, CSL-Behring, Daiichi-Sankyo, GlaxoSmithKline, Janssen, Lilly, Novartis, Pfizer, Regeneron, Roche, Sanofi, Servier, and the Medicines Company, outside the submitted work. Dr McGuire reports receiving personal fees for clinical trial leadership from Boehringer-Ingelheim, Janssen Research and Development LLC, Merck Sharp and Dohme, Lilly USA, Novo Nordisk, GlaxoSmithKline, Takeda Pharmaceuticals North America, AstraZeneca, Lexicon, Eisai, and Akebia Pharmaceuticals; and personal consulting fees from Sanofi-Aventis Group, Merck Sharp and Dohme, Novo Nordisk, Lilly USA, and Regeneron. Dr Im and Ms Kanevsky report research funding via the TIMI Study and Brigham and Women's Hospital from AstraZeneca. Drs Stahre and Sjöstrand are employees of AstraZeneca. Dr Raz reports being on the advisory board of AstraZeneca/Bristol-Meyers Squibb, Eli Lilly and Company, Merck Sharp and Dohme Limited, Novo Nordisk, Inc, Sanofi, Orgenesis, SmartZyme Innovation Ltd, Labstyle Innovations Ltd, and Boehringer Ingelheim; consulting for AstraZeneca/Bristol-Meyers Squibb, Insuline Medical, Gili Medical, Kamada Ltd, FuturRx Ltd, Nephrogenex Inc, and Diabetes Medical Center (Tel Aviv, Israel); being on the speaker's bureau for AstraZeneca/Bristol-Meyers Squibb, Eli Lilly and Company, Johnson & Johnson, Merck Sharp and Dohme Limited, Novartis Pharma AG, Novo Nordisk, Inc, Sanofi, Teva, and Boehringer Ingelheim; being a stock shareholder of Insuline Medical, Labstyle Innovations, SmartZyme Innovation Ltd, Orgenesis, and Glucome Ltd. Dr Braunwald reports grants from AstraZeneca, Daiichi-Sankyo, GlaxoSmithKline, Merck, and Novartis; personal fees from the Medicines Company, Theravance, Daiichi Sankyo, Menarini International, and Medscape; and uncompensated consultancies and lectures from Merck and Novartis.

Funding/Support: This study was supported by AstraZeneca and Bristol-Myers Squibb.

Role of the Funder/Sponsor: The Thrombolysis in Myocardial Infarction Study Group, Hadassah Medical Organization, and the sponsors were responsible for the design and conduct of the study. The Thrombolysis in Myocardial Infarction Study Group and Hadassah Medical Organization are responsible for the current analysis, collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. *JAMA*. 2011;305(24):2532-2539.

2. Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf. Published January 2013. Accessed September 28, 2017.

3. Levey AS, Becker C, Inker LA. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. *JAMA*. 2015;313(8):837-846.

4. Molitch ME, Adler AI, Flyvbjerg A, et al. Diabetic kidney disease: a clinical update from Kidney Disease: improving global outcomes. *Kidney Int*. 2015;87(1):20-30.

5. American Diabetes Association. Microvascular complications and foot care. *Diabetes Care*. 2016;39(suppl 1):S72-S80.

6. Gerstein HC, Mann JF, Yi Q, et al; HOPE Study Investigators. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA*. 2001;286(4):421-426.

7. Fox CS, Matsushita K, Woodward M, et al; Chronic Kidney Disease Prognosis Consortium. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet*. 2012;380(9854):1662-1673.

8. Tonelli M, Muntner P, Lloyd A, et al; Alberta Kidney Disease Network. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. *Lancet*. 2012;380(9844):807-814.

9. Matsushita K, Coresh J, Sang Y, et al; CKD Prognosis Consortium. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol*. 2015;3(7):514-525.

10. Preiss D, Thomas LE, Sun JL, et al. Predictors of cardiovascular events in a contemporary population with impaired glucose tolerance: an observational analysis of the Nateglinide and Valsartan in impaired glucose tolerance outcomes research (NAVIGATOR) trial. *BMJ Open*. 2012;2(6):e001925.

11. Scirica BM, Bhatt DL, Braunwald E, et al. The design and rationale of the saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus-thrombolysis in myocardial infarction (SAVOR-TIMI) 53 study. *Am Heart J*. 2011;162(5):818-825.e6.

12. 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(18):1579-1588.

13. Scirica BM, Bhatt DL, Braunwald E, et al; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369(14):1317-1326.

14. Mosenzon O, Bhatt DL, Litwak LE, et al Effect of saxagliptin on renal outcomes in the SAVOR-TIMI 53 Trial. *Diabetes Care*. 2014;57(suppl 1):S84.

15. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association Task Force on clinical data standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). American College of Cardiology. http://www.acc.org/latest-in-cardiology/ten-points-to-remember/2015/01/07/17/59/2014-acc-aha-key-data-elements-and-definitions. Accessed September 28, 2017.

16. Demler OV, Paynter NP, Cook NR. Tests of calibration and goodness-of-fit in the survival setting. *Stat Med*. 2015;34(10):1659-1680.

