Efficacy and Safety of Saxagliptin as Add-On Therapy in Type 2 Diabetes

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Type 2 diabetes is a complex and progressive disease characterized by hyperglycemia resulting from defects in insulin sensitivity and insulin secretion.[1] Inadequate control of hyperglycemia increases the risk of microvascular (nephropathy, retinopathy, and neuropathy)[2–4] and macrovascular (stroke, myocardial infarction, and cardiovascular death) complications.[5–7] Although diet and exercise can improve glycemic control[8] and are important aspects of type 2 diabetes management,[9,10] most patients require pharmacotherapy to meet individualized glycemic goals.[11] Moreover, because of the progressive nature of type 2 diabetes,[12] failure to maintain glycemic control with oral agent monotherapy over the long term is common,[11,13,14] and most patients require two or more agents to achieve individualized treatment goals.

The 2012 American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) position statement on hyperglycemia management in type 2 diabetes[15] contains several recommendations for dual and triple therapy, with the choice of agent(s) guided by patient- and drug-specific characteristics. Saxagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor approved in the United States, Canada, Europe, and certain countries in Latin America, Asia, the Middle East, and Africa as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes in various clinical settings. It has been shown to be effective as monotherapy and as add-on combination therapy.[16] This article summarizes the efficacy and safety of saxagliptin when given as add-on therapy to metformin, a sulfonylurea (SU), a thiazolidinedione (TZD), or insulin (with or without metformin) and as triple therapy with metformin and an SU.

Rationale for Combination Therapy With Saxagliptin

Combination therapy using agents with complementary but different mechanisms of action that address different pathophysiologic defects of type 2 diabetes may improve glycemic control to a greater extent than monotherapy.[17] Combination therapy may also allow the use of lower doses of concomitant antihyperglycemic agents, which may minimize unwanted side effects.[18] For example, weight gain and hypoglycemia are associated with some antihyperglycemic agents,[19] occur more frequently with higher doses,[18] and may hinder achievement of glycemic and metabolic goals.[20,21]

DPP-4 inhibitors are oral agents that prolong the half-life of endogenous glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 has numerous metabolic actions, including stimulation of glucose-dependent insulin secretion, inhibition of glucose-dependent glucagon secretion, reduction in the gastric emptying rate, and an increase in satiety (Figure 1).[22,23] DPP-4 inhibitors improve glycemic control with a low risk of hypoglycemia or weight gain.[24] The most recent ADA/EASD position statement[15] recommends DPP-4 inhibitors as an option for first-line therapy when metformin is contraindicated, as an option for add-on therapy to metformin (dual therapy), and as an option for add-on therapy to metformin + SU, metformin + TZD, and metformin + insulin (triple therapy). The position statement also notes that DPP-4 inhibitors are well tolerated and

IN BRIEF

Combination therapy for type 2 diabetes using agents with complementary mechanisms of action may improve glycemic control to a greater extent than monotherapy and allow the use of lower doses of antihyperglycemic medications. Dipeptidyl peptidase-4 inhibitors, including saxagliptin, are recommended as add-on therapy to metformin and as part of two- or three-drug combinations in patients not meeting individualized glycemic goals with metformin alone or as part of a dual-therapy regimen. This article reviews the efficacy and safety of saxagliptin as an add-on therapy to metformin, glyburide, a thiazolidinedione, or insulin (with or without metformin) and as a component of triple therapy with metformin and a sulfonylurea.

