

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

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Abstract

Background: DPP-4 inhibitors may have a protective effect in diabetic nephropathy.

Methods: We studied renal outcomes of 16,492 patients with type 2 diabetes, randomized to saxagliptin vs. placebo and followed for a median of 2.1 years in 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%) microalbuminuria (ACR 30-300 mg/g) and 1,638 (9.9%) 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, 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 eGFR>50 mL/min/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, EOT p=0.0158). The change in ACR did not correlate with that in HbA1c (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.

Conclusion: Treatment with saxagliptin improved ACR, even in the normo-albuminuric range, without affecting eGFR. The beneficial effect of saxagliptin on albuminuria could not be explained by its effect on glycaemic control.

ABBREVIATIONS

ACR: albumin to creatinine ratio

ACEI: angiotensin converting enzyme inhibitor

ARB: angiotensin receptor blockers

BMI: Body mass index

CI: confidence interval

CKD: chronic kidney disease

CV: Cardiovascular

CVD: Cardiovascular disease

eGFR: estimated glomerular filtration rate

EOT: end of trial

ESRD: end-stage renal disease

FPG: fasting plasma glucose

HR: hazard ratio

MI: myocardial infarction

T2D: type 2 diabetes

ACRONYMS

SAVOR: Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus

TIMI: Thrombolysis in Myocardial Infarction

Introduction:

Diabetic nephropathy is the most common cause for end-stage renal disease (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 (CV) disease (4-6). Several clinical trials have shown that decreased albuminuria in response to treatment with angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) is associated with slower progression of both renal and CV disease (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 protein kinase A (PKA), 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 type 2 diabetic patients 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 here the pre-defined 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.

Methods

Study Design, Patients and Primary and Secondary Endpoints

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 type 2 diabetes (T2D), HbA1c between 6.5% and <12.0% (47.5 and <107.7 mmol/mol) within 6 months of randomization, and either a history of established cardiovascular disease (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/BSA or less) or matching placebo. A history of end-stage renal disease (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 pre-specified 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 by cardiovascular disease 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 (Quintiles Ltd UK) were analyzed at the combined screening and randomization visit, at 1-year (>180, <540 days from randomization), 2- year (\geq 540 days 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 continuous and categorical variables: normal or mildly reduced renal function (eGFR>50 mL/min per 1.73 m²), moderate renal dysfunction (eGFR 30-50 mL/min per 1.73 m²), and severe renal dysfunction (eGFR<30 mL/min per 1.73 m²). All eGFR analyses were performed on the intention to treat (ITT) population.

Urinary albumin and creatinine were measured at the central laboratory in a single voided urine sample, and albumin 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 \leq ACR-<30 mg/g), ACR 30 to 300 mg/g (3.4 to 34.0 mg/mmol) defined as microalbuminuria (also called "high albuminuria") (further subdivided into 30 \leq ACR <100 mg/g and 100 \leq ACR- \leq 300 mg/g) and ACR >300 mg/g (>34.0 mg/mmol) defined as macroalbuminuria (also called "very high albuminuria").

The predefined renal efficacy endpoints included:

- New and/or progression of diabetic nephropathy
 - o Change from baseline in ACR
 - o Categorical change from baseline in ACR
 - o Doubling of serum creatinine levels (time to first event)
 - o Initiation of chronic dialysis and/or renal transplant and/or serum creatinine >6.0 mg/dL (530 μ mol/L) (time to first event)
- Time to first event of the composite endpoint of death, doubling of serum creatinine levels or creatinine >6.0 mg/dl (530 μ mol/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 \geq 30 mg/g, a median 2 sample test (Brown-Mood test) for continuous variables and chi-square 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, HbA1C, fasting plasma glucose, eGFR, ACE inhibitors, ARB, beta-blockers, statin, aspirin, sulfonylurea, metformin, insulin and thiazolidinediones. This model was performed using a log transformation of ACR, due to 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 that shifted in ACR categories from baseline to EOT by treatment arm. The difference between arms at each baseline level was tested using Chi-square test.

