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ORIGINAL RESEARCH

Saxagliptin Efficacy and Safety in Patients With Type 2 Diabetes and Moderate Renal Impairment

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ABSTRACT

Introduction: Type 2 diabetes (T2D) is the leading cause of chronic kidney disease (CKD). The recommended dose of the dipeptidyl peptidase-4 inhibitor saxagliptin is 2.5 mg in patients with moderate or severe renal impairment (creatinine clearance ≤50 mL/min). In this post hoc analysis, we assessed the effect of saxagliptin 2.5 and 5 mg/day versus placebo on glycemic measures in patients with T2D and estimated glomerular filtration rate 45–60 mL/min/1.73 m^2.

Methods: Efficacy and safety data were pooled from nine 24-week, randomized, placebo-controlled clinical trials.

Results: The majority (56–61%) of patients were women aged <65 years with glycated hemoglobin (A1C) 8.1–8.2%; half of the patients had a T2D duration ≥5 years. Mean change from baseline in A1C was significantly greater with saxagliptin 2.5 (–0.6%, $P = 0.036$ vs placebo) and 5 mg/day (–0.9%, $P < 0.001$ vs placebo) compared with placebo (–0.2%). There were numerically greater reductions in fasting plasma glucose and 2-h postprandial glucose, and a significantly greater proportion of patients achieved A1C <7% with saxagliptin 5 mg/day (44.8%) compared with placebo (20.0%, $P = 0.004$ vs placebo). The incidence of hypoglycemia was not significantly different across groups (16.2% in the saxagliptin 5-mg/day, 12.2% in the saxagliptin 2.5-mg/day, and 11.3% in the placebo groups).

Conclusion: These results suggest that saxagliptin 2.5 and 5 mg/day improve glycemic control and are generally well tolerated in patients with T2D and moderate CKD.

Trial registration: ClinicalTrials.gov identifier, NCT00121641, NCT00316082, NCT00698932, NCT00918879, NCT00121667, NCT00661362, NCT00313313, NCT00295633, NCT00757588.

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Keywords: Chronic kidney disease; Dipeptidyl peptidase-4 inhibitor; Estimated glomerular filtration rate; Saxagliptin; Type 2 diabetes

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INTRODUCTION

Worldwide, diabetes is the leading cause of chronic kidney disease (CKD) [1], which is defined by an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 or an albumin/creatinine ratio ≥30 mg/g for more than 3 months [2]. In the United States, the prevalence of CKD among individuals with diabetes is estimated to be ~40% based on eGFR and/or albuminuria [3]. A recent analysis of the National Health and Nutrition Examination Survey (1999–2012) database reported that 12.9% of patients with type 2 diabetes (T2D) had eGFR in the upper range of moderate CKD (stage 3a: 45 to <60 mL/min/1.73 m^2) [4].

Treatment of patients with T2D and CKD is challenging because many antidiabetes medications are cleared by the kidneys and require dosage adjustment to avoid hypoglycemia [5]. Saxagliptin is a dipeptidyl peptidase-4 inhibitor that improves glycemic control in patients with T2D as monotherapy or in combination with other antidiabetes medications and imparts a very low risk of hypoglycemia [6–14]. Saxagliptin is metabolized to an active metabolite by the liver and, along with the parent molecule, is eliminated mainly by the kidney [15]. Therefore, the recommended dose of saxagliptin is 2.5 mg/day in patients with moderate or severe renal impairment (creatinine clearance [CrCl] ≤50 mL/min), which is half the recommended dose (5 mg/day) for patients with normal kidney function [16]. The objective of this post hoc analysis was to assess the efficacy and safety of saxagliptin 2.5 and 5 mg/day versus placebo using data pooled from saxagliptin clinical trials in patients with T2D and moderate renal impairment (eGFR 45–60 mL/min/1.73 m^2).

