Effect of Saxagliptin on Renal Outcomes in the SAVOR-TIMI 53 Trial

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OBJECTIVE

Dipeptidyl peptidase 4 inhibitors may have a protective effect in diabetic nephropathy.

RESEARCH DESIGN AND METHODS

We studied renal outcomes of 16,492 patients with type 2 diabetes, randomized to saxagliptin versus placebo and followed for a median of 2.1 years in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial.

RESULTS

At baseline, 9,696 (58.8%) subjects had normoalbuminuria (albumin/creatinine ratio [ACR] <30 mg/g), 4,426 (26.8%) had microalbuminuria (ACR 30–300 mg/g), and 1,638 (9.9%) had macroalbuminuria (ACR >300 mg/g). Treatment with saxagliptin was associated with improvement in and/or less deterioration in ACR categories from baseline to end of trial (EOT) (P = 0.021, P < 0.001, and P = 0.049 for individuals with baseline normoalbuminuria, microalbuminuria, and macroalbuminuria, respectively). At 2 years, the difference in mean ACR change between saxagliptin and placebo arms was −19.3 mg/g (P = 0.033) for estimated glomerular filtration rate (eGFR) >50 mL/min/body surface area per 1.73 m^2 (BSA), −105 mg/g (P = 0.011) for 50 ≥ eGFR ≥ 30 mL/min/BSA, and −245.2 mg/g (P = 0.086) for eGFR <30 mL/min/BSA. Analyzing ACR as a continuous variable showed reduction in ACR with saxagliptin (1 year, P < 0.0001; 2 years, P = 0.0143; and EOT, P = 0.0158). The change in ACR did not correlate with that in HbA_{1c} (r = 0.041, 0.052, and 0.036; 1 year, 2 years, and EOT, respectively). The change in eGFR was similar in the saxagliptin and placebo groups. Safety renal outcomes, including doubling of serum creatinine, initiation of chronic dialysis, renal transplantation, or serum creatinine >6.0 mg/dL, were similar as well.

CONCLUSIONS

Treatment with saxagliptin improved ACR, even in the normoalbuminuric range, without affecting eGFR. The beneficial effect of saxagliptin on albuminuria could not be explained by its effect on glycemic control.

Diabetic nephropathy is the most common cause for end-stage renal disease (ESRD) (1). The earliest major clinical manifestation of diabetic nephropathy is albuminuria, which occurs in most, but not all, patients with diabetic kidney disease (2,3). Albuminuria is associated with the progression of diabetic nephropathy and premature cardiovascular disease (CVD) (4–6). Several clinical trials have shown that decreased

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albuminuria in response to treatment with ACE inhibitors (ACEI) or angiotensin receptor blockers (ARBs) is associated with slower progression of both renal and CVD (7–11).

There is growing evidence that the use of incretin-based therapies, specifically dipeptidyl peptidase 4 (DPP-4) inhibitors, may ameliorate albuminuria (12–15). The protective effects of DPP-4 inhibitors against albuminuria may be mediated by increasing glucagon-like peptide 1 (GLP-1) levels. The latter may protect renal cells from hyperglycemia-induced oxidative stress by increasing cAMP and consequently activating cAMP-dependent protein kinase, which inhibits NAD(P)H oxidase, a major source of superoxide generation (16).

The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial randomized 16,492 patients with type 2 diabetes (T2D) with high CV risk and varying degrees of renal function and albuminuria to treatment with the DPP-4 inhibitor saxagliptin or placebo and followed them prospectively for a median of 2.1 years (17). We report in this study the predefined exploratory end points of renal safety and efficacy in the SAVOR-TIMI 53 trial as well as analyses of the ACR change over time in this large and heterogeneous population of subjects with diabetes.

RESEARCH DESIGN AND METHODS

Study Design, Patients, and Primary and Secondary End Points

SAVOR-TIMI 53 was a multicenter, multinational, randomized, double-blind, placebo-controlled trial that followed 16,492 patients, previously described in detail (18,19). Inclusion criteria were T2D, HbA_{1c} between 6.5 and <12.0% (47.5 and <107.7 mmol/mol) within 6 months of randomization, and either a history of established CVD or multiple risk factors (MRF) for CVD. Patients were randomized to receive either saxagliptin 5 mg daily (or 2.5 mg daily in patients with an estimated glomerular filtration rate [eGFR] of ≤50 mL/min/body surface area per 1.73 m^2 [BSA]) or matching placebo. A history of ESRD on chronic dialysis, renal transplant, a serum creatinine >6.0 mg/dL, or eGFR <15 mL/min/BSA were exclusion criteria.