The change from baseline in ACR assessed as a continuous variable by baseline eGFR categories was analyzed using repeated measures analysis of variance, with baseline CV risk group- previous CV disease 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 Pearson correlation coefficients and comparison of changes in ACR categories according to decrease in HbA1c levels using the Chi-square 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 on-treatment period. The statistical software package SAS (version 9.3, SAS Institute, Cary, NC, USA) 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 (WCT) 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 (Appendix Table 1). The number of patients in each eGFR and ACR group at baseline was balanced between treatment

arms. While 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 (Appendix Figure 1). 44.4% and 19.5% of the patients with moderate and severe renal impairment, had normoalbuminuria (Appendix Figure 1).

Subjects with abnormal ACR at baseline were more likely to be non-Caucasian, Hispanic and with longer diabetes duration (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 HbA1c [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 [HbA1c \geq 9% (>74.9 mmol/mol)] compared to patients with normal ACR.

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

Renal safety outcomes

There were no meaningful differences in any of the pre-specified renal safety outcomes between saxagliptin and placebo treatment arms: doubling of serum creatinine occurred in 183 (2.02%) vs. 166 (1.82%) subjects; [HR 1.1 (0.89-1.36)], initiation of chronic dialysis, renal transplant or serum creatinine >6.0 mg/dl occurred in 51 (0.61%) vs. 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%) vs. 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. -2.37 ml/min in the saxagliptin and placebo groups, respectively, p=0.5794).

The effect of saxagliptin vs 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<0.001), mainly driven by the difference in change in ACR amongst 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 5 categories (<15mg/g, 15-<30 mg/g, 30-<100 mg/g, 100-300 mg/g and >300 mg/g) (Appendix Table 3).

Stratification of the mean change in ACR by baseline eGFR categories for the saxagliptin and placebo groups at 1 year and 2 years is shown in Figure 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 $50 \geq \text{eGFR} \geq 30$ 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 to placebo was associated with decreased albuminuria at all time-points (P<0.05, at 1, 2 years and EOT) (Appendix figure 2).

Correlation between changes in ACR and changes in HbA1c (on treatment analysis)

During follow up, there was a mean HbA1c 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 HbA1c and ACR. For the entire trial population, a very weak correlation was demonstrated between the change in ACR and HbA1c 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 HbA1c compared to those whose HbA1C decreased by <0.5%, remained unchanged or increased (Figure 2). Treatment with saxagliptin was associated with a similar decrease of albuminuria, irrespective of the change in HbA1C.

Discussion:

The SAVOR-TIMI 53 study included a large population of patients with type 2 diabetes 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 regards 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 pre-specified 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 either as a continuous or as a categorical variable, at all baseline ACR and eGFR categories. Since the association between ACR levels and increased CV risk can be demonstrated even within the normo-albuminuric 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 and progression of renal dysfunction and cardiovascular morbidity are 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 (RAAS) 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 macro-albuminuria, and not in normo-albuminuric patients, thus presenting a potential benefit that may be unique to this drug or class (22,

25). The reduction of ACR in the normo-albuminuric range might be important, considering the finding that the rate of adverse CV outcomes is increased in subjects with higher ACR in the normo-albuminuric 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, 78,342 patients, and demonstrated that reducing albuminuria by various pharmacological interventions was strongly associated with decreased progression to ESRD (25). In the present 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, where the addition of aliskiren, a renin inhibitor, to treatment with ACEI or ARB was associated with decrease in ACR without renal or cardiovascular protective effect (27). Additionally, the multi-variable analysis of variables associated with eGFR and ACR (appendix table 2), showed incomplete overlap between variables affecting albuminuria and eGFR, as was previously shown at the 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 endpoint of non-fatal MI, non-fatal 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 (Appendix Figure1). This finding is consistent with other studies in both patients with diabetic nephropathy (1-4) and in 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 (GLP-1RA) on kidney function

and structure has been shown in different animal models using various DPP-4 inhibitors and GLP-1 RA (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-PKA pathway activation, which are both putatively involved in renal complications (16, 34, 35).

The strengths and weaknesses of this manuscript

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 pre-specified.

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 intra-individual 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 (38) 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 endpoints 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 type 2 diabetic patients. This was observed in patients with normoalbuminuria, 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 cardiovascular outcomes. Further studies of longer duration could help to better define the renal outcomes of treatment with DPP-4 inhibitors.

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KI has no conflicts of interest to declare

AR has no conflicts of interest to declare

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Author contributions:

OM researched, analyzed, and interpreted the data, drafted the manuscript and revised the manuscript for important intellectual content and approved the final draft of the manuscript.