METHODS

Efficacy and safety data were pooled from nine 24-week, randomized, placebo-controlled clinical trials, which included 4 trials of saxagliptin monotherapy (NCT00121641 [6], NCT00316082 [7], NCT00698932 [8], and NCT00918879 [9]), 2 trials of saxagliptin add-on to metformin (NCT00121667 [10] and NCT00661362 [11]), and 1 trial each of saxagliptin add-on to glyburide (NCT00313313 [12]), add-on to a thiazolidinedione (NCT00295633 [13]), and add-on to insulin with or without metformin (NCT00757588 [14]). Study designs and inclusion and exclusion criteria have been previously reported in detail [6–14]. Only patients with eGFR of 45–60 mL/min/1.73 m^2 at baseline were included in this analysis. eGFR was calculated from serum creatinine using the Modification of Diet in Renal Disease equation [17]. Safety was assessed by adverse events (AEs), serious AEs (SAEs), and laboratory values.

Differences in changes from baseline in glycated hemoglobin (A1C), fasting plasma glucose (FPG), and 2-h postprandial glucose (PPG) following an oral glucose tolerance test were assessed using an analysis of covariance model with treatment as the factor, baseline value as the covariate, and study as the random effect for the saxagliptin versus the placebo groups. The proportion of patients achieving A1C <7% at the end of the 24-week treatment period was analyzed using the Cochran–Mantel–Haenszel general association test stratified by study. The incidence of hypoglycemia with saxagliptin compared with placebo was assessed by Fisher exact test. Statistical analyses were performed with Statistical Analysis System (SAS) software (SAS Institute, Cary, NC, USA).

Compliance with Ethics Guidelines

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for inclusion in the study. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS

A total of 188 patients with eGFR 45–60 mL/min/1.73 m^2 at baseline were identified. The majority of patients were white women <65 years old with a mean baseline A1C of 8.1–8.2% and a mean T2D duration of 6.5–8.6 years (Table 1). Mean eGFR at baseline was 54–55 mL/min/1.73 m^2. Demographics and baseline characteristics were similar across treatment groups.

At 24 weeks, the mean change from baseline in A1C was significantly greater with saxagliptin 2.5 mg/day (mean [95% CI] difference from placebo –0.6% [–0.8%, –0.0%]; $P = 0.036$) and 5 mg/day (–0.9% [–1.0%, –0.4%]; $P < 0.001$) compared with placebo (Fig. 1a). There were numerically greater, but not statistically significant, reductions from baseline in FPG (Fig. 1b; mean [95% CI] difference from placebo 2.5 mg/day, –10 [–21.7, 10.2] mg/dL; 5 mg/day, –16 [–27.7, 1.9] mg/dL) and 2-h PPG (Fig. 1c; mean [95% CI] difference from placebo 2.5 mg/day, −48.6 [–51.4, 8.4] mg/dL; 5 mg/day, −57.7 [–47.0, 8.8] mg/dL) with saxagliptin 2.5 and 5 mg/day compared with placebo. A greater proportion of patients

Table 1 Demographics and baseline characteristics of patients with eGFR 45–60 mL/min/1.73 m^2

Characteristic	Placebo ($n = 71$)	Saxagliptin 2.5 mg/day ($n = 49$)	Saxagliptin 5 mg/day ($n = 68$)
Age, years	62.9 (7.1)	63.4 (7.9)	61.8 (9.3)
Women, *n* (%)	40 (56)	30 (61)	41 (60)
Race, *n* (%)			
White	46 (65)	43 (88)	47 (69)
Black	1 (1)	2 (4)	1 (2)
Asian	23 (32)	4 (8)	19 (28)
Other	1 (1)	0	1 (2)
BMI, kg/m^2	29.8 (4.8)	30.5 (4.7)	30.1 (5.5)
Duration of T2D, years	8.6 (8.4)	6.5 (7.0)	7.1 (7.5)
A1C, %	8.2 (0.95)	8.1 (0.81)	8.1 (0.91)
eGFR, mL/min/1.73 m^2	55.2 (3.9)	54.2 (4.6)	55.3 (3.6)

Data are mean (SD) unless otherwise noted

A1C glycated hemoglobin, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *SD* standard deviation, *T2D* type 2 diabetes

