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REVIEW

Overview of saxagliptin efficacy and safety in patients with type 2 diabetes and cardiovascular disease or risk factors for cardiovascular disease

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Abstract: Most individuals with type 2 diabetes mellitus have or will develop multiple independent risk factors for cardiovascular disease, particularly coronary artery disease (CAD). CAD is the leading cause of morbidity and mortality among individuals with type 2 diabetes mellitus, and treating these patients is challenging. The risk of hypoglycemia, weight gain, or fluid retention with some diabetes medications should be considered when developing a treatment plan for individuals with a history of CAD or at risk for CAD. Dipeptidyl peptidase-4 inhibitors are oral antihyperglycemic agents that inhibit the breakdown of the incretin hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, resulting in increased glucose-dependent insulin secretion and suppression of glucagon secretion. Saxagliptin is a potent and selective dipeptidyl peptidase-4 inhibitor that improves glycemic control and is generally well tolerated when used as monotherapy and as add-on therapy to other antihyperglycemic medications. This review summarizes findings from recently published post hoc analyses of saxagliptin clinical trials that have been conducted in patients with and without a history of cardiovascular disease and in patients with and without various risk factors for cardiovascular disease. The results show that saxagliptin was generally well tolerated and consistently improved glycemic control, as assessed by reductions from baseline in glycated hemoglobin, fasting plasma glucose concentration, and postprandial glucose concentration, regardless of the presence or absence of baseline cardiovascular disease, hypertension, statin use, number of cardiovascular risk factors, or high Framingham 10-year cardiovascular risk score.

Keywords: cardiovascular disease, dipeptidyl peptidase-4 inhibitors, incretin, saxagliptin, type 2 diabetes mellitus

Introduction

Diagnosed and undiagnosed diabetes, primarily type 2 diabetes mellitus (T2DM), affects an estimated 9.3% of the US population, and 25.9% of these are aged ≥65 years.[1] Most individuals with T2DM have or will develop multiple independent risk factors for cardiovascular disease (CVD), including hypertension, dyslipidemia, obesity, chronic kidney disease, and microalbuminuria.[1–4] Therefore, it is not surprising that CVD, in particular coronary artery disease (CAD), is the leading cause of morbidity and mortality among individuals with T2DM.[5] Adults with T2DM have a 2-fold to 5-fold higher risk of CVD compared with those without T2DM,[6,7] and 68% of deaths in individuals with T2DM aged ≥65 years are the result of CVD.[8]

Although observational studies suggest that hyperglycemia is associated with adverse cardiovascular events,[9–11] there is little evidence from interventional studies

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that reducing hyperglycemia reduces the number of adverse cardiovascular outcomes.[12–14] However, a long-term follow-up of the United Kingdom Prospective Diabetes Study[15] and a meta-analysis of five major diabetes trials[16] showed that, in individuals with T2DM, intensive glycemic control compared with dietary or standard care reduced mortality and some adverse cardiovascular outcomes, such as myocardial infarction (MI) and CAD. Moreover, intensive glycemic control, aggressive management of risk factors for CVD (eg, with antihypertensives, lipid-lowering agents, and aspirin therapy), and behavior modification have been shown to reduce the risk of adverse cardiovascular events and mortality in patients with T2DM and microalbuminuria.[17,18]

Treating patients with T2DM and a history of or risk factors for CVD is challenging because they are usually receiving several medications to treat multiple comorbidities, may be elderly, may be part of patient populations for whom various drugs are contraindicated (eg, nephropathy, congestive heart failure), and may have decreased medication adherence.[19,20] Moreover, the risk of hypoglycemia, weight gain, or fluid retention with some diabetes medications, such as sulfonylureas and thiazolidinediones, should be considered when developing a treatment plan for individuals with a history of or risk factors for CVD.[21,22]

The incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide are released by the gut in response to ingestion of food and have a number of actions on multiple organs (Figure 1).[23] Both hormones increase glucose-dependent insulin secretion. GLP-1 also suppresses glucagon secretion, inhibits gastric emptying, and induces satiety. Dipeptidyl peptidase-4 (DPP-4) is a ubiquitous enzyme that is responsible for the proteolytic inactivation of GLP-1 and glucose-dependent insulinotropic polypeptide. DPP-4 inhibitors are oral antihyperglycemic agents that inhibit the breakdown of GLP-1 and glucose-dependent insulinotropic polypeptide, and thus augment plasma levels of these hormones.[23] Saxagliptin is a potent and selective DPP-4 inhibitor that improves glycemic control and is generally well tolerated when used as monotherapy[24,25] and as add-on therapy to metformin,[26] glyburide,[27] pioglitazone,[28] or insulin ± metformin.[29] In contrast with insulin, sulfonylureas, and thiazolidinediones, DPP-4 inhibitors are weight neutral and are associated with a low rate of hypoglycemia when used as monotherapy.[30,31] In recent years, multiple post hoc analyses of saxagliptin clinical trials have been conducted to examine the efficacy and safety of saxagliptin in subgroups of patients with and without a history of CVD, with and without various cardiovascular risk factors, and with and without concomitant