GL 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

DLB 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

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CS Study physician in SAVOR, collections and interpretation of data, review of publication

KKR reviewed and revised manuscript for important intellectual content, and approved the final version of the manuscript submitted

NI assisted in acquiring and interpreting data; reviewed, revised and approved final version of the manuscript

EB 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

BMS 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

IR 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

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Figure legends

Figure 1: Difference in mean change in ACR (mg/g) as continuous variable between treatment arms, by eGFR baseline categories

The change in ACR as a continuous variable by baseline eGFR categories was analyzed using repeated measures analysis of variance, with baseline CV risk group- previous CV disease or MRF, and treatment arm as model terms.

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 HbA1c>0.5%, in the saxagliptin and placebo arms

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 chi-squared 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.

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Table 1. Baseline characteristics according to ACR

Statistical tests were produced to test the difference between ACR <30 mg/g vs. ACR>30 mg/g groups, using a median 2 sample test (Brown-Mood test) for continuous variables and chi square test for categorical variables.

| Characteristic | ACR | ACR | ACR | P |
|---|-------------------------|------------------------------|--------------------------|----------------------------------|
| | <30 mg/G (n = 9,696) | 30 - 300 mg/G (n = 4,426) | >300 mg/G (n = 1,638) | (between<3 0 to all other) |
| 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 |
| Body-mass index - 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 |

| Characteristic | ACR | ACR | ACR | P |
|---|-------------------------|------------------------------|--------------------------|----------------------------------|
| | <30 mg/G (n = 9,696) | 30 - 300 mg/G (n = 4,426) | >300 mg/G (n = 1,638) | (between<3 0 to all other) |
| 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 umol/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, n (%) | | | | |
| >50 mL/min/BSA | 8,691 (89.6) | 3,624 (81.9) | 1,004 (61.3) | <0.0001 |
| 50-30 mL/min/BSA | 944 (9.7) | 708 (16.0) | 476 (29.1) | |
| <30 mL/min/BSA | 61 (0.6) | 94 (2.1) | 158 (9.6) | |
| Glycated hemoglobin %, Median (IQR) | 7.5 (6.8-8.4) | 7.9 (7.1-9.1) | 8.2 (7.3-9.4) | <0.0001 |
| Glycated hemoglobin<7 %, n (%) | 2,903 (29.9) | 856 (19.3) | 234 (14.3) | <0.0001 |
| Glycated hemoglobin %≥ 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 cardiovascular medications, n(%) | | | | |
| Aspirin, n(%) | 7,299 (75.3) | 3,322 (75.1) | 1,211 (73.9) | 0.4578 |
| Statins, n(%) | 7,585 (78.2) | 3,448 (77.9) | 1,277 (78.0) | 0.6478 |
| Beta-blockers, n(%) | 5,900 (60.8) | 2,751 (62.2) | 1,018 (62.1) | 0.1019 |
| Diuretics, n(%) | 4,080 (42.1) | 1,954 (44.1) | 850 (51.9) | <0.0001 |
| ACE Inhibitors, n(%) | 5,322 (54.9) | 2,374 (53.6) | 857 (52.3) | 0.0488 |
| Angiotensin receptor blockers, n(%) | 2,504 (25.8) | 1,313 (29.7) | 579 (35.3) | <0.0001 |

| Characteristic | ACR | ACR | ACR | P |
|--|-------------------------|------------------------------|--------------------------|----------------------------------|
| | <30 mg/G (n = 9,696) | 30 - 300 mg/G (n = 4,426) | >300 mg/G (n = 1,638) | (between<3 0 to all other) |
| Calcium antagonists, n(%) | 2,737 (28.2) | 1,645 (37.2) | 764 (46.6) | <0.0001 |
| Baseline anti-hyperglycemic medications, n(%) | 9,146 (94.3) | 4,290 (96.9) | 1,584 (96.7) | <0.0001 |
| Metformin, n(%) | 6,945 (71.6) | 3,061 (69.2) | 928 (56.7) | <0.0001 |
| Sulfonylurea, n(%) | 3,976 (41.0) | 1,793 (40.5) | 574 (35.0) | 0.0140 |
| Thiazolidinediones, n(%) | 586 (6.0) | 268 (6.1) | 80 (4.9) | 0.4302 |
| Insulin, n(%) | 3,428 (35.4) | 2,075 (46.9) | 991 (60.5) | <0.0001 |
| None, n(%) | 550 (5.7) | 136 (3.1) | 54 (3.3) | <0.0001 |