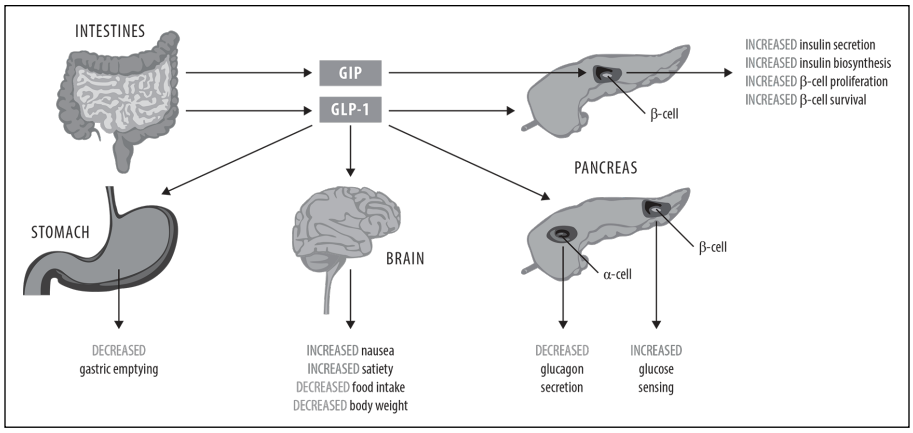

Figure 1. Action of GLP-1 in various organs. Adapted from Ref. 23.

do not contribute to hypoglycemia when used as monotherapy.[15]

Metabolism and Drug-Drug Interactions

Saxagliptin is eliminated by both hepatic and renal mechanisms.[25] It is primarily metabolized by cytochrome P450 (CYP) 3A4/5 to form an active metabolite, 5-hydroxy saxagliptin. Saxagliptin and its active metabolite are primarily excreted in the urine.[26] Although saxagliptin is eliminated in part by hepatic metabolism, no dose adjustments are recommended for patients with hepatic impairment.[16,27] In patients with moderate and severe renal impairment (creatinine clearance [CrCl] ≤ 50 ml/min) as well as for those on dialysis, the recommended dose of saxagliptin is 2.5 mg/day.[16,27]

In healthy volunteers, coadministration of simvastatin (a CYP3A4 substrate), diltiazem (a moderate inhibitor of CYP3A4), or ketoconazole (a potent inhibitor of CYP3A4) increased the mean area under the curve (AUC) for plasma concentration versus time of saxagliptin by 12, 109, and 145%, respectively. The mean AUC of 5-hydroxy saxagliptin was decreased by 2, 34, and 88% by simvastatin, diltiazem, and ketoconazole, respectively.[26] Saxagliptin produced small changes (≤ 13%) in the AUC of simvastatin, diltiazem, and ketoconazole that were not considered to be clinically significant. Based on these results, a maximum dose of 2.5 mg/day of saxagliptin is recommended when administered with a strong inhibitor of CYP3A4, such as ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, or telithromycin.[16]

Administration of rifampicin, a potent inducer of CYP3A4, with saxagliptin resulted in a 76% decrease in the AUC of saxagliptin and no change in the AUC of 5-hydroxy saxagliptin or in plasma DPP-4 activity.[28] Thus, no dosage adjustment is recommended by the manufacturer when saxagliptin is prescribed with rifampicin. In addition, saxagliptin exhibited no interactions with metformin, glyburide, or pioglitazone and can be administered with these antihyperglycemic medications without the need for dose adjustment of saxagliptin.[29] Finally, saxagliptin does not appear to inhibit or induce other important CYP450 isozymes or P-glycoprotein.[16,25]

Clinical Experience With Saxagliptin as Add-on Therapy for Type 2 Diabetes

Saxagliptin has been studied as monotherapy[30] and as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control despite receiving one or more of a variety of commonly used antihyperglycemic agents (Table 1).

Saxagliptin as add-on to metformin

Saxagliptin add-on therapy was evaluated in a 24-week, randomized, double-blind, placebo-controlled trial of patients inadequately controlled on metformin alone (mean baseline A1C 8.0%, mean disease duration 6.5 years).[31] Significant improvements in A1C, fasting plasma glucose (FPG), and 2-hour postprandial glucose (PPG) were seen with saxagliptin 2.5 and 5 mg/day + metformin versus placebo + metformin (Table 1). A greater percentage of patients receiving saxagliptin 2.5 mg + metformin (37.1%) and saxagliptin 5 mg + metformin (43.5%) achieved an A1C < 7.0% versus those taking placebo + metformin (16.6%, $P \leq 0.0001$ for both doses). Patients receiving saxagliptin had increased mean postprandial insulin and C-peptide AUC values and improvements in β-cell function (calculated using homeostatic model assessment [HOMA-2β][32]) at all doses versus metformin + placebo. There were small mean decreases (0.5–1.4 kg) in body weight across all treatment groups. In the extension to this study, which continued for up to 4 years, numerically greater reductions in A1C were observed for saxagliptin 5 mg + metformin versus placebo + metformin.[33]