The number of patients with moderate to severe renal impairment (eGFR <50 mL/min/BSA) was prespecified to be at least 800, with 300 of them with severe renal impairment (eGFR <30 mL/min/BSA) (20). Randomization to saxagliptin or placebo was stratified by baseline renal function category and CVD status (established CVD vs. MRF). The study protocol was approved by the relevant institutional review board at each participating site, and written informed consent was obtained from all patients. The primary results of the SAVOR-TIMI 53 trial have been reported previously (17).

Predefined Renal Baseline Characteristics and Renal Outcomes

Blood samples sent to the central laboratory (QuintilesIMS) were analyzed at the combined screening and randomization visit, at 1 year (>180 and <540 days from randomization), 2 years (≥540 and <900 days), and at the end-of-trial (EOT) visit. Creatinine levels were directly measured, and the eGFR was determined according to the Modification of Diet in Renal Disease formula (21). eGFR was predefined both as a continuous and categorical variable: normal or mildly reduced renal function (eGFR >50 mL/min/BSA), moderate renal dysfunction (eGFR 30–50 mL/min/BSA), and severe renal dysfunction (eGFR <30 mL/min/BSA). All eGFR analyses were performed on the intention-to-treat population.

Urinary albumin and creatinine were measured at the central laboratory in a single voided urine sample, and albumin-to-creatinine ratio (ACR; mg/g and mg/mmol) was calculated. ACR was analyzed both as a continuous and categorical variable. The predefined ACR categories were (20): ACR <30 mg/g (<3.4 mg/mmol) defined as normoalbuminuria (further split into ACR <15 mg/g and 15 ≤ ACR < 30 mg/g), ACR 30–300 mg/g (3.4–34.0 mg/mmol) defined as microalbuminuria (also called high albuminuria) (further subdivided into 30 ≤ ACR <100 mg/g and 100 ≤ ACR ≤ 300 mg/g), and ACR >300 mg/g (>34.0 mg/mmol) defined as macroalbuminuria (also called very high albuminuria).

The predefined renal efficacy end points included:

- New and/or progression of diabetic nephropathy
  - Change from baseline in ACR
  - Categorical change from baseline in ACR
  - Doubling of serum creatinine levels (time to first event)
  - Initiation of chronic dialysis and/or renal transplant and/or serum creatinine >6.0 mg/dL (530 μmol/L) (time to first event)
- Time to first event of the composite end point of death, doubling of serum creatinine levels or creatinine >6.0 mg/dL (530 μmol/L), initiation of chronic dialysis, and/or renal transplantation.

Statistical Analysis

Baseline characteristics were analyzed according to baseline ACR categories. To assess the difference between ACR <30 mg/g and ACR ≥30 mg/g, a median two-sample test (Brown-Mood test) for continuous variables and χ^2 test for categorical variables was used. Single and multivariable analyses were performed to test the association between continuous ACR at baseline and the following baseline characteristics: age, sex, race, BMI, duration of diabetes, current smoker, history of CVD, HbA_{1c}, fasting plasma glucose, eGFR, ACEI, ARB, β-blockers, statin, aspirin, sulfonylurea, metformin, insulin, and thiazolidinediones. This model was performed using a log transformation of ACR because of its skewed nature. Similar models (without log transformation) were performed for eGFR.

Time-to-event analyses were done using the Cox proportional hazards model stratified by baseline CV risk group and baseline renal function category, with treatment as a model term.

Change in ACR categories was tested separately for each baseline ACR category and expressed as the proportion of patients who shifted in ACR categories from baseline to EOT by treatment arm. The difference between arms at each baseline level was tested using χ^2 test.

The change from baseline in ACR assessed as a continuous variable by baseline eGFR categories was analyzed using repeated-measures ANOVA, with baseline CV risk group (previous CVD or MRF) and treatment arm as model terms. The difference in the distributions of the change from baseline in ACR by treatment arms was analyzed using a Kolmogorov-Smirnov test.

Post hoc analyses were performed to analyze the relation between change in ACR and glycemic control using both

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Pearson correlation coefficients and compression of changes in ACR categories according to decrease in HbA_{1c} levels using the χ^2 test.

All analyses were conducted on an intention-to-treat basis among patients who underwent randomization. Post-randomization ACR values were based on measurements made during the on-treatment period. The statistical software package SAS (version 9.3; SAS Institute, Cary, NC) was used for all analyses with a two-sided P value <0.05 considered to be statistically significant. No adjustment was made for multiple comparisons. All analyses were performed by Worldwide Clinical Trials and validated by Hadassah and TIMI statisticians.