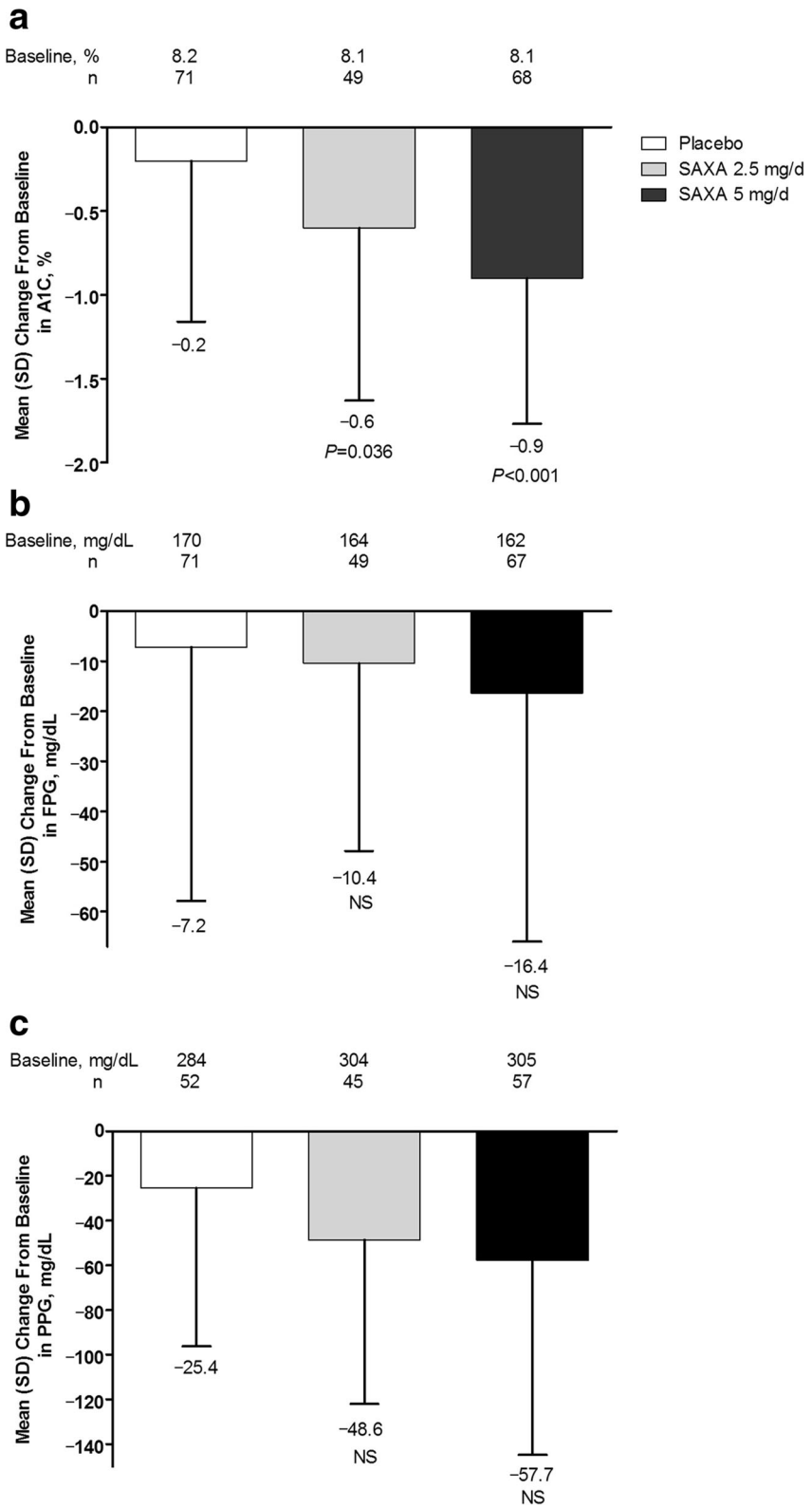

Fig. 1 Mean change from baseline to week 24 in **a** A1C, **b** FPG, and **c** 2-h PPG. *A1C* glycated hemoglobin, *FPG* fasting plasma glucose, *NS* nonsignificant, *PPG* 2-h postprandial glucose, *SAXA* saxagliptin, *SD* standard deviation