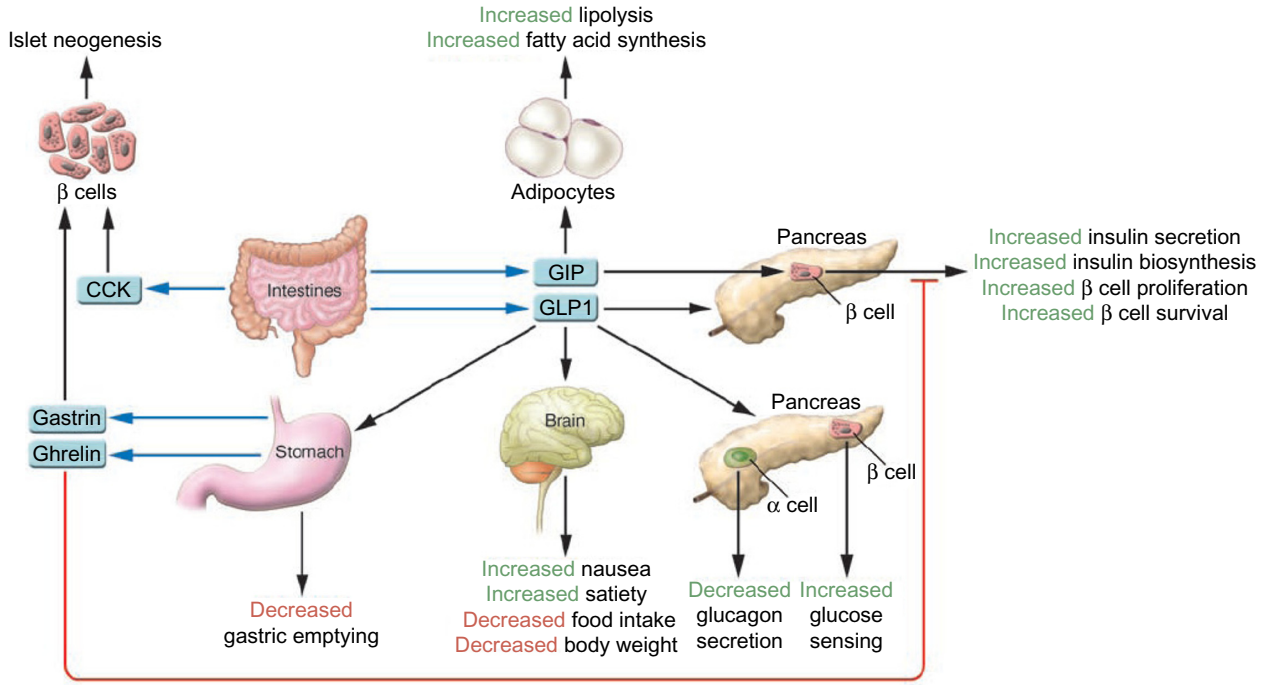

Figure 1 Role of incretin hormones in glucose regulation.
Note: Reproduced with permission from Drucker DJ. The role of gut hormones in glucose homeostasis. *J Clin Invest.* 2007;117:24–32.[23]
Abbreviations: CCK, cholecystokinin; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1.

statin therapy. The purpose of this review is to summarize the findings from these analyses.

Efficacy and safety of saxagliptin in patients with a history of or risk factors for CVD

Analyses of the efficacy and safety of saxagliptin in patients with a history of or risk factors for CVD (eg, hypertension, dyslipidemia, smoking, or a family history of CVD) were performed in two groups of patients. In the first analysis, data from five randomized, placebo-controlled, 24-week, Phase III clinical trials were pooled and compared saxagliptin 5 mg/day with placebo.[32] The five-study pool (Table 1) consisted of two studies of saxagliptin as monotherapy in drug-naïve patients[24,25] and one study each of saxagliptin as add-on therapy to metformin,[26] glyburide,[27] or pioglitazone.[28] In the second analysis, three randomized, controlled Phase III clinical trials were compared side by side.[33] These studies were of saxagliptin 5 mg/day in combination with metformin as initial therapy in treatment-naïve patients for 24 weeks,[34] saxagliptin add-on to metformin versus glipizide add-on

Table 1 Saxagliptin clinical trials

Study	N*	Treatment	Mean baseline HbA_{1c}, %†	Mean duration of T2DM, years†
Five-study pool				
NCT00121641[25]	401	SAXA 2.5, 5, or 10 mg/day versus PBO	7.8–8.0	2.3–3.1
NCT00316082[24]	365	SAXA 2.5 mg QAM ± titration to 5 mg, 5 mg QAM, or 5 mg QPM versus PBO	7.8–8.0	1.2–2.0
NCT00121667[26]	743	SAXA 2.5, 5, or 10 mg/day + MET versus PBO + MET	8.0	6.5
NCT00313313[27]	768	SAXA 2.5 or 5 mg/day + GLY versus PBO + uptitrated GLY	8.4–8.5	6.8–7.1
NCT00295633[28]	565	SAXA 2.5 or 5 mg/day + TZD versus PBO + TZD	8.2–8.4	5.1–5.3
Three side-by-side				
NCT00327015‡[34]	1,306	SAXA 5 or 10 mg/day + MET versus SAXA 10 mg/day + PBO or MET + PBO	9.4–9.6	1.4–2.0
NCT00575588[35]	858	SAXA 5 mg/day + MET versus glipizide + MET	7.7	5.4–5.5
NCT00757588[29]	455	SAXA 5 mg/day + INS ± MET versus PBO + INS ± MET	8.6–8.7	11.8–12.2
Nine-study pool				
NCT00121641[25]	401	SAXA 2.5, 5, or 10 mg/day versus PBO	7.8–8.0	2.3–3.1
NCT00316082[24]	365	SAXA 2.5 mg QAM ± titration to 5 mg, 5 mg QAM, or 5 mg QPM versus PBO	7.8–8.0	1.2–2.0
NCT00698932[42]	568	SAXA 5 mg/day versus PBO	8.1–8.2	0.8–1.2
NCT00918879[43]	213	SAXA 5 mg/day versus PBO	8.3	0.9
NCT00121667[26]	743	SAXA 2.5, 5, or 10 mg/day + MET versus PBO + MET	8.0	6.5
NCT00661362[44]	570	SAXA 5 mg/day + MET versus PBO + MET	7.9	5.1
NCT00313313[27]	768	SAXA 2.5 or 5 mg/day + GLY versus PBO + uptitrated GLY	8.4–8.5	6.8–7.1
NCT00295633[28]	565	SAXA 2.5 or 5 mg/day + TZD versus PBO + TZD	8.2–8.4	5.1–5.3
NCT00757588[29]	455	SAXA 5 mg/day + INS ± MET versus PBO + INS ± MET	8.6–8.7	11.8–12.2
Additional studies in eleven-study safety pool				
NCT01006590[45]	286	SAXA 5 mg/day + MET versus MET uptitration	7.7–7.8	6.0–6.9
NCT00327015‡[34]	1,306	SAXA 5 or 10 mg/day + MET versus SAXA 10 mg/day + PBO or MET + PBO	9.4–9.6	1.4–2.0
Additional studies in the 20-study safety pool				
NCT00614939[46]	170	SAXA 2.5 mg/day versus PBO (± other OADs or INS)	8.1–8.5	15.1–18.2
NCT00950599[48]	338	SAXA 2.5, 5, 10, 20, 40, or 100 mg/day versus PBO	7.5–8.0	0.3–1.8
NCT00374907[49]	36	SAXA 5 mg/day versus PBO	6.6–6.9	2.7–3.7
NCT00575588[35]	858	SAXA 5 mg/day + MET versus glipizide + MET	7.7	5.4–5.5
NCT00666458[50]	801	SAXA 5 mg/day + MET versus SITA 100 mg/day + MET	7.7	6.3
NCT00683657[51]	93	SAXA 5 mg/day + MET XR versus PBO + MET XR	8.1	6.9
NCT00885378[52]	160	SAXA (2.5 mg twice daily) + MET versus PBO + MET	7.9–8.0	5.8–6.2
NCT00918138[53]	93	SAXA 5 mg/day + MET XR versus MET XR uptitration	8.4–8.6	5.1–6.2
NCT00960076[54]	282	SAXA 5 mg/day + MET XR versus MET XR uptitration	8.3–8.4	5.9–6.5

Notes: *Randomized and treated patients. †Range of values where indicated. ‡Only the saxagliptin + metformin and metformin + placebo arms were included in the analyses.
Abbreviations: GLY, glyburide; HbA_{1c}, glycated hemoglobin; INS, insulin; MET, metformin; OAD, oral antihyperglycemic drug; PBO, placebo; QAM, once daily AM; QPM, once daily PM; SAXA, saxagliptin; SITA, sitagliptin; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione; XR, extended release.