Saxagliptin as add-on to glyburide

In a 24-week, randomized, double-blind, placebo-controlled trial, saxagliptin (2.5 and 5 mg/day) as an add-on to a submaximal dose of glyburide (7.5 mg/day) was compared with uptitrated glyburide + placebo in patients inadequately controlled with an SU.[34] Uptitration of glyburide to a maximum daily dose of 15 mg was allowed in patients receiving

Table 1. Combination Therapy With Saxagliptin: Results From Clinical Trials

		A1C						Adjusted Mean Change From Baseline					
		Change From Baseline (%)			A1C < 7% (% of patients)			FPG (mg/dl)			PPG at 2 hours (mg/dl)		
		Placebo	Saxagliptin (mg/day)		Placebo	Saxagliptin (mg/day)		Placebo	Saxagliptin (mg/day)		Placebo	Saxagliptin (mg/day)	
Add-On Trials	***n***		**2.5**	**5**		**2.5**	**5**		**2.5**	**5**		**2.5**	**5**
Saxa + Met versus Placebo + Met (30)	743*	+0.13	–0.59†	–0.69†	16.6	37.1†	43.5†	+1	–14†	–22†	–18	–62†	–58†
Saxa + Gly versus Placebo + Gly (33)	768	+0.08	–0.54†	–0.64†	9.1	22.4†	22.8†	+1	–7‡	–10§	+8	–31†	34†
Saxa + TZD versus Placebo + TZD (35)	565	–0.30	–0.66‖	–0.94†	25.6	42.2¶	41.8¶	–4	–14#	–18**	–18†	–54†	–72†
Saxa + Ins versus Placebo + Ins (± Met) (39)	455	–0.32	–	–0.73†	6.7	–	17.3	–6	–	–10	–4	–	–27§
Saxa + Met versus Glip + Met (40)	858	–0.80	–	–0.74††	47.8	–	42.6	–16	–	–9	–	–	–
Saxa + Met + SU versus Placebo + Met + SU (41)	257	–0.08	–	–0.74†	9.4	–	30.7	+3	–	–5	+5	–	–12‡‡
Initial Combination Trial	*n*	Met	Saxa 5 mg + Met		Met	Saxa 5 mg + Met		Met	Saxa 5 mg + Met		Met	Saxa 5 mg + Met	
	648*	–2.0	–2.5§§		41.1	60.3‖ ‖		–47	–60§§		–97	–138‖ ‖	

*FPG, fasting plasma glucose; Glip, glipizide; Gly, glyburide; Ins, insulin; Met, metformin; PPG, postprandial plasma glucose; Saxa, saxagliptin; SU, sulfonylurea; TZD, thiazolidinedione. *Trial also included treatment arms with saxagliptin 10 mg/day, an unapproved dose, †P ≤ 0.0001 versus placebo, ‡P = 0.02 versus placebo, §P = 0.002 versus placebo, ‖P = 0.0007 versus placebo, ¶P = 0.001 versus placebo, #P = 0.005 versus placebo, **P = 0.0005 versus placebo, ††noninferior to placebo, ‡‡P = 0.03 versus placebo, §§P = 0.0002 versus metformin, ‖ ‖P < 0.0001 versus metformin.*

glyburide + placebo. Patients had a mean baseline A1C of 8.4–8.5% and a disease duration of 6.8–7.1 years.