RESULTS

Baseline Characteristics

Of the 16,492 patients, 13,916 (84.4%) had normal or mildly impaired renal function, 2,240 (13.6%) had moderate renal impairment, and 336 (2.0%) had severe renal impairment. A total of 9,696 (58.8%) patients had normoalbuminuria, 4,426 (26.8%) patients had microalbuminuria, 1,638 (9.9%) patients had macroalbuminuria, and 732 (4.4%) patients had no ACR measurement at baseline. The saxagliptin and placebo arms were balanced with regard to baseline eGFR and ACR categories. The population distribution by eGFR and ACR categories at baseline, 1 year, and EOT is shown (Supplementary Table 1). The number of patients in each eGFR and ACR group at baseline was balanced between treatment arms. Although there was a tendency for higher ACR values with lower eGFR categories, there were still a substantial number of patients with normoalbuminuria among those with reduced eGFR (Supplementary Fig. 1). Of those patients, 44.4 and 19.5% with moderate and severe renal impairment, respectively, had normoalbuminuria (Supplementary Fig. 1).

Subjects with abnormal ACR at baseline were more likely to be non-Caucasian, Hispanic, and have a longer duration of diabetes (Table 1). Abnormal ACR was also associated with higher prevalence of established CVD, prior heart failure, hypertension, and hyperlipidemia. Abnormal ACR at baseline was strongly associated with higher creatinine and lower eGFR. Patients with abnormal ACR at baseline had higher median HbA_{1c} (7.5 vs. 7.9 vs. 8.2% [58.5 vs. 62.8 vs. 66.1 mmol/mol]) and were more likely to have poor glycemic control ($HbA_{1c} \geq 9\%$ [>74.9 mmol/mol]) compared with patients with normal ACR.

Multivariable analyses were used to define baseline characteristics associated with higher baseline ACR and lower eGFR as continuous variables (Supplementary Table 2). Sex, race, BMI, smoking status, history of CVD, and β-blocker and statin use were associated with eGFR, whereas treatment with ACEI and thiazolidinediones was associated with ACR, but not with eGFR.

Renal Safety Outcomes

There were no meaningful differences in any of the prespecified renal safety outcomes between saxagliptin and placebo treatment arms: doubling of serum creatinine occurred in 183 (2.02%) versus 166 (1.82%) subjects (hazard ratio [HR] 1.1 [95% CI 0.89–1.36]) and initiation of chronic dialysis, renal transplant, or serum creatinine >6.0 mg/dL occurred in 51 (0.61%) versus 55 (0.67%) subjects (HR 0.90 [0.61–1.32]), respectively. The composite end point of death and any of the above occurred in 577 (6.58%) versus 528 (5.86%) subjects (HR 1.08 [0.96–1.22]). The overall change in eGFR during follow-up was similar in the saxagliptin and placebo arms, as well as in the different ACR and eGFR categories (at the EOT, the mean change from baseline was -2.49 vs. -2.36 mL/min in the saxagliptin and placebo groups, respectively; $P = 0.5794$).

The Effect of Saxagliptin Versus Placebo on the Change in ACR

The difference in mean change in ACR between saxagliptin arm and placebo arm at 2 years was -34.3 mg/g ($P < 0.004$), mainly driven by the difference in change in ACR among patients with ACR >300 mg/g at baseline (-283 mg/g; $P = 0.002$). A three-way shift table showing the change in ACR category from baseline to the EOT (Table 2) shows a significant difference between the saxagliptin and placebo treatment groups. Among those assigned to saxagliptin, a higher percentage of patients shifted to a lower ACR category, and a smaller fraction had increased ACR, irrespective of baseline ACR category ($P = 0.021$ for normoalbuminuria, $P < 0.001$ for microalbuminuria, and $P = 0.049$ for macroalbuminuria). Similar findings were obtained when ACR was divided into five categories (<15, 15 to <30, 30 to <100, 100–300, and >300 mg/g) (Supplementary Table 3).

Stratification of the mean change in ACR by baseline eGFR categories for the saxagliptin and placebo groups at 1 and 2 years is shown in Fig. 1. Comparing the mean difference in ACR from baseline to 2 years, between saxagliptin and placebo arms (within each of the eGFR categories), there was a larger decrease for the saxagliptin arm: -19.3 mg/g ($P = 0.033$) for eGFR >50 mL/min/BSA, -105 mg/g ($P = 0.011$) for $50 \geq$ eGFR ≥ 30 mL/min/BSA, and -245.2 mg/g ($P = 0.086$) for eGFR <30 mL/min/BSA. Similar results were found for the mean difference from baseline to 1 year.

Analyzing ACR as a continuous variable revealed that treatment with saxagliptin compared with placebo was associated with decreased albuminuria at all time points ($P < 0.05$ at 1 and 2 years and EOT) (Supplementary Fig. 2).