Table 2 Efficacy of saxagliptin in patients with cardiovascular disease history or cardiovascular risk factors: five-study pool

	Adjusted mean change from baseline									Patients achieving HbA_{1c} <7.0%, %		
	HbA_{1c}, %			FPG, mg/dL			PPG, mg/dL					
	SAXA (n)	PBO (n)	Difference (95% CI)	SAXA (n)	PBO (n)	Difference (95% CI)	SAXA (n)	PBO (n)	Difference (95% CI)	SAXA (n)	PBO (n)	Difference (95% CI)
CVD history												
Yes	−0.70	−0.06	−0.64	−18	−2	−16	−55	−16	−38	44	20	22
	(110)	(96)	(−0.90, −0.38)	(110)	(96)	(−26.2, −5.3)	(88)	(64)	(−60.2, −31.2)	(110)	(96)	(8.2, 35.4)
No	−0.70	−0.01	−0.68	−13	1	−14	−52	−11	−41	35	18	16
	(746)	(680)	(−0.78, −0.58)	(756)	(686)	(−18.3, −10.4)	(574)	(520)	(−49.2, −33.7)	(747)	(680)	(10.9, 20.4)
Treatment-by-subgroup interaction	*P*=0.95			*P*=0.41			*P*=0.52					
CV risk factors												
≥2	−0.75	−0.02	−0.73	−15	0	−15	−53	−17	−36	38	20	17
	(459)	(410)	(−0.85, −0.60)	(463)	(411)	(−19.8, −9.7)	(354)	(308)	(−46.0, −26.2)	(460)	(410)	(10.4, 23.0)
≤1	−0.64	−0.02	−0.62	−12	2	−15	−52	−5	−47	35	17	16
	(402)	(369)	(−0.75, −0.48)	(408)	(374)	(−20.1, −9.4)	(312)	(278)	(−57.5, −36.5)	(402)	(369)	(9.8, 22.6)
Treatment-by-subgroup interaction	*P*=0.49			*P*=0.65			*P*=0.06					
Hypertension												
Yes	−0.73	−0.04	−0.69	−15	−1	−14	−54	−13	−41	38	20	17
	(457)	(437)	(−0.82, −0.57)	(461)	(439)	(−19.2, −9.2)	(351)	(327)	(−50.5, −30.9)	(458)	(437)	(10.6, 22.7)
No	−0.66	0	−0.66	−12	3	−16	−51	−9	−42	34	17	16
	(402)	(340)	(−0.80, −0.52)	(408)	(344)	(−21.2, −10.3)	(313)	(257)	(−52.6, −31.2)	(402)	(340)	(9.6, 23.0)
Treatment-by-subgroup interaction	*P*=0.80			*P*=0.74			*P*=0.39					
Statin use												
Yes	−0.66	0.04	−0.70	−13	3	−16	−56	−10	−46	38	18	18
	(211)	(211)	(−0.89, −0.52)	(211)	(211)	(−23.3, −8.8)	(158)	(150)	(−60.2, −31.2)	(211)	(211)	(9.0, 27.3)
No	−0.71	−0.05	−0.66	−14	0	−14	−51	−12	−40	36	19	16
	(650)	(568)	(−0.77, −0.56)	(660)	(574)	(−18.5, −10.0)	(508)	(436)	(−48.2, −31.6)	(651)	(568)	(10.6, 20.9)
Treatment-by-subgroup interaction	*P*=0.92			*P*=0.86			*P*=0.54					

Note: Data from Cook et al.[32]

Abbreviations: CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; PBO, placebo; PPG, postprandial glucose; SAXA, saxagliptin.

to metformin for 52 weeks,[35] and saxagliptin add-on to insulin ± metformin versus placebo add-on to insulin ± metformin for 24 weeks[29] (Table 1).

In all studies analyzed, patients were aged 18–77 years with T2DM and had a glycated hemoglobin (HbA_{1c}) level of 7%–10%,[24–26] 7.5%–10%,[27] 7%–10.5%,[28] 8%–12%,[34] >6.5%–10%,[35] or 7.5%–11%.[29] Major exclusion criteria that were common to all studies included: symptoms of poorly controlled diabetes; a significant cardiovascular event within 6 months of study entry or New York Heart Association class III or IV congestive heart failure and/or left ventricular ejection fraction ≤40%; and a significant history of renal or hepatic disease.

Efficacy end points were adjusted mean change from baseline to study end in HbA_{1c}, 120-minute postprandial glucose (PPG) concentration, fasting plasma glucose (FPG) concentration, and the proportion of patients achieving a therapeutic target of HbA_{1c} <7% at the end of the study. Safety data were analyzed for adverse events and all reported and confirmed hypoglycemia (fingerstick blood glucose level ≤50 mg/dL with associated symptoms). Efficacy was compared between patients with and without a history of CVD, patients with two or more cardiovascular risk factors and with no more than one cardiovascular risk factor, patients with and without hypertension, and patients with and without statin use. In all studies reported in this overview, treatment-by-subgroup interactions were analyzed to detect the inconsistency of treatment effects between saxagliptin and control across subgroups. Analyses that resulted in $P<0.1$ were considered to be suggestive of differential treatment effects among subgroups without judgment as to the statistical significance of the findings.

Table 3 Change in HbA_{1c} with saxagliptin in patients with cardiovascular disease history or cardiovascular risk factors: three side-by-side studies