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

| | | ACR at EOT | | | | | |
|-----------------|----------------------|-----------------|----------------|----------------|-----------------|----------------|----------------|
| | | SAXAGLIPTIN | | | PLACEBO | | |
| | | <30 | 30-300 | >300 | <30 | 30-300 | >300 |
| ACR at baseline | <30 P *=0.021 | 3152 (84.2%) | 555 (14.8%) | 36 (1.0%) | 2993 (82.2%) | 617 (16.9%) | 31 (0.8%) |
| | 30-300 P **<0.001 | 451 (28.9%) | 929 (59.5%) | 181 (11.6%) | 352 (23.4%) | 904 (60.1%) | 249 (16.5%) |
| | >300 P ***=0.049 | 23 (4.3%) | 148 (27.7%) | 363 (68.0%) | 15 (3.0%) | 115 (23.4%) | 362 (73.6%) |

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 chi-squared 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.

White: The number of patients (%) at each ACR category at baseline, with no change in ACR category to EOT.

Light Green: The number of patients (%) at each ACR category at baseline, with improvement in one ACR category to EOT.

Dark Green: The number of patients (%) at each ACR category at baseline, with improvement in two ACR categories to EOT.

Light Red: The number of patients (%) at each ACR category at baseline, with worsening in one ACR category to EOT.

Dark Red: The number of patients (%) at each ACR category at baseline, with worsening in two ACR categories to EOT.

Figure 1: Difference in mean change in ACR (mg/g) as continuous variable between treatment arms, by eGFR baseline categories

The change in ACR as a continuous variable by baseline eGFR categories was analyzed using repeated measures analysis of variance, with baseline CV risk group- previous CV disease or MRF, and treatment arm as model terms.