Correlation Between Changes in ACR and Changes in HbA_{1c} (on Treatment Analysis)

During follow-up, there was a mean HbA_{1c} difference of 0.3% in favor of saxagliptin at all time points (17). We aimed to ascertain the impact of glycemia on ACR by correlating the changes in HbA_{1c} and ACR. For the entire trial population, a very weak correlation was demonstrated between the change in ACR and HbA_{1c} at all time points (Pearson coefficients: 0.041, 0.052, and 0.036, respectively). Similar findings were obtained for the saxagliptin and placebo treatment arms (Pearson coefficients at 1 year: 0.036 and 0.038; and 0.050 and 0.047 at 2 years in the saxagliptin and placebo treatment groups, respectively).

To further investigate correlation between changes in glucose control and ACR, patients with microalbuminuria at baseline were divided into those who experienced a $\geq 0.5\%$ decrease of HbA_{1c} compared with those whose HbA_{1c} decreased by $<0.5\%$, remained unchanged, or increased (Fig. 2). Treatment with saxagliptin was associated

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Table 1—Baseline characteristics according to ACR

Characteristic	ACR <30 mg/g (*n* = 9,696)	ACR 30–300 mg/g (*n* = 4,426)	ACR >300 mg/g (*n* = 1,638)	*P* value (between <30 mg/g and all other ACRs)
Demographic characteristics and baseline measurements				
Age (years), median (IQR)	65 (59–70)	66 (60–72)	64 (59–71)	<0.0001
Male sex, *n* (%)	6,398 (66)	3,052 (69)	1,105 (67.5)	0.0009
Race (Caucasian), *n* (%)	7,519 (77.5)	3,213 (72.6)	1,047 (63.9)	<0.0001
Ethnicity (Hispanic/Latino), *n* (%)	1,940 (20.0)	1,011 (22.8)	482 (29.4)	<0.0001
Weight (kg), median (IQR)	86.2 (75–99.7)	85.6 (74–99)	84.6 (72.1–99.5)	0.0166
BMI (kg/m^2), median (IQR)	30.5 (27.2–34.4)	30.3 (27.2–34.3)	30.6 (27.1–34.6)	0.5121
BMI >30 (kg/m^2), *n* (%)	5,172 (53.3)	2,322 (52.5)	899 (54.9)	0.7964
Duration of diabetes, median (IQR)	9.3 (4.4–15.3)	11.2 (6.0–18.5)	14.7 (9.1–20.6)	<0.0001
Current smoker, *n* (%)	1,256 (13.0)	608 (13.7)	224 (13.7)	0.1673
Established CVD, *n* (%)	7,369 (76.0)	3,604 (81.4)	1,371 (83.7)	<0.0001
Dyslipidemia, *n* (%)	6,761 (69.7)	3,228 (72.9)	1,224 (74.7)	<0.0001
Hypertension, *n* (%)	7,780 (80.2)	3,701 (83.6)	1,420 (86.7)	<0.0001
Coronary artery disease	5,943 (61.3)	2,830 (63.9)	990 (60.4)	0.0323
Prior MI, *n* (%)	3,670 (37.9)	1,683 (38.0)	580 (35.4)	0.5024
Prior heart failure, *n* (%)	1,169 (12.1)	571 (12.9)	246 (15.0)	0.0090
Prior coronary revascularization, *n* (%)	4,055 (41.8)	2,004 (45.3)	678 (41.4)	0.0030
Creatinine (μmol/L), median (IQR)	83 (71–98)	88 (73–109)	103 (82–141)	<0.0001
eGFR (mL/min/BSA), median (IQR)	74.1 (61.2–88.3)	69.6 (55.0–85.4)	56.9 (41.4–75.2)	<0.0001
eGFR by category (mL/min/BSA), *n* (%)				
>50	8,691 (89.6)	3,624 (81.9)	1,004 (61.3)	<0.0001
50–30	944 (9.7)	708 (16.0)	476 (29.1)	
<30	61 (0.6)	94 (2.1)	158 (9.6)	
HbA_{1c} (%), median (IQR)	7.5 (6.8–8.4)	7.9 (7.1–9.1)	8.2 (7.3–9.4)	<0.0001
HbA_{1c} <7%, *n* (%)	2,903 (29.9)	856 (19.3)	234 (14.3)	<0.0001
HbA_{1c} ≥9%, *n* (%)	1,643 (16.9)	1,218 (27.5)	554 (33.8)	<0.0001
Fasting serum glucose (mg/dL), median (IQR)	141 (117–174)	151 (121–192)	155 (118–201)	<0.0001
Baseline CV medications, *n* (%)				
Aspirin	7,299 (75.3)	3,322 (75.1)	1,211 (73.9)	0.4578
Statins	7,585 (78.2)	3,448 (77.9)	1,277 (78.0)	0.6478
β-Blockers	5,900 (60.8)	2,751 (62.2)	1,018 (62.1)	0.1019
Diuretics	4,080 (42.1)	1,954 (44.1)	850 (51.9)	<0.0001
ACEI	5,322 (54.9)	2,374 (53.6)	857 (52.3)	0.0488
ARB	2,504 (25.8)	1,313 (29.7)	579 (35.3)	<0.0001
Calcium antagonists	2,737 (28.2)	1,645 (37.2)	764 (46.6)	<0.0001
Baseline antihyperglycemic medications	9,146 (94.3)	4,290 (96.9)	1,584 (96.7)	<0.0001
Metformin	6,945 (71.6)	3,061 (69.2)	928 (56.7)	<0.0001
Sulfonylurea	3,976 (41.0)	1,793 (40.5)	574 (35.0)	0.0140
Thiazolidinediones	586 (6.0)	268 (6.1)	80 (4.9)	0.4302
Insulin	3,428 (35.4)	2,075 (46.9)	991 (60.5)	<0.0001
None	550 (5.7)	136 (3.1)	54 (3.3)	<0.0001