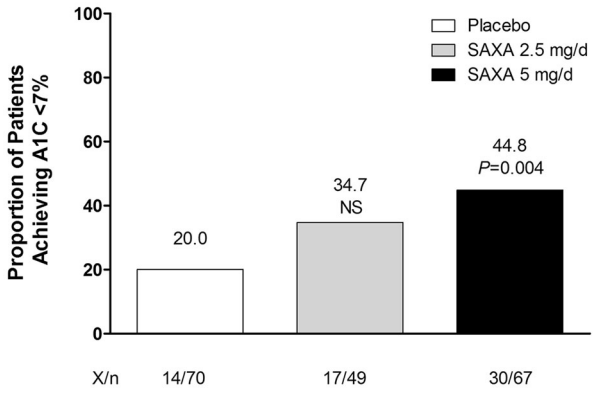

Fig. 2 Proportion of patients achieving A1C <7% at week 24. *A1C* glycated hemoglobin, *NS* nonsignificant, *SAXA* saxagliptin

achieved A1C <7% at week 24 with saxagliptin 2.5 mg/day (34.7%, NS) and 5 mg/day (44.8%, $P = 0.004$ vs placebo) compared with placebo (20.0%; Fig. 2).

Overall, AEs were reported more frequently with saxagliptin treatment compared with placebo (Table 2). AEs and SAEs related to kidney function were infrequent. The proportion of patients with increased blood creatinine was generally similar with placebo (5.6%) and saxagliptin treatment (4.4–8.2%). There was 1 SAE of acute renal failure in the saxagliptin 2.5-mg/day group and none in the saxagliptin 5-mg/day and placebo groups. The 61-year-old woman was overweight and had a history of hypertension, hypercholesterolemia, hypertriglyceridemia, and probable baseline CKD exacerbated by relative volume depletion and concomitant medications. Saxagliptin was discontinued, and the event resolved following treatment. The acute renal failure was considered unlikely to be related to saxagliptin. In general, AEs were similar with saxagliptin 2.5 and 5 mg/day, although AEs related to pain were more frequent with saxagliptin 5 than 2.5 mg/day. The proportion of patients with hypoglycemia was numerically greater, but not significantly different, compared with placebo (11.3%) in the saxagliptin 2.5-mg/day (12.2%, $P = 1.000$) and 5-mg/day groups (16.2%, $P = 0.464$). At 24 weeks, there were small mean increases in eGFR from baseline in all treatment groups (Fig. 3).

DISCUSSION

Impaired renal function is common in patients with T2D, especially in those ≥65 years [4], and is independently associated with increased mortality, cardiovascular events, and hospitalization [18, 19]. Pharmacotherapy in patients with T2D can be challenging and therapeutic options may be limited because a reduced GFR results in the accumulation of certain drugs and/or their metabolites that may increase the risk of side effects or hypoglycemia [5, 20]. In this analysis of patients with T2D and moderate CKD, saxagliptin 2.5 and 5 mg/day significantly reduced A1C and resulted in numerically larger reductions in FPG and PPG compared with placebo. In addition, saxagliptin 5 mg/day doubled the proportion of patients achieving A1C <7% after 24 weeks of treatment compared with placebo. These improvements in glycemic control with saxagliptin 2.5 and 5 mg/day were accompanied by small increases in overall AEs and SAEs compared with placebo, but AEs related to renal function were infrequent and episodes of hypoglycemia were generally similar across treatment groups. Of note, eGFR remained stable over the 24 weeks of treatment with saxagliptin as well as with placebo.

Our results using data pooled from 9 randomized clinical trials of saxagliptin 2.5 and 5 mg/day are in agreement with the results of a previously reported 12-week

