ORIGINAL ARTICLE

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

BACKGROUND

The cardiovascular safety and efficacy of many current antihyperglycemic agents, including saxagliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor, are unclear.

METHODS

We randomly assigned 16,492 patients with type 2 diabetes who had a history of, or were at risk for, cardiovascular events to receive saxagliptin or placebo and followed them for a median of 2.1 years. Physicians were permitted to adjust other medications, including antihyperglycemic agents. The primary end point was a composite of cardiovascular death, myocardial infarction, or ischemic stroke.

RESULTS

A primary end-point event occurred in 613 patients in the saxagliptin group and in 609 patients in the placebo group (7.3% and 7.2%, respectively, according to 2-year Kaplan–Meier estimates; hazard ratio with saxagliptin, 1.00; 95% confidence interval [CI], 0.89 to 1.12; P=0.99 for superiority; P<0.001 for noninferiority); the results were similar in the "on-treatment" analysis (hazard ratio, 1.03; 95% CI, 0.91 to 1.17). The major secondary end point of a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, coronary revascularization, or heart failure occurred in 1059 patients in the saxagliptin group and in 1034 patients in the placebo group (12.8% and 12.4%, respectively, according to 2-year Kaplan–Meier estimates; hazard ratio, 1.02; 95% CI, 0.94 to 1.11; P=0.66). More patients in the saxagliptin group