	Adjusted mean change from baseline in HbA_{1c}								
	SAXA + MET (n)	**PBO + MET (n)**	**Difference (95% CI)**	**SAXA + MET (n)**	**GLIP + MET (n)**	**Difference (95% CI)**	**SAXA + INS ± MET (n)**	**PBO + INS ± MET (n)**	**Difference (95% CI)**
CVD history									
Yes	−2.14 (32)	−1.76 (52)	−0.38 (−0.91, 0.15)	−0.49 (76)	−0.70 (89)	0.21 (−0.04, 0.46)	−0.73 (84)	−0.50 (39)	−0.23 (−0.57, 0.10)
No	−2.53 (274)	−1.97 (261)	−0.56 (−0.77, −0.36)	−0.58 (347)	−0.64 (334)	0.06 (−0.06, 0.18)	−0.73 (216)	−0.25 (110)	−0.48 (−0.68, −0.27)
Treatment-by-subgroup interaction	*P*=0.53			*P*=0.28			*P*=0.22		
CV risk factors									
≥2	−2.54 (124)	−2.16 (124)	−0.38 (−0.68, −0.08)	−0.56 (259)	−0.64 (273)	0.08 (−0.06, 0.22)	−0.70 (145)	−0.43 (80)	−0.26 (−0.50, −0.02)
≤1	−2.45 (182)	−1.78 (189)	−0.67 (−0.91, −0.42)	−0.58 (164)	−0.68 (150)	0.10 (−0.08, 0.28)	−0.76 (155)	−0.18 (69)	−0.58 (−0.83, −0.33)
Treatment-by-subgroup interaction	*P*=0.15			*P*=0.84			*P*=0.07		
Hypertension									
Yes	−2.50 (154)	−2.02 (167)	−0.47 (−0.74, −0.21)	−0.58 (313)	−0.69 (305)	0.11 (−0.02, 0.24)	−0.75 (232)	−0.33 (112)	−0.41 (−0.61, −0.21)
No	−2.48 (152)	−1.82 (145)	−0.66 (−0.93, −0.38)	−0.52 (109)	−0.56 (118)	0.03 (−0.18, 0.25)	−0.65 (66)	−0.27 (36)	−0.38 (−0.75, −0.02)
Treatment-by-subgroup interaction	*P*=0.34			*P*=0.54			*P*=0.89		
Statin use									
Yes	−2.40 (19)	−1.84 (27)	−0.56 (−1.28, 0.15)	−0.50 (177)	−0.63 (169)	0.13 (−0.04, 0.30)	−0.82 (102)	−0.40 (71)	−0.42 (−0.69, −0.15)
No	−2.49 (287)	−1.94 (286)	−0.55 (−0.75, −0.36)	−0.61 (246)	−0.67 (254)	0.06 (−0.08, 0.20)	−0.69 (198)	−0.25 (78)	−0.44 (−0.67, −0.21)
Treatment-by-subgroup interaction	*P*=0.98			*P*=0.56			*P*=0.93		

Note: Data from Minervini et al[33] and Cook et al.[36]

Abbreviations: CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; GLIP, glipizide; HbA_{1c}, glycated hemoglobin; INS, insulin; MET, metformin; PBO, placebo; SAXA, saxagliptin.

Efficacy

In the five-study pooled analysis, greater reductions from baseline in HbA_{1c}, FPG, and PPG were observed with saxagliptin compared with placebo in patients with or without a history of CVD, in patients with two or more cardiovascular risk factors or with no more than one cardiovascular risk factor, in patients with or without hypertension, and in patients with or without statin use (Table 2).[32] There was no evidence of a treatment-by-subgroup interaction for HbA_{1c} or FPG, indicating that there was no difference in the treatment effect of saxagliptin on these parameters based on the presence or absence of CVD history, cardiovascular risk factors, hypertension, or statin use. However, there was a strong trend toward an interaction (P=0.06) for PPG and the number of cardiovascular risk factors. This appears to be the result of a numerically greater reduction from baseline in placebo-treated patients with two or more cardiovascular risk factors compared with those with no more than one cardiovascular risk factor. PPG reductions from baseline in the saxagliptin-treated patients did not differ between subgroups. At week 24, the proportion of patients achieving HbA_{1c} <7% was higher with saxagliptin compared with placebo regardless of subgroup.[32]

In the three-study side-by-side analyses of changes from baseline in HbA_{1c} (Table 3), saxagliptin reduced HbA_{1c} to a greater extent than placebo in the add-on to metformin and add-on to insulin studies, whereas similar decreases in HbA_{1c} were seen with saxagliptin compared with glipizide.[33,36] There was a suggestion of a treatment-by-subgroup interaction in the cardiovascular risk factor analysis in the add-on

Table 4 Change in fasting plasma glucose with saxagliptin in patients with cardiovascular disease history or cardiovascular risk factors: three side-by-side studies

	Adjusted mean change from baseline in FPG, mg/dL								
	SAXA + MET (n)	PBO + MET (n)	Difference (95% CI)	SAXA + MET (n)	GLIP + MET (n)	Difference (95% CI)	SAXA + INS ± MET (n)	PBO + INS ± MET (n)	Difference (95% CI)
CVD history									
Yes	−47 (34)	−45 (52)	−2 (−19.9, 15.7)	−7 (74)	−19 (87)	12 (1.8, 22.0)	−5 (84)	−13 (39)	8 (−10.3, 25.7)
No	−60 (281)	−46 (268)	−14 (−21.0, −7.3)	−10 (346)	−15 (333)	5 (−0.3, 9.5)	−12 (216)	−4 (110)	−8 (−19.2, 2.5)
Treatment-by-subgroup interaction	P=0.22			P=0.20			P=0.13		
CV risk factors									
≥2	−61 (127)	−47 (124)	−14 (−24.2, 5.19)	−8 (257)	−16 (272)	8 (2.2, 13.3)	−4 (144)	−10 (80)	6 (−7.4, 18.4)
≤1	−57 (188)	−45 (196)	−12 (−20.4, −3.9)	−11 (163)	−14 (148)	3 (−4.1, 10.4)	−16 (156)	−2 (69)	−14 (−27.0, −0.3)
Treatment-by-subgroup interaction	P=0.77			P=0.32			P=0.04		
Hypertension									
Yes	−60 (158)	−45 (169)	−14 (−23.3, −5.4)	−9 (310)	−16 (304)	8 (2.4, 12.7)	−9 (231)	−8 (112)	−1 (−11.2, 10.2)
No	−58 (157)	−47 (150)	−11 (−20.7, −2.2)	−12 (109)	−14 (116)	2 (−6.4, 10.6)	−15 (67)	−1 (36)	−15 (−33.8, 4.6)
Treatment-by-subgroup interaction	P=0.66			P=0.29			P=0.21		
Statin use									
Yes	−55 (19)	−49 (27)	−7 (−30.8, 17.7)	−9 (175)	−18 (167)	10 (2.8, 16.6)	−18 (102)	−9 (71)	−9 (−23.3, 5.4)
No	−59 (296)	−46 (293)	−13 (−20.1, −6.8)	−10 (245)	−14 (253)	4 (−2.1, 9.4)	−7 (198)	−4 (78)	−2 (−14.8, 10.0)
Treatment-by-subgroup interaction	P=0.59			P=0.19			P=0.50		

Note: Data from Minervini et al[33] and Cook et al.[36]

Abbreviations: CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; FPG, fasting plasma glucose; GLIP, glipizide; INS, insulin; MET, metformin; PBO, placebo; SAXA, saxagliptin.

to insulin study. This appears to be the result of a greater reduction from baseline in placebo-treated patients with two or more cardiovascular risk factors versus those with no more than one cardiovascular risk factor. The change from baseline in HbA_{1c} with saxagliptin in this study was similar in the two risk groups. Changes from baseline in FPG with saxagliptin were greater than those with placebo in the add-on to metformin study (Table 4), less with saxagliptin compared with glipizide, and similar with saxagliptin and placebo in the add-on to insulin study. Similar to the HbA_{1c} analysis, a greater reduction from baseline in FPG in placebo-treated patients with two or more cardiovascular risk factors versus those with no more than one cardiovascular risk factor resulted in a suggestion of a treatment-by-subgroup interaction in the add-on to insulin study. In most subgroups in the add-on to metformin and add-on to insulin studies, more patients treated with saxagliptin than placebo achieved HbA_{1c} <7% (Table 5). Similar proportions of patients in the saxagliptin versus glipizide study achieved HbA_{1c} <7% across the subgroups.