17. Harrell FE Jr, Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modelling strategies for improved prognostic prediction. *Stat Med*. 1984;3(2):143-152.

18. Pencina MJ, Steyerberg EW, D'Agostino RB Sr. Net reclassification index at event rate: properties and relationships [published online July 18, 2016]. *Stat Med*.

19. Pencina MJ, D'Agostino RB, Pencina KM, Janssens AC, Greenland P. Interpreting incremental value of markers added to risk prediction models. *Am J Epidemiol*. 2012;176(6):473-481.

20. Everett BM, Brooks MM, Vlachos HE, Chaitman BR, Frye RL, Bhatt DL; BARI 2D Study Group. Troponin and cardiac events in stable ischemic heart disease and diabetes. *N Engl J Med*. 2015;373(7):610-620.

21. Scirica BM, Bhatt DL, Braunwald E, et al. Prognostic implications of biomarker assessments in patients with type 2 diabetes at high cardiovascular risk: a secondary analysis of a randomized clinical trial. *JAMA Cardiol*. 2016;1(9):989-998.

22. Standards of medical care in diabetes–2015: summary of revisions. *Diabetes Care*. 2015;38(suppl):S4.

23. Jackson CE, Solomon SD, Gerstein HC, et al; CHARM Investigators and Committees. Albuminuria in chronic heart failure: prevalence and prognostic importance. *Lancet*. 2009;374(9689):543-550.

24. Masson S, Latini R, Milani V, et al; GISSI-HF Investigators. Prevalence and prognostic value of elevated urinary albumin excretion in patients with chronic heart failure: data from the GISSI-Heart Failure trial. *Circ Heart Fail*. 2010;3(1):65-72.

25. Blecker S, Matsushita K, Köttgen A, et al. High-normal albuminuria and risk of heart failure in the community. *Am J Kidney Dis*. 2011;58(1):47-55.

26. Hockensmith ML, Estacio RO, Mehler P, et al. Albuminuria as a predictor of heart failure hospitalizations in patients with type 2 diabetes. *J Card Fail*. 2004;10(2):126-131.

27. Vaur L, Gueret P, Lievre M, Chabaud S, Passa P; DIABHYCAR Study Group (type 2 DIABetes, Hypertension, CARdiovascular Events and Ramipril) study. Development of congestive heart failure in type 2 diabetic patients with microalbuminuria or proteinuria: observations from the DIABHYCAR (type 2 DIABetes, Hypertension, CArdiovascular Events and Ramipril) study. *Diabetes Care*. 2003;26(3):855-860.

28. Udell JA, Bhatt DL, Braunwald E, et al; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes and moderate or severe renal impairment: observations from the SAVOR-TIMI 53 Trial. *Diabetes Care*. 2015;38(4):696-705.

29. Astor BC, Matsushita K, Gansevoort RT, et al; Chronic Kidney Disease Prognosis Consortium. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease: a collaborative meta-analysis of kidney disease population cohorts. *Kidney Int*. 2011;79(12):1331-1340.

30. Gansevoort RT, Matsushita K, van der Velde M, et al; Chronic Kidney Disease Prognosis Consortium. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes: a collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int*. 2011;80(1):93-104.

31. Matsushita K, van der Velde M, Astor BC, et al; Chronic Kidney Disease Prognosis Consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010;375(9731):2073-2081.

32. Waheed S, Matsushita K, Sang Y, et al. Combined association of albuminuria and cystatin C-based estimated GFR with mortality, coronary heart disease, and heart failure outcomes: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis*. 2012;60(2):207-216.

33. Gori M, Gupta DK, Claggett B, et al. Natriuretic peptide and high-sensitivity troponin for cardiovascular risk prediction in diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. *Diabetes Care*. 2016;39(5):677-685.

34. Clodi M, Resl M, Neuhold S, et al. A comparison of NT-proBNP and albuminuria for predicting cardiac events in patients with diabetes mellitus. *Eur J Prev Cardiol*. 2012;19(5):944-951.

35. Olsen MH, Wachtell K, Nielsen OW, et al. N-terminal brain natriuretic peptide predicted cardiovascular events stronger than high-sensitivity C-reactive protein in hypertension: a LIFE substudy. *J Hypertens*. 2006;24(8):1531-1539.

36. Ruggenenti P, Porrini E, Motterlini N, et al; BENEDICT Study Investigators. Measurable urinary albumin predicts cardiovascular risk among normoalbuminuric patients with type 2 diabetes. *J Am Soc Nephrol*. 2012;23(10):1717-1724.

37. Mori H, Okada Y, Arao T, Tanaka Y. Sitagliptin improves albuminuria in patients with type 2 diabetes mellitus. *J Diabetes Investig*. 2014;5(3):313-319.

38. Barnett AH, Mithal A, Manassie J, et al; EMPA-REG RENAL trial investigators. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2014;2(5):369-384.

39. Marso SP, Daniels GH, Brown-Frandsen K, et al; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375(4):311-322.