Significant improvements were seen in A1C, FPG, and PPG with saxagliptin + glyburide compared to placebo + uptitrated glyburide (Table 1). The proportion of patients achieving an A1C < 7.0% at week 24 was significantly greater for patients receiving saxagliptin 2.5 mg/day + glyburide (22.4%) and saxagliptin 5 mg/day + glyburide (22.8%) compared to those receiving uptitrated glyburide + placebo (9.1%, both $P < 0.0001$). There was no difference in change in β-cell function assessed with HOMA-2β among treatment groups. Saxagliptin + glyburide treatment was associated with greater increases in postprandial insulin and C-peptide AUC values and greater decreases in postprandial glucagon AUC compared with uptitrated glyburide + placebo. There were small mean increases in body weight in all treatment groups that were significantly greater in the saxagliptin + glyburide groups (0.7 and 0.8 kg) compared with the uptitrated glyburide + placebo group (0.3 kg). The improvements in glycemic control with saxagliptin compared to uptitrated glyburide were sustained over a 52-week, long-term extension of this trial.[35]

Saxagliptin as an add-on to TZDs

Saxagliptin (2.5 and 5 mg/day) as an add-on to TZD therapy was evaluated in a 24-week, randomized, double-blind, placebo-controlled trial of patients (mean baseline A1C 8.2–8.4%, disease duration 5.1–5.3 years) inadequately controlled on pioglitazone (30 or 45 mg/day) or rosiglitazone (4 or 8 mg/day).[36] At 24 weeks, significant improvements were seen with saxagliptin versus placebo add-on therapy in A1C, FPG, and PPG (Table 1). More patients achieved an A1C < 7.0% at 24 weeks for saxagliptin 2.5 mg/day + TZD (42.2%, $P = 0.001$) and saxagliptin 5 mg/day + TZD (41.8%, $P = 0.001$) than with placebo + TZD (25.6%).

Treatment with saxagliptin 5 mg/day + TZD significantly increased postprandial insulin and C-peptide AUC values and decreased postprandial glucagon AUC versus placebo + TZD. β-Cell function (by HOMA-2β) improved in patients receiving saxagliptin 2.5 and 5 mg/day + TZD compared to those receiving placebo + TZD. Small mean increases in body weight were observed in patients receiving saxagliptin + TZD (1.3–1.4 kg) and placebo + TZD (0.9 kg), which is consistent with other studies examining DPP-4 agents as add-on to TZD therapy.[37,38] The improvements in A1C, FPG, and PPG observed with saxagliptin + TZD versus placebo + TZD at 24 weeks were sustained for up to 76 weeks in a follow-on study.[39]

Saxagliptin as an add-on to insulin (± metformin)

Patients inadequately controlled with insulin alone or in combination with a stable dose of metformin were randomized to receive saxagliptin (5 mg/day) or placebo add-on therapy for 24 weeks.[40] Patients had a mean baseline A1C of 8.6–8.7% and a mean disease duration of 11.8–12.2 years. At baseline, the mean daily dose of insulin was 55.3 and 53.6 units for the placebo and saxagliptin groups, respectively. Insulin use in this study consisted of either an intermediate- or long-acting insulin, or a premixed insulin product with or without a separate intermediate- or long-acting insulin product. The distribution of insulin regimens used was similar between treatment groups. The majority of patients in the placebo (70%) and saxagliptin (69%) groups were taking metformin at mean doses of 1,861 and 1,805 mg/day, respectively.

Statistically significant improvements were seen with saxagliptin versus placebo add-on to insulin therapy for A1C and PPG, but not for FPG (Table 1). Placebo-subtracted mean reductions in A1C from baseline to week 24 for saxagliptin + insulin were the same with (–0.41% [95% CI –0.62 to –0.20%]) or without (–0.41% [–0.72 to –0.10%]) metformin use. In the saxagliptin + insulin group, a numerically greater proportion of patients achieved A1C < 7% (17.3%) than in the placebo + insulin group (6.7%). At 24 weeks, the adjusted mean increase in total daily insulin dose was numerically smaller for the saxagliptin group than for the placebo group (difference: –3.3 units per day [95% CI –5.6 to –1.1 units]). There were small increases in postprandial C-peptide AUC in both the saxagliptin + insulin and placebo + insulin groups. Additionally, a greater decrease from baseline to week 24 for postprandial glucagon AUC in the saxagliptin group was noted compared to the placebo group. There were small increases in body weight in both the placebo + insulin (0.2 kg) and saxagliptin + insulin (0.4 kg) groups.