Safety

In the five-study pool, rates of one or more adverse events for saxagliptin and placebo were similar in each of the subgroups and ranged from 68% to 77% (Table 6). The proportion of patients with serious adverse events ranged from 2% to 7% across subgroups, with higher rates in patients with a history of CVD. The incidence of serious adverse events was similar or lower with saxagliptin compared with placebo. Reported hypoglycemic events ranged from 6% to 11% across subgroups. The rate of confirmed hypoglycemic events was <1% in all groups except the placebo group with a history of CVD (2%; Table 6).

In the three-study side-by-side analysis, rates of adverse events were comparable between saxagliptin and placebo across all subgroups (Table 7). There were no cases of confirmed hypoglycemia with saxagliptin in any of the cardiovascular subgroups in the add-on to metformin study or in the glipizide study. As expected, the incidence of confirmed hypoglycemia was higher in the add-on to insulin study, but was generally similar across subgroups.

Efficacy and safety of saxagliptin in patients with high Framingham 10-year cardiovascular risk scores

Individuals with T2DM are at high risk for development of CVD.[6,7] Therefore, the efficacy and safety of saxagliptin were analyzed in patients stratified by Framingham 10-year

Table 5 Proportion of patients with cardiovascular disease history or cardiovascular risk factors achieving HbA_{1c} <7.0%: three side-by-side studies

	Patients achieving HbA_{1c} <7.0%, % (n/N)								
	SAXA + MET	PBO + MET	Difference (95% CI)	SAXA + MET	GLIP + MET	Difference (95% CI)	SAXA + INS ± MET	PBO + INS ± MET	Difference (95% CI)
CVD history									
Yes	41 (13/32)	35 (18/52)	6 (−16.0, 27.7)	47 (36/76)	55 (49/89)	−8 (−22.8, 7.7)	13 (11/84)	10 (4/39)	3 (−12.0, 17.6)
No	63 (173/274)	42 (110/261)	21 (12.6, 29.2)	56 (193/347)	57 (191/334)	−2 (−9.1, 6.0)	19 (41/216)	6 (6/110)	14 (6.7, 20.4)
CV risk factors									
≥2	63 (78/124)	48 (59/124)	15 (2.5, 27.8)	54 (140/259)	59 (160/273)	−5 (−13.0, 4.0)	17 (25/145)	10 (8/80)	7 (−2.5, 17.0)
≤1	59 (108/182)	37 (69/189)	23 (12.7, 32.6)	54 (89/164)	53 (80/150)	1 (−10.1, 12.0)	17 (27/155)	3 (2/69)	15 (7.5, 21.5)
Hypertension									
Yes	63 (97/154)	44 (74/167)	19 (7.8, 29.3)	54 (168/313)	61 (185/305)	−7 (−14.8, 1.0)	17 (40/232)	8 (9/112)	9 (1.4, 17.0)
No	59 (89/152)	37 (53/145)	22 (10.7, 33.0)	55 (60/109)	47 (55/118)	8 (−4.7, 21.3)	17 (11/66)	3 (1/36)	14 (3.9, 23.8)
Statin use									
Yes	63 (12/19)	37 (10/27)	26 (−3.8, 52.6)	51 (91/177)	58 (98/169)	7 (−17.1, 4.0)	20 (20/102)	11 (8/71)	8 (−2.5, 19.2)
No	61 (174/287)	41 (118/286)	19 (11.1, 27.4)	56 (138/246)	56 (142/254)	0.2 (−8.6, 9.0)	16 (32/198)	3 (2/78)	14 (7.3, 19.9)

Note: Data from Minervini et al[33] and Cook et al.[36]

Abbreviations: CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; GLIP, glipizide; HbA_{1c}, glycated hemoglobin; INS, insulin; MET, metformin; n/N, number of patients achieving target/total number of patients in that group; PBO, placebo; SAXA, saxagliptin.

Table 6 Adverse events and incidence of hypoglycemia in patients with cardiovascular disease history or cardiovascular risk factors: five-study pool

n (%)	CVD history				CV risk factors				Hypertension				Statin use			
	Yes		No		≥2		≤1		Yes		No		Yes		No	
	SAXA n=111	PBO n=97	SAXA n=766	PBO n=699	SAXA n=468	PBO n=419	SAXA n=414	PBO n=380	SAXA n=466	PBO n=448	SAXA n=414	PBO n=349	SAXA n=214	PBO n=212	SAXA n=668	PBO n=587
≥1 AE	78 (70)	70 (72)	554 (72)	491 (70)	353 (75)	306 (73)	284 (69)	258 (68)	331 (71)	325 (73)	305 (74)	237 (68)	165 (77)	160 (76)	472 (71)	404 (69)
≥1 SAE	5 (5)	7 (7)	24 (3)	20 (3)	18 (4)	17 (4)	12 (3)	10 (3)	17 (4)	20 (5)	13 (3)	7 (2)	10 (5)	8 (4)	20 (3)	19 (3)
Hypoglycemia																
Reported	8 (7)	6 (6)	60 (8)	48 (7)	36 (8)	29 (7)	33 (8)	25 (7)	39 (8)	29 (7)	30 (7)	25 (7)	24 (11)	15 (7)	45 (7)	39 (7)
Confirmed*	0	2 (2)	4 (0.5)	1 (0.1)	3 (0.6)	3 (0.7)	1 (0.2)	0	3 (0.6)	3 (0.7)	1 (0.2)	0	1 (0.5)	2 (0.9)	3 (0.4)	1 (0.2)

Note: *Fingerstick glucose ≤50 mg/dL with symptoms. Data from Cook et al.[32]
Abbreviations: AE, adverse event; CV, cardiovascular; CVD, cardiovascular disease; PBO, placebo; SAE, serious adverse event; SAXA, saxagliptin.

cardiovascular risk score[37] ≥20% versus <20% from the same five-study pool discussed earlier.[38] The Framingham cardiovascular risk score is a multivariable risk prediction tool that estimates CVD risk in patients based on multiple risk factors, such as age, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, smoking, and diabetes status, and can be used as a guide for preventive care.[37] In this analysis, efficacy variables were adjusted mean change from baseline HbA_{1c}, FPG, and 120-minute PPG, and the proportion of patients achieving HbA_{1c} <7% at week 24. In patients with a Framingham 10-year cardiovascular risk score ≥20% versus <20%, mean age was higher (range across treatment groups, 60.0–60.6 years versus 49.9–50.1 years, respectively), mean duration of T2DM was longer (range across groups, 6.0 years versus 4.3–4.9 years), and a smaller proportion were women (32.1%–34.2% versus 68.3%–68.9%).