Statistical tests were produced to test the difference between ACR <30 and ≥30 mg/g groups using a median two-sample test (Brown-Mood test) for continuous variables and χ^2 test for categorical variables. IQR, interquartile range; MI, myocardial infarction.

with a similar decrease of albuminuria, irrespective of the change in HbA_{1c}.

CONCLUSIONS

The SAVOR-TIMI 53 study included a large population of patients with T2D at high CV risk with diverse baseline renal characteristics, including a substantial number of patients with renal dysfunction and/or albuminuria. Treatment with saxagliptin was found to be safe with regard to renal outcomes; however, the study did not demonstrate improvement in hard renal outcomes such as doubling of creatinine or initiation of renal replacement therapy. The main finding of this prespecified secondary analysis is that treatment with saxagliptin was associated with a reduction in ACR compared with placebo. The clinical significance of this observation is not known. The improvement in ACR was observed when ACR was analyzed as either a continuous or categorical variable at all baseline ACR and eGFR categories. Because the association between ACR levels and increased CV risk can be demonstrated even within the normoalbuminuric range, ACR reduction by saxagliptin in this range might have future possible positive effects not demonstrated in the present trial (22). Lastly, decreased ACR in saxagliptin-treated patients seemed to be independent of saxagliptin's effect on glycemia. The clinical significance of the reduction of albuminuria by saxagliptin, without any effect on other renal outcomes, on the development

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Table 2—Change in categorical ACR (<30, 30–300, and >300 mg/g) from baseline to EOT by baseline ACR categories and treatment arms

		ACR at EOT					
		Saxagliptin			Placebo		
ACR at baseline (mg/g)	*P* value	<30	30–300	>300	<30	30–300	>300
<30	0.021*	3,152 (84.2)[a]	555 (14.8)[d]	36 (1.0)[e]	2,993 (82.2)[a]	617 (16.9)[d]	31 (0.8)[e]
30–300	<0.001**	451 (28.9)[b]	929 (59.5)[a]	181 (11.6)[d]	352 (23.4)[b]	904 (60.1)[a]	249 (16.5)[d]
>300	0.049***	23 (4.3)[c]	148 (27.7)[b]	363 (68.0)[a]	15 (3.0)[c]	115 (23.4)[b]	362 (73.6)[a]

**P* value is based on a two-tailed normal distribution approximation test for the proportion of patients who worsened; ***P* value is based on a χ^2 test for independence; ****P* value is based on a two-tailed normal distribution approximation test for the proportion of patients who improved. *P* values were calculated for each level of ACR at baseline separately. [a]The number of patients (%) at each ACR category at baseline, with no change in ACR category to EOT. [b]The number of patients (%) at each ACR category at baseline, with improvement in one ACR category to EOT. [c]The number of patients (%) at each ACR category at baseline, with improvement in two ACR categories to EOT. [d]The number of patients (%) at each ACR category at baseline, with worsening in one ACR category to EOT. [e]The number of patients (%) at each ACR category at baseline, with worsening in two ACR categories to EOT.

and progression of renal dysfunction and CV morbidity is unknown.

Evidence regarding the beneficial effect of DPP-4 inhibitors on ACR is mounting. This has been previously demonstrated for sitagliptin (12,13,23), linagliptin (14,15), and vildagliptin (24); however, these studies were relatively small, with some being retrospective observational (12,23), uncontrolled (12,23,24), or post hoc meta-analyses (14,15). The majority of these studies analyzed the effects of DPP-4 inhibitors on ACR only in patients with prevailing albuminuria and not in patients with albumin excretion within the normal range (13–16,23,24).