Saxagliptin as an add-on to metformin versus glipizide as an add-on to metformin

Saxagliptin as an add-on to metformin therapy was also compared to glipizide as an add-on to metformin therapy in a 52-week, randomized, active-controlled trial of patients inadequately controlled on metformin alone (mean baseline A1C 7.7%, disease duration 5.4–5.5 years).[41] The combination of saxagliptin (5 mg/day) and metformin was noninferior to glipizide (5 mg/day titrated to 20 mg/day as needed) and metformin in improving A1C (Table 1). The proportion of patients with a baseline A1C ≥ 7.0% achieving an A1C < 7.0% was similar with saxagliptin + metformin (42.6%) and glipizide + metformin (47.8%). Patients treated

with glipizide + metformin had a greater mean increase in HOMA-2β (21.7% [standard error (SE) 2.6%]) compared to patients treated with saxagliptin + metformin (7.4% [SE 2.5%]). Saxagliptin + metformin treatment was associated with weight loss (–1.1 kg), whereas glipizide + metformin treatment was associated with weight gain (+1.1 kg) ($P < 0.0001$).

Saxagliptin as an add-on to metformin + SU

Saxagliptin (5 mg/day) as an add-on therapy was evaluated in a 24-week, randomized, double-blind, placebo-controlled trial of patients (baseline A1C 8.2–8.4%) inadequately controlled on combination therapy with metformin (≥ 1,500 mg/day) and an SU (≥ 50% of the maximum recommended dose).[42] Reductions in A1C ($P < 0.0001$) and PPG ($P = 0.03$) were significantly greater and reductions in FPG were numerically greater with saxagliptin + metformin + SU than with placebo added to metformin + SU (Table 1). The proportion of patients who achieved an A1C < 7% with saxagliptin + metformin + SU was 30.7% compared to 9.4% with placebo + metformin + SU. The mean change from baseline in body weight was 0.2 kg in the saxagliptin + metformin + SU group and −0.6 kg in the placebo + metformin + SU group.

Saxagliptin in combination with metformin as initial therapy

Saxagliptin 5 mg/day was combined with metformin (titrated to a maximum dose of 2,000 mg/day) as initial therapy in treatment-naive patients (mean baseline A1C 9.4%, disease duration 1.7–2 years) for 24 weeks.[43] Patients randomized to saxagliptin 5 mg/day + metformin demonstrated statistically significant reductions in A1C, FPG, and PPG from baseline compared to the metformin monotherapy group (Table 1). The proportion of patients achieving an A1C < 7% at week 24 was significantly greater for saxagliptin 5 mg/day + metformin (60.3%) compared to metformin monotherapy (41.1%, $P < 0.0001$ vs. monotherapy). The reductions in A1C, FPG, and PPG with saxagliptin + metformin were sustained up to 76 weeks in a long-term extension of this trial.[44]

At week 24, patients taking saxagliptin 5 mg/day + metformin had numerically greater increases in postprandial insulin AUC compared to metformin monotherapy. Effects on postprandial glucagon AUC at week 24 were minimal and similar across treatment groups. Significant improvements in β-cell function (by HOMA-2β) from baseline to week 24 occurred with saxagliptin 5 mg/day + metformin compared to metformin monotherapy ($P < 0.001$). Mean changes in body weight from baseline were –1.8 kg with saxagliptin 5 mg/day + metformin and –1.6 kg with metformin monotherapy.