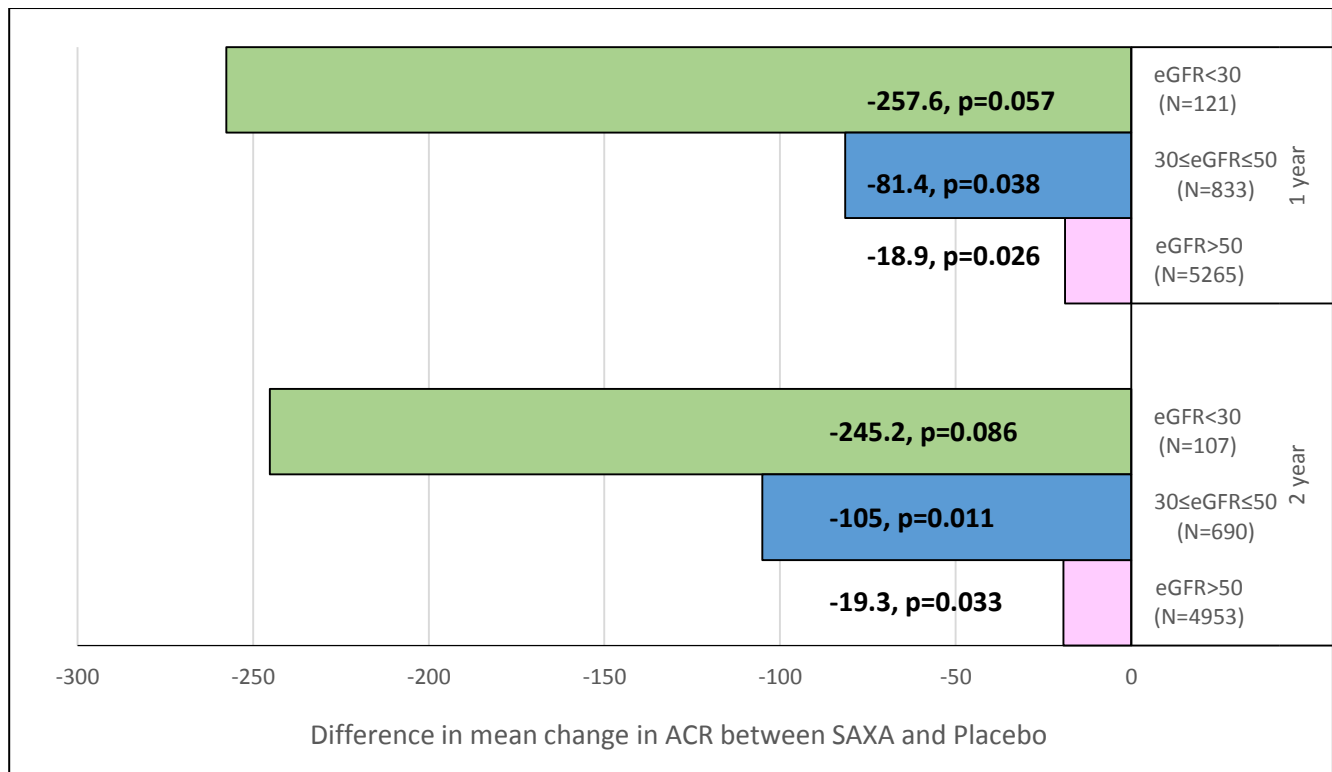
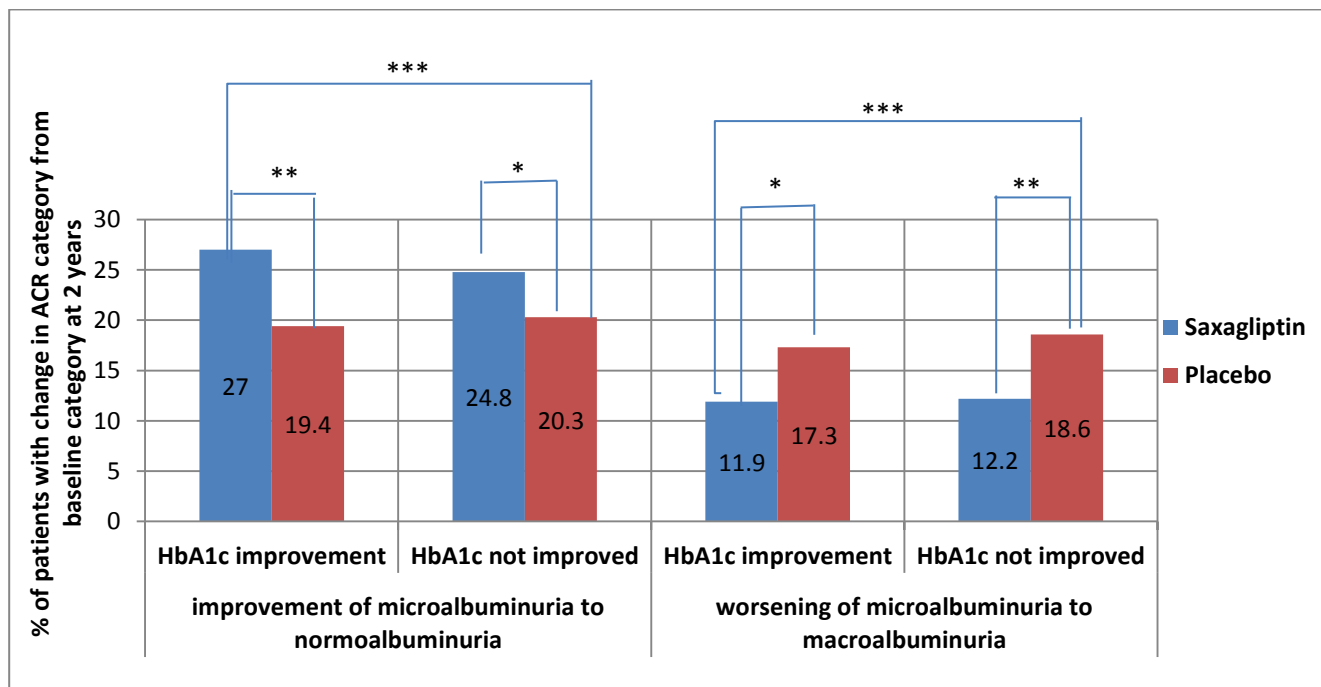


Figure 2: Improvement and worsening in ACR (mg/g) category at 2 years in patients with microalbuminuria at baseline and with or without improvement in HbA1c>0.5%, in the saxagliptin and placebo arms



*P<0.05, **P<0.01, ***P>0.05