In the SAVOR-TIMI 53 trial, ~80% of the patients were treated with ACEI and/or ARB at baseline and during follow-up (17). Blockade of the renin angiotensin aldosterone system is the backbone of treatment of diabetic nephropathy (1). The addition of saxagliptin to this population further reduced ACR and was not associated with increased risk of hyperkalemia or acute renal failure.

ACEI and ARB have been previously shown to be beneficial in reducing the progression of albuminuria only in patients with microalbuminuria and macroalbuminuria, and not in normoalbuminuric patients, thus presenting a potential benefit that may be unique to this drug or class (22,25). The reduction of ACR in the normoalbuminuric range might be important, considering the finding that the rate of adverse CV

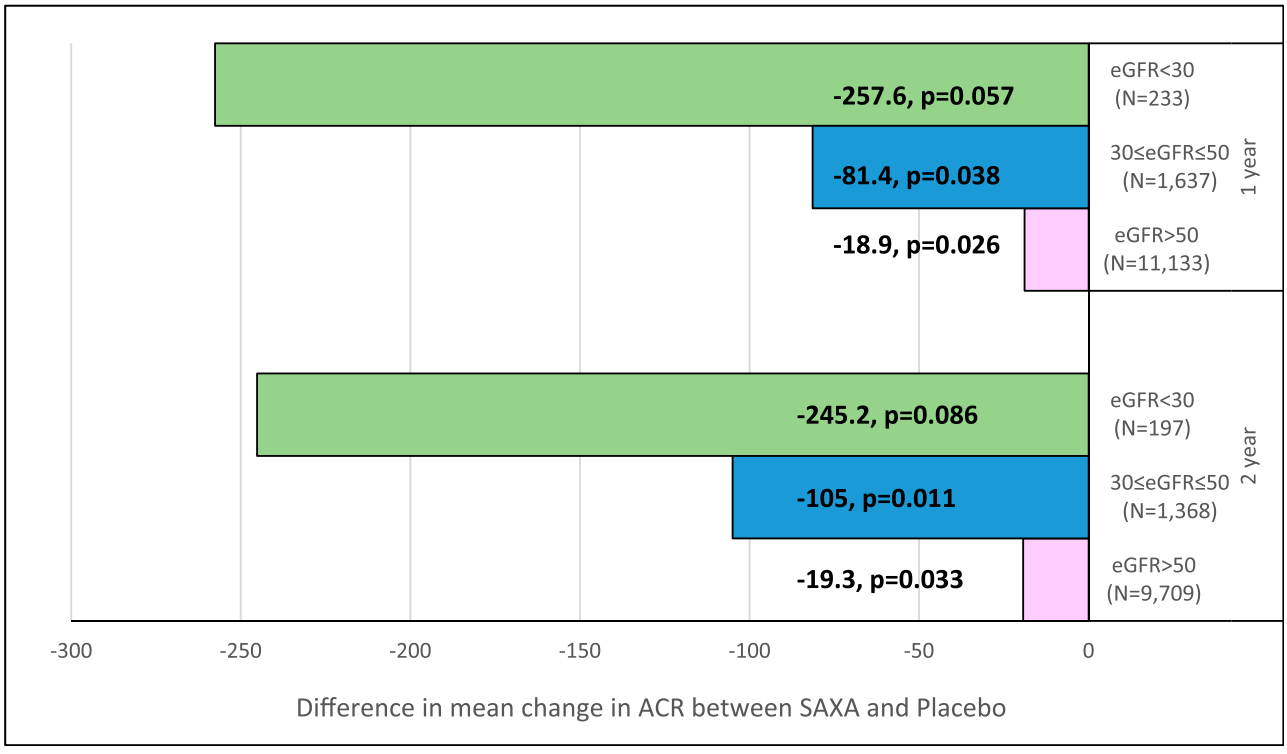

Figure 1—Difference in mean change in ACR (mg/g) as continuous variable among treatment arms by eGFR baseline categories. The change in ACR as a continuous variable by baseline eGFR categories was analyzed using repeated-measures ANOVA, with baseline CV risk group (previous CVD or MRF) and treatment arm as model terms. SAXA, saxagliptin.