Safety and Tolerability

In clinical trials, saxagliptin was generally well tolerated, and the proportion of patients reporting any adverse event (AE) was similar across treatment groups. In a pooled analysis of five placebo-controlled, 24-week monotherapy and add-on therapy trials, AEs reported in ≥ 5% of patients treated with saxagliptin 5 mg/day and more frequently than in patients treated with placebo were upper respiratory tract infection, urinary tract infection, and headache.[16] In the absence of insulin or SU combination therapy, reported events of hypoglycemia were low and similar to those with placebo.[31,36,43] In the trial of saxagliptin added on to insulin, hypoglycemia was reported in 18.4% of patients in the saxagliptin + insulin group (confirmed hypoglycemia by fingerstick glucose ≤ 50 mg/dl with associated symptoms 5.3%) and in 19.9% of patients in the placebo + insulin group (confirmed hypoglycemia 3.3%).[40] When saxagliptin was added to glyburide therapy, reported hypoglycemia was 13.3–14.6% (confirmed hypoglycemia 0.8–2.4%) with saxagliptin and 10.1% (confirmed hypoglycemia 0.7%) with uptitrated glyburide + placebo.[34] However, in the study comparing saxagliptin + metformin to glipizide + metformin, the proportion of patients reporting hypoglycemic events was 12-fold less in the saxagliptin group compared to the glipizide group (3.0 vs. 36.3%).[41]

Approximately 20–30% of individuals with diabetes will develop chronic kidney disease (CKD).[45] Metformin and an active metabolite of glyburide are cleared by the kidney; consequently, metformin is contraindicated and glyburide should be avoided in patients with advanced kidney disease.[46] Because saxagliptin and its major metabolite are excreted by the kidney,[25] the efficacy, safety, and tolerability of saxagliptin were evaluated in a randomized, parallel-group, double-blind, placebo-controlled study that enrolled 170 adult patients with type 2 diabetes and moderate (CrCl ≥ 30 and < 50 ml/min) or severe (CrCl < 30 ml/min) CKD and patients with end-stage renal disease (ESRD) undergoing dialysis.[47] Patients received saxagliptin 2.5 mg or placebo once daily for 12 weeks. Oral antihyperglycemic drugs and insulin therapy present at enrollment were continued throughout the study.

At 12 weeks, patients receiving saxagliptin achieved significantly ($P = 0.007$) greater adjusted mean reductions from baseline in A1C (–0.86%) compared to those receiving placebo (–0.44%). There were numerically greater reductions in A1C with saxagliptin compared to placebo in patients with moderate (–0.64 vs. –0.05%) and severe (–0.95 vs. –0.50%) renal impairment. In patients with ESRD, mean A1C reductions were similar for

saxagliptin (–0.84%) and placebo (–0.87%). The changes in A1C observed at 12 weeks were sustained over a 40-week, long-term extension of this trial.[48]

Mean saxagliptin plasma concentrations were generally similar across renal impairment categories, whereas mean plasma concentrations of 5-hydroxy saxagliptin were generally higher with increasing severity of renal impairment.[47] Saxagliptin was generally well tolerated, and no AE occurred at an incidence ≥ 5% in any treatment group. No persistent or clinically meaningful changes from baseline in renal function parameters were observed in either treatment group.

Pooled analyses of major adverse cardiovascular (CV) events (e.g., myocardial infarction [MI], stroke, or CV death) occurring during clinical development of DPP-4 inhibitors suggest that there is no increased risk of CV events with this class of compounds.[49–53] More definitively, two large randomized CV outcomes clinical trials with DPP-4 inhibitors have recently been completed. In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) trial,[54] adult patients (n = 16,492) with type 2 diabetes and a history of established CV disease or multiple CV risk factors received saxagliptin or placebo and were followed for a median of 2.1 years. Patients also received standard care for type 2 diabetes and CV risk factors. The primary composite endpoint of CV death, nonfatal MI, or nonfatal stroke occurred in 7.3% of patients receiving saxagliptin compared to 7.2% of those receiving placebo (hazard ratio [HR] 1.00, 95% CI 0.89–1.12, noninferiority $P < 0.001$, superiority $P = 0.99$), indicating that saxagliptin had no CV risk or benefit. The major secondary composite endpoint (CV death, nonfatal MI, nonfatal stroke, hospitalization for heart failure, hospitalization for unstable angina, or hospitalization for coronary revascularization) occurred in 12.8% of patients in the saxagliptin group compared to 12.4% of patients in the placebo group (HR 1.02, 95% CI 0.94–1.11, $P = 0.66$). A component of the secondary composite endpoint, hospitalization for heart failure, occurred more frequently with saxagliptin (3.5%) than with placebo (2.8%) (HR 1.27, 95% CI 1.07–1.51, $P = 0.007$). A secondary endpoint of all-cause mortality occurred in 4.9% of patients in the saxagliptin group compared to 4.2% in the placebo group (HR 1.11, 95% CI 0.96–1.27, $P = 0.15$).