Table 2 Adverse events

Adverse event	Patients, *n* (%)		
	Placebo ***n* = 71**	**Saxagliptin 2.5 mg/day** ***n* = 49**	**Saxagliptin 5 mg/day** ***n* = 68**
≥1 AE	46 (64.8)	41 (83.7)	51 (75.0)
≥1 SAE	5 (7.0)	6 (12.2)	6 (8.8)
Most common AEs (≥5%)			
Urinary tract infection	6 (8.5)	6 (12.2)	6 (8.8)
Influenza	5 (7.0)	5 (10.2)	7 (10.3)
Nasopharyngitis	3 (4.2)	4 (8.2)	4 (5.9)
Pharyngitis	4 (5.6)	4 (8.2)	2 (2.9)
Upper respiratory infection	4 (5.6)	4 (8.2)	4 (5.9)
Bronchitis	4 (5.6)	3 (6.1)	2 (2.9)
Arthralgia	4 (5.6)	6 (12.2)	2 (2.9)
Back pain	3 (4.2)	2 (4.1)	5 (7.4)
Pain in extremity	3 (4.2)	1 (2.0)	5 (7.4)
Musculoskeletal pain	1 (1.4)	0	4 (5.9)
Diarrhea	0	3 (6.1)	3 (4.4)
Dyspepsia	3 (4.2)	3 (6.1)	2 (2.9)
Headache	2 (2.8)	2 (4.1)	4 (5.9)
Increased blood creatinine	4 (5.6)	4 (8.2)	3 (4.4)
Pruritus	0	3 (6.1)	0
Peripheral edema	4 (5.6)	2 (4.1)	4 (5.9)
Hypertension	6 (8.5)	4 (8.2)	3 (4.4)
Hypotension	0	3 (6.1)	1 (1.5)
Dyslipidemia	4 (5.6)	2 (4.1)	1 (1.5)
Hypoglycemia	8 (11.3)	6 (12.2)	11 (16.2)

AE adverse event, *SAE* serious adverse event

clinical trial [21] with an extension to 52 weeks [22] of saxagliptin 2.5 mg/day (plus background antidiabetes medications) in patients with T2D and moderate (CrCl 30 to <50 mL/min), severe (CrCl <30 mL/min and not receiving hemodialysis), or end-stage (receiving hemodialysis) kidney disease. In that study, saxagliptin was well tolerated across all stages of CKD and reduced A1C, compared with placebo, in patients with moderate and severe CKD.

Limitations of this study include its post hoc nature, relatively small number of patients, and duration of 24 weeks. However, the results of

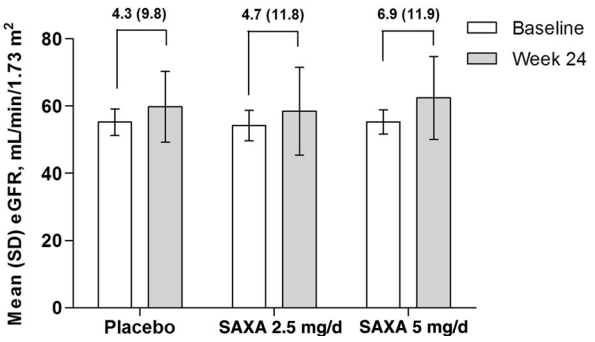

Fig. 3 Mean eGFR at baseline and 24 weeks. Mean (SD) change from baseline is shown above the bars. *eGFR* estimated glomerular filtration rate, *SAXA* saxagliptin, *SD* standard deviation

this analysis are consistent with a recently published subgroup analysis of the large saxagliptin cardiovascular outcomes trial Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus (SAVOR) (ClinicalTrial.gov identifier, NCT01107886) [23]. In that analysis, patients were stratified according to baseline eGFR as having normal or mildly impaired renal function (eGFR >50 mL/min/1.73 m^2, $n = 13{,}916$), moderate renal impairment (eGFR 30–50 mL/min/1.73 m^2, $n = 2240$), or severe renal impairment (eGFR <30 mL/min/1.73 m^2, $n = 336$). Compared with placebo, saxagliptin (5 or 2.5 mg/day in patients with eGFR ≤50 mL/min/1.73 m^2) significantly reduced A1C in all eGFR subgroups at 1 year, which persisted through a median follow-up of 2 years. Saxagliptin also significantly reduced progressive microalbuminuria in patients with normal or mildly reduced renal function ($P < 0.0001$) and in those with moderate-to-severe renal impairment ($P = 0.04$) based on improvement or less worsening of urinary albumin:creatinine ratio compared with placebo [23].

CONCLUSION

In conclusion, saxagliptin at doses of 2.5 or 5 mg/day was equally well tolerated and improved glycemic control in patients with moderate renal impairment who have limited treatment options.

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Compliance with Ethics Guidelines. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of

1964, as revised in 2013. Informed consent was obtained from all patients for inclusion in the study. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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