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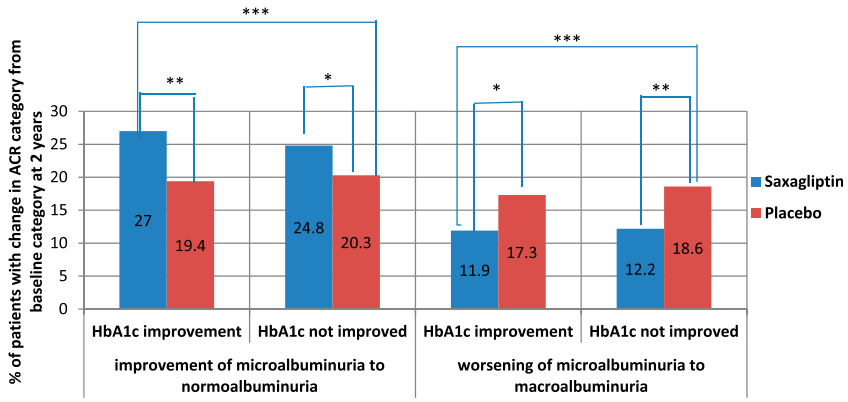

Figure 2—Improvement and worsening in ACR (mg/g) category at 2 years in patients with microalbuminuria at baseline and with or without improvement in HbA_{1c} >0.5% in the saxagliptin and placebo arms. χ^2 test: *$P < 0.05$; **$P < 0.01$; ***$P > 0.05$.

outcomes is increased in subjects with higher ACR in the normoalbuminuric range (26). However, despite reduction in albuminuria by saxagliptin in the SAVOR-TIMI 53 trial, it did not demonstrate any beneficial CV effect.

A recent meta-analysis included 21 trials and 78,342 patients and demonstrated that reducing albuminuria by various pharmacological interventions was strongly associated with decreased progression to ESRD (25). In the current study, treatment with saxagliptin reduced ACR without affecting the eGFR. Possible explanations for this inconsistency might be the short duration of follow-up in SAVOR-TIMI 53 and/or the extent of the change in ACR. A somewhat similar result and conclusion was reported in the post hoc analysis of the ALTITUDE trial, in which the addition of aliskiren, a renin inhibitor, to treatment with ACEI or ARB was associated with decrease in ACR without renal or CV-protective effect (27). Additionally, the multivariable analysis of variables associated with eGFR and ACR (Supplementary Table 2) showed incomplete overlap between variables affecting albuminuria and eGFR, as was previously shown in the U.K. Prospective Diabetes Study 74 (UKPDS) trial (28); therefore, the effects of treatment on albuminuria and eGFR might be dissimilar.

The extent of ACR reduction is an important predictor of future renal and CV outcome (25). The SAVOR-TIMI 53 trial demonstrated that saxagliptin neither increased nor decreased the risk of the primary composite end point of nonfatal myocardial infarction, nonfatal stroke, or CV death (17); this finding was true also regarding the different renal function categories (29). An increase in the rate of hospitalization for heart failure in patients treated with saxagliptin regardless of renal function was observed (17,29).

The SAVOR-TIMI 53 population included many patients with reduced eGFR but minimal or no albuminuria (Supplementary Fig. 1). This finding is consistent with other studies in both patients with diabetic nephropathy (1–4) and patients with chronic stable coronary artery disease (30). In patients with similar eGFR, the clinical significance of varying degrees of albuminuria on renal and CV outcomes is an ongoing debate (1).

We found that the reduction of ACR by saxagliptin occurred, irrespective of its effects on glycemia. The protective effect of DPP-4 inhibitors and GLP-1 receptor agonists on kidney function and structure has been shown in different animal models using various DPP-4 inhibitors and GLP-1 receptor agonists (16,31–35). Reduction in ACR was also demonstrated in smaller, uncontrolled human studies of short duration with other DPP-4 inhibitors (13,23).

There is speculation regarding the mechanisms by which DPP-4 inhibitors reduce ACR independently of their effect on glycemia. GLP-1 receptors are expressed in glomerular blood vessels (16), and an increase in GLP-1 plasma concentration by DPP-4 inhibitors may protect against renal oxidative stress under chronic hyperglycemia by inhibition of NAD(P)H oxidase, a major source of superoxide, and by cAMP–cAMP-dependent protein kinase pathway activation, which are both putatively involved in renal complications (16,34–37).

The Strengths and Weaknesses of This Study

The main strength of this trial is the size and diversity of the SAVOR-TIMI 53 population. All laboratory data, including ACR and creatinine, were collected at a central laboratory; renal outcomes, both safety and efficacy, were for the most part prespecified.

The main limitation of this study is the relatively short duration of follow-up (17), which is especially important with regard to changes in eGFR, which occur more slowly than changes in ACR (1). ACR was not collected for all patients at each time point, and the time lapse between each measurement was long (mostly 1 year). ACR was measured from a single voided urine sample, rather than repeated measurements or 24-h urine collections. There is considerable intraindividual daily variation in albuminuria, and a coefficient of variation of 40% been previously reported for those with an ACR of 30–300 mg/g creatinine (1), perhaps contributing to our modest findings. eGFR was calculated using a serum creatinine measurement and not measured directly.