In the second trial, Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care in Patients With Type 2 Diabetes and Acute Coronary Syndrome (EXAMINE),[55] the effects of alogliptin versus placebo were assessed in patients (n = 5,380) with type 2 diabetes and an acute coronary syndrome within 15 to 90 days before randomization. Patients continued to receive standard care for type 2 diabetes and CV risk factors and were followed up for a median 18 months. The primary composite endpoint of CV death, nonfatal MI, or nonfatal stroke occurred in 11.3% of patients randomized to alogliptin versus 11.8% of those randomized to placebo (HR 0.96, upper bound of CI ≤ 1.16, $P < 0.001$ for noninferiority, $P = 0.32$ for superiority), indicating no CV risk or benefit with alogliptin. There was no difference between alogliptin and placebo in the major secondary composite endpoint of CV death, nonfatal MI, nonfatal stroke, or urgent revascularization due to unstable angina (HR 0.95, upper bound of CI ≤ 1.14, $P = 0.26$ for superiority).

Summary and Conclusions

Because of the progressive nature of type 2 diabetes, most patients eventually require two or more drugs to achieve individualized glycemic goals. Combination therapy using agents with complementary but different mechanisms of action may improve glycemic control to a greater extent than monotherapy and allow the use of lower doses of combined antihyperglycemic medications. DPP-4 inhibitors are recommended as add-on therapy to metformin and as part of two- or three-drug combinations in patients not achieving or maintaining glycemic goals with metformin alone or as a component of a dual-therapy regimen. Saxagliptin is generally well tolerated and improves glycemic control with a low risk of hypoglycemia or weight gain. Saxagliptin has been shown to be effective when used as add-on therapy to metformin, SUs, TZDs, and insulin (with or without metformin) and as triple therapy with metformin and an SU.

As noted in the prescribing information and in this review, saxagliptin is a substrate of CYP3A4/5, and a dosage of 2.5 mg is recommended when it is administered with a strong CYP3A4/5 inhibitor (e.g., ketoconazole). Likewise, a 2.5-mg daily dose is recommended for individuals with an estimated CrCl < 50 ml/min. Pharmacokinetic studies indicate a low risk for drug-drug interactions with saxagliptin when administered with other drugs commonly used in people with type 2 diabetes. This could prove to be an advantage during regimen intensification in patients on multiple concomitant medications.

Implications for Clinicians

Desirable characteristics of DPP-4 inhibitors include once-daily oral dosing, low risk of hypoglycemia, and overall weight neutrality. These favorable attributes have led to DPP-4

inhibitors being recommended by several organizations as an option for monotherapy in patients with a contraindication to metformin or as a component of a multidrug regimen.[15] As illustrated previously, clinical trial data with saxagliptin demonstrate clinical efficacy in terms of A1C, FPG, and PPG reductions when used either as monotherapy or in combination with other oral antihyperglycemic medications. DPP-4 inhibition leads to glucose-dependent reductions in PPG, thus making these agents unique in that they can reduce PPG excursions with a low risk of hypoglycemia. Accordingly, DPP-4 inhibitors such as saxagliptin may be a useful add-on therapy for patients who are close to achieving their glycemic goal (A1C < 7.0% in most patients but individualized as needed) and who could benefit from a targeted reduction in PPG without significantly increasing their risk for hypoglycemic events.

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