Efficacy

Change from baseline HbA_{1c} at week 24 was greater with saxagliptin compared with placebo in both patients with a Framingham cardiovascular risk score ≥20% and <20%. There was a significant treatment-by-subgroup interaction (P=0.01) in patients with a Framingham risk score ≥20% versus <20%, indicating a greater treatment effect of saxagliptin in patients with a risk score ≥20% (Table 8). Improvements from baseline in FPG and PPG were greater with saxagliptin versus placebo in both cardiovascular risk groups, with no evidence of a treatment-by-subgroup interaction (Table 8). In both cardiovascular risk groups, the HbA_{1c} target of <7% at week 24 was achieved by more patients treated with saxagliptin compared with placebo (Table 8).

Safety

Rates of adverse events and serious adverse events were similar across Framingham risk score groups and treatment groups (Table 9). The incidence of reported and confirmed hypoglycemia was low in both risk score groups and similar between saxagliptin and placebo.

Efficacy and safety of saxagliptin in patients with or without concomitant statin use

The American Diabetes Association recommends that statin therapy together with lifestyle changes be used in all patients with diabetes and CVD, regardless of baseline lipid values.[39] Statin therapy is also recommended for patients with diabetes who are aged >40 years without CVD and have one or more

Table 7 Adverse events and confirmed hypoglycemia in patients with cardiovascular disease history or cardiovascular risk factors: three side-by-side studies

Subgroup	SAXA + MET n=320	PBO + MET n=328	SAXA + MET n=428	GLIP + MET n=430	SAXA + INS ± MET n=304	PBO + INS ± MET n=151
CVD history						
Yes	n=34	n=53	n=79	n=91	n=85	n=39
≥1 AE	20 (59)	31 (59)	39 (49)	61 (67)	40 (47)	22 (56)
≥1 SAE	2 (6)	6 (11)	8 (10)	14 (15)	3 (4)	4 (10)
Confirmed hypoglycemia*	0	0	0	6 (7)	1 (1)	0
No	n=286	n=275	n=349	n=339	n=219	n=112
≥1 AE	158 (55)	161 (59)	224 (64)	233 (69)	133 (61)	68 (61)
≥1 SAE	6 (2)	2 (1)	31 (9)	21 (6)	9 (4)	3 (3)
Confirmed hypoglycemia	0	1 (0)	0	29 (9)	15 (7)	6 (5)
CV risk factor						
≥2	n=129	n=127	n=262	n=277	n=145	n=81
≥1 AE	81 (63)	76 (60)	168 (64)	200 (72)	78 (54)	47 (58)
≥1 SAE	5 (4)	2 (2)	28 (11)	25 (9)	7 (5)	5 (6)
Confirmed hypoglycemia	0	0	0	28 (10)	7 (5)	3 (4)
≤1	n=191	n=201	n=166	n=153	n=159	n=70
≥1 AE	97 (51)	116 (58)	95 (57)	94 (61)	95 (60)	43 (61)
≥1 SAE	3 (2)	6 (3)	11 (7)	10 (7)	5 (3)	2 (3)
Confirmed hypoglycemia	0	1 (1)	0	7 (5)	9 (6)	3 (4)
Hypertension						
Yes	n=160	n=172	n=318	n=311	n=234	n=113
≥1 AE	91 (57)	101 (59)	196 (62)	208 (67)	126 (54)	63 (56)
≥1 SAE	5 (3)	6 (4)	32 (10)	29 (9)	7 (3)	5 (4)
Confirmed hypoglycemia	0	0	0	26 (8)	11 (5)	3 (3)
No	n=160	n=155	n=109	n=119	n=68	n=37
≥1 AE	87 (54)	90 (58)	67 (62)	86 (72)	45 (66)	27 (73)
≥1 SAE	3 (2)	2 (1)	7 (6)	6 (5)	4 (6)	2 (5)
Confirmed hypoglycemia	0	1 (1)	0	9 (8)	5 (7)	3 (8)
Statin use						
Yes	n=20	n=27	n=180	n=172	n=103	n=71
≥1 AE	13 (65)	17 (63)	121 (67)	122 (71)	57 (55)	48 (68)
≥1 SAE	0	2 (7)	23 (13)	13 (8)	6 (6)	5 (7)
Confirmed hypoglycemia	0	0	0	16 (9)	8 (8)	4 (6)
No	n=300	n=301	n=248	n=258	n=201	n=80
≥1 AE	165 (55)	175 (58)	142 (57)	172 (67)	116 (58)	42 (53)
≥1 SAE	8 (3)	6 (2)	16 (7)	22 (9)	6 (3)	2 (3)
Confirmed hypoglycemia	0	1 (0)	0	19 (7)	8 (4)	2 (3)

Notes: Data from Minervini et al[33] and Cook et al.[36] Data are n (%). *Fingerstick glucose ≤50 mg/dL with symptoms.
Abbreviations: AE, adverse event; CV, cardiovascular; CVD, cardiovascular disease; GLIP, glipizide; INS, insulin; MET, metformin; PBO, placebo; SAE, serious adverse event; SAXA, saxagliptin.

CVD risk factors. Statin use in patients with T2DM is high. In an analysis of a primary care network, 63% of patients with T2DM were prescribed a statin.[40] In this analysis, the efficacy and safety of saxagliptin 2.5 and 5 mg/day, compared with placebo, in patients with or without concomitant statin use were analyzed from data pooled from nine placebo-controlled Phase III studies with a primary 24-week treatment period.[41] Studies included in the nine-study pool were four saxagliptin monotherapy trials,[24,25,42,43] two trials of saxagliptin as add-on to metformin,[26,44] and one each of saxagliptin as add-on to a sulfonylurea,[27] thiazolidinedione,[28] and insulin ± metformin.[29] Efficacy end points were change from baseline to week 24 in HbA_{1c}, FPG, and 120-minute PPG, and the proportion of patients achieving HbA_{1c} <7% at week 24.

Analyses of safety were performed on an eleven-study pool of 24-week clinical trials and an additional 20-study pool. The eleven-study safety pool included data for saxagliptin 2.5 and 5 mg/day and placebo or control from the nine studies in the efficacy pool plus two 24-week, randomized controlled studies of saxagliptin as add-on therapy

Table 8 Efficacy of saxagliptin in patients with high Framingham 10-year cardiovascular risk: five-study pool

	Adjusted mean change from baseline						Patients achieving HbA_{1c} <7.0%, % (n/N)	
	HbA_{1c}, % (n)		FPG, mg/dL (n)		PPG, mg/dL (n)			
	SAXA	PBO	SAXA	PBO	SAXA	PBO	SAXA	PBO
Framingham CV risk <20%	−0.61 (443)	−0.07 (390)	−13 (447)	0.2 (396)	−50 (347)	−9 (297)	35 (154/443)	19 (73/390)
Difference versus PBO (95% CI)	−0.54 (−0.67, −0.41)		−13 (−18.1, −7.8)		−42 (−51.7, −31.6)		14 (8.1, 20.7)	
Framingham CV risk ≥20%	−0.81 (400)	0 (374)	−16 (404)	0.6 (374)	−56 (306)	−15 (278)	38 (152/400)	19 (72/374)
Difference versus PBO (95% CI)	−0.81 (−0.94, −0.67)		−16 (−21.5, −10.8)		−41 (−51.3, −30.2)		18 (11.4, 24.6)	
Treatment-by-subgroup interaction	*P*=0.01		*P*=0.55		*P*=0.85			

Note: Data from Bonora et al.[38]

Abbreviations: CI, confidence interval; CV, cardiovascular; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; n/N, number of patients achieving target/total number of patients in that group; PBO, placebo; PPG, postprandial glucose; SAXA, saxagliptin.

to metformin[34,45] (only the saxagliptin + metformin and metformin + placebo arms were included in the analyses). The 20-study pool included data for all saxagliptin doses (2.5, 5, 10, 20, 40, and 100 mg/day) and placebo or control from the eleven studies in the 24-week safety pool and nine randomized clinical trials of 4–206 weeks' duration for saxagliptin as monotherapy[46–49] or as add-on to metformin.[35,50–54]

Patient demographics and baseline disease characteristics were generally consistent between treatment groups within the patient subpopulations of any statin use versus no statin use. However, compared with patients not using statins, patients receiving statins were slightly older (58 years versus 53–54 years) and more likely to be white (68%–77% versus 35%–65%), be men (50%–56% versus 45%–49%), have a body mass index ≥30 kg/m^2 (53%–59% versus 31%–49%), and have a diabetes duration ≥5 years (50%–57% versus 34%–42%).[41]

Efficacy

Significantly greater adjusted mean reductions from baseline were observed with saxagliptin versus control (Table 10).[41]

Table 9 Adverse events and confirmed hypoglycemia in patients with high Framingham 10-year cardiovascular risk

	Framingham 10-year CV risk score			
	<20%		≥20%	
	SAXA (n=454)	PBO (n=404)	SAXA (n=408)	PBO (n=380)
≥1 AE	318 (70)	275 (68)	302 (74)	277 (73)
≥1 SAE	13 (3)	9 (2)	16 (4)	18 (5)
Hypoglycemia				
Reported	36 (8)	28 (7)	29 (7)	26 (7)
Confirmed*	2 (0)	0	2 (1)	3 (1)

Notes: Data are n (%). *Fingerstick glucose ≤50 mg/dL with symptoms. Data from Bonora et al.[38]

Abbreviations: AE, adverse event; CV, cardiovascular; PBO, placebo; SAE, serious adverse event; SAXA, saxagliptin.

Also, greater proportions of patients achieved HbA_{1c} <7% with saxagliptin versus control, regardless of statin use (Table 10). There were no treatment-by-subgroup interactions detected for HbA_{1c}, FPG, or PPG between patients with or without baseline statin use.

Safety

In the eleven-study pool, the proportion of patients with one or more adverse events was slightly higher in patients using statins (63%–78%) compared with those with no statin use (55%–71%; Table 11). The incidence of one or more adverse events appeared to be higher with saxagliptin 2.5 mg/day than with saxagliptin 5 mg/day and control, irrespective of statin use. The incidence of reported hypoglycemia was similar across treatment groups but was slightly higher in patients with any statin use (range across treatment groups, 10%–12%) compared with patients with no statin use (4%–7%; Table 11). The incidence of events of confirmed hypoglycemia was low and similar in patients with any statin use (0%–2%) and with no statin use (0%–1%).

Discussion

Individuals with T2DM are at high risk for CVD[6,7] and often have multiple CVD risk factors.[1-4] Therefore, it is important to consider the effects of glucose-lowering medications not only on glycemic control, but also on cardiovascular risk.[55,56] This overview of published analyses of saxagliptin clinical trials in patients with T2DM demonstrates that saxagliptin consistently improved glycemic control, compared with placebo, as assessed by reductions from baseline in HbA_{1c}, FPG, and PPG, and the proportion of patients achieving a therapeutic goal of HbA_{1c} <7%, regardless of the presence or absence of baseline CVD history, hypertension, statin use, number of cardiovascular risk factors, or high Framingham 10-year cardiovascular

Table 10 Efficacy of saxagliptin in patients with or without statin use at baseline

	HbA_{1c}, %			FPG, mg/dL			PPG, mg/dL			Patients achieving HbA_{1c} <7.0%, % (n/N)		
	SAXA 2.5 mg (n)	SAXA 5 mg (n)	PBO (n)	SAXA 2.5 mg (n)	SAXA 5 mg (n)	PBO (n)	SAXA 2.5 mg (n)	SAXA 5 mg (n)	PBO (n)	SAXA 2.5 mg	SAXA 5 mg	PBO
Any statin use	−0.64	−0.73	−0.10	−11	−19	−3	−49	−58	−18	36	34	17
	(177)	(337)	(318)	(179)	(337)	(318)	(131)	(230)	(186)	(64/181)	(113/342)	(55/322)
Difference versus PBO	−0.53	−0.62		−9	−16		−31	−40		18	17	
(95% CI)	(−0.71, −0.36)	(−0.77, −0.48)		(−15.7, −1.4)	(−22.1, −10.3)		(−45.3, −16.6)	(−52.3, −27.8)		(8.5, 27.7)	(9.4, 23.7)	
No statin	−0.66	−0.70	−0.16	−14	−13	−2	−51	−46	−13	33	36	22
	(614)	(1,480)	(1,268)	(620)	(1,498)	(1,280)	(501)	(905)	(718)	(200/630)	(529/1,518)	(278/1,305)
Difference versus PBO	−0.51	−0.54		−12	−11	−2	−37	−33		13	15	
(95% CI)	(−0.60, −0.41)	(−0.61, −0.47)		(−16.0, −8.1)	(−14.0, −8.3)		(−44.7, −29.7)	(−38.9, −26.4)		(8.3, 18.2)	(11.7, 18.5)	
Treatment-by-subgroup interaction	P=0.47			P=0.81			P=0.93					

Note: Data from Bryzinski et al.[41]

Abbreviations: CI, confidence interval; FPG, fasting plasma glucose; HbA_{1c} glycated hemoglobin; PBO, placebo; PPG, postprandial glucose; SAXA, saxagliptin.

risk score. Moreover, in all analyses, including studies up to 206 weeks in duration, saxagliptin was generally well tolerated in patients with and without a history of CVD or cardiovascular risk factors. The frequencies of adverse events, serious adverse events, and confirmed hypoglycemia were comparable across treatment and cardiovascular risk subgroups. These results are consistent with the overall safety profile of the DPP-4 inhibitor class, as reported by a number of published meta-analyses.[57–61]

The analyses summarized in this review included patients with a history of or risk factors for CVD. Comparable safety data for saxagliptin have recently been reported from a post hoc pooled analysis performed on 20 Phase II/III trials of saxagliptin (N=9,156) in a more general population of patients with T2DM. The analysis focused on adverse events of special interest, including infections, hypersensitivity, pancreatitis, malignancies, and bone fractures.[62] In this population, the incidence of death, serious adverse events, discontinuations due to adverse events, pancreatitis, malignancy, and most of the other events of interest were similar in the saxagliptin and control groups. Only the incidence rates for bone fractures and hypersensitivity were higher with saxagliptin compared with control. An additional pooled analysis of the same 20 clinical trials found that saxagliptin was not associated with an increased risk of adjudicated major adverse cardiovascular events (cardiovascular deaths, MI, or stroke), compared with control, and saxagliptin was not associated with an increased risk of nonadjudicated heart failure.[63]

Although the results of this summary and the aforementioned meta-analysis suggest that saxagliptin is effective and well tolerated in patients with T2DM with a history of or risk factors for CVD, all of these analyses are post hoc and, as such, have inherent limitations and can provide only suggestive evidence. Because of concerns over the safety of some antidiabetes medications,[64] in 2008, the US Food and Drug Administration determined that new antihyperglycemic therapies must demonstrate cardiovascular safety. Two prospective trials designed to evaluate the cardiovascular safety of saxagliptin and alogliptin have recently been published. In the SAVOR (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus) trial,[65] 16,492 patients with T2DM and either established CVD or multiple risk factors for CVD were randomly assigned to receive saxagliptin 5 mg/day (or 2.5 mg/day in patients with an estimated glomerular filtration rate ≤50 mL/min) or placebo and were followed for a median of 2.1 years. The primary end point, a composite

Table 11 Adverse events and confirmed hypoglycemia in patients with or without statin use at baseline: eleven-study pool

n (%)	Any statin use			No statin use		
	SAXA		PBO	SAXA		PBO
	2.5 mg (n=192)	5 mg (n=436)	(n=418)	2.5 mg (n=690)	5 mg (n=1,891)	(n=1,676)
≥1 AE	150 (78)	279 (64)	264 (63)	487 (71)	1,094 (58)	921 (55)
≥1 SAE	11 (6)	19 (4)	16 (4)	20 (3)	57 (3)	38 (2)
Hypoglycemia						
Reported	22 (12)	50 (12)	40 (10)	47 (7)	107 (6)	71 (4)
Confirmed*	0	9 (2)	10 (2)	7 (1)	10 (1)	4 (0)

Notes: Data from Bryzinski et al.[41] *Fingerstick glucose ≤50 mg/dL with symptoms.
Abbreviations: AE, adverse event; PBO, placebo; SAE, serious adverse event; SAXA, saxagliptin.

of cardiovascular death, MI, or ischemic stroke, occurred in 7.3% of patients in the saxagliptin group and a similar proportion (7.2%) of those in the placebo group, resulting in a hazard ratio (95% confidence interval [CI]) of 1.00 (0.89, 1.12). There was also no difference between the saxagliptin and placebo groups for the major secondary composite end point of cardiovascular death, MI, stroke, hospitalization for unstable angina, hospitalization for coronary revascularization, or hospitalization for heart failure (hazard ratio 1.02; 95% CI 0.94, 1.11). A secondary end point of all-cause mortality occurred in 4.9% of patients in the saxagliptin group compared with 4.2% in the placebo group (hazard ratio 1.11; 95% CI 0.96, 1.27; P=0.15). A subanalysis of the individual components of the secondary composite end point revealed that a greater number of patients receiving saxagliptin compared with those receiving placebo were hospitalized for heart failure (3.5% versus 2.8%; hazard ratio 1.27; 95% CI 1.07, 1.51; P=0.007). The numbers of patients with hypersensitivity, infections, bone fractures, cancer, and pancreatitis were low and similar between the saxagliptin and placebo groups. A greater number of patients in the saxagliptin group (15.3%) versus the placebo group (13.4%) had at least one hypoglycemic event. After 2 years, HbA_{1c} and FPG were significantly lower with saxagliptin compared with placebo (7.5% versus 7.8%, respectively; 153 mg/dL versus 158 mg/dL; $P<0.001$ for both). Also, a significantly ($P<0.001$) greater proportion of patients achieved an HbA_{1c} <7% with saxagliptin (40%) versus placebo (30%).

In the second cardiovascular outcomes trial of a DPP-4 inhibitor, ie, EXAMINE (Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care),[66] 5,380 patients with T2DM and either an acute MI or unstable angina requiring hospitalization within the previous 15–90 days were randomized to alogliptin (6.25, 12.25, or 25 mg/day depending on estimated glomerular filtration rate) or placebo and followed for a median of 18 months. The primary end point was a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke, which occurred in a similar proportion of patients receiving alogliptin (11.3%) and placebo (11.8%; hazard ratio 0.96; upper boundary of the one-sided repeated CI, 1.16). A post hoc analysis of the composite end point of cardiovascular mortality and hospitalization for heart failure found a numerically greater proportion of patients hospitalized for heart failure in the alogliptin group (3.9%) than in the placebo group (3.3%). However, the difference between the groups was not statistically significant (hazard ratio 1.19; 95% CI 0.90, 1.58).[67] The incidence of serious adverse events, hypoglycemia, and pancreatitis was similar between the alogliptin and placebo groups. Compared with placebo, alogliptin significantly reduced HbA_{1c} (mean difference, –0.36%; $P<0.001$).

Summary and conclusion

Because of the high prevalence of CVD in patients with T2DM, antihyperglycemic therapies that improve or at least have no deleterious effects on CVD or cardiovascular risk factors are preferable.[68–70] The findings to date show that saxagliptin was generally well tolerated and consistently improved glycemic control, as assessed by reductions from baseline in HbA_{1c}, FPG, and PPG, regardless of the presence or absence of baseline CVD history, hypertension, statin use, number of cardiovascular risk factors, or high Framingham 10-year cardiovascular risk score. This overview of the efficacy and safety of saxagliptin in meta-analyses of clinical trials in patients with T2DM and CVD or cardiovascular risk factors and, more importantly, the results of SAVOR, the prospective cardiovascular outcomes trial, demonstrate that saxagliptin appears to be safe and is not associated with an increased risk of CVD, nor does it appear to reduce the incidence of adverse cardiovascular

events in patients with T2DM and increased cardiovascular risk.

Disclosure

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