Despite the fact that most renal outcomes were predefined, it is important to note the limitation of interpolation of exploratory end points when the primary results of the entire trial (17) as well as the renal analysis were null. Additionally, the occurrence of the predefined renal safety outcomes was rare, and even more subtle changes in eGFR may take several years to appear. The *P* values of some of the analyses showing reduction in ACR were borderline, and no correction was done for multiple testing.

Conclusion

Saxagliptin decreased ACR in a large and heterogeneous population of patients with T2D. This was observed in patients with normo-, micro-, and macroalbuminuria, irrespective of eGFR at baseline. For the most part, the reduction in ACR could not be explained by saxagliptin's effects on glycemia. However, saxagliptin did not affect other renal or CV

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outcomes. Further studies of longer duration could help to better define the renal outcomes of treatment with DPP-4 inhibitors.

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D.L.B. 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 Society of Cardiovascular Patient Care; serves as Chair for the American Heart Association Quality Oversight Committee; is on data-monitoring committees for Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, and Population Health Research Institute; received honoraria from the American College of Cardiology (Senior Associate Editor, *Clinical Trials and News*, http://acc.org), Belvoir Publications (Editor-in-Chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor-in-Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Guest Editor and 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 (CME steering committees); served on other boards for *Clinical Cardiology* (Deputy Editor), National Cardiovascular Data Registry ACTION Registry Steering Committee (Vice-Chair), and VA Cardiovascular Assessment, Reporting, and Tracking System (CART) Research and Publications Committee (Chair); received research funding from Amarin Corporation, AstraZeneca, Bristol-Myers Squibb, Eisai Co., Ltd., Ethicon, Forest Laboratories, Ischemix, Medtronic, Pfizer, Roche, Sanofi, and The Medicines Company; received royalties from Elsevier (Editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); served as site co-investigator for Biotronik, Boston Scientific, and St. Jude Medical; served as trustee for the American College of Cardiology; and performed unfunded research for Flowco Solutions, PLx Pharma Inc., and Takeda Bio. 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I.R. is on the advisory board for AstraZeneca, Bristol-Meyers Squibb, Eli Lilly and Company, Merck Sharp & Dohme, Novo Nordisk, Sanofi, Orgenesis Inc., SmartZyme Biopharma, LabStyle Innovations, and Boehringer Ingelheim; is a consultant for AstraZeneca, Bristol-Meyers Squibb, Insuline Medical, Gili Medical, KAMADA, FutuRx, NephroGenex Inc., and Diabetes Medical Center (Tel Aviv, Israel); is on the speaker's bureau of AstraZeneca, Bristol-Meyers Squibb, Eli Lilly and Company, Johnson & Johnson, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi, Teva Pharmaceutical Industries Ltd., and Boehringer Ingelheim; and is a stock/shareholder of Insuline Medical, LabStyle Innovations, SmartZyme Biopharma, Orgenesis Inc., and Glucome Ltd. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. O.M. researched, analyzed, and interpreted the data; drafted and revised the manuscript for important intellectual content; and approved the final draft of the manuscript. G.L. and A.C. helped to acquire, analyze, and interpret the data; reviewed and revised the manuscript for important intellectual content; and approved the final version of the manuscript submitted. D.L.B., B.H., E.B., B.M.S., and I.R. conceived and designed the study; helped to acquire, analyze, and interpret the data; reviewed the manuscript for important intellectual content; and approved the final version of the manuscript submitted. C.W. was the SAVOR study statistician, reviewed the manuscript for important intellectual content, and approved the final version of the manuscript submitted. K.I., A.R., and I.Y. helped to acquire, analyze, and interpret the data; revised the manuscript for important intellectual content; and approved the final version of the manuscript submitted. C.S. was the study physician for SAVOR and responsible for collection and interpretation of data and review of publication. K.K.R. reviewed and revised the manuscript for important intellectual content and approved the final version of the manuscript submitted. N.I. assisted in acquiring and interpreting data and reviewed, revised, and approved the final version of the manuscript. O.M., D.L.B., B.H., C.S., E.B., B.M.S., and I.R. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix

Executive Committee of the SAVOR-TIMI 53 Trial: Eugene Braunwald, study chair; Deepak L. Bhatt, co–principal investigator; Itamar Raz, co–principal investigator; and Jaime A. Davidson, Boaz Hirshberg (nonvoting), and Ph. Gabriel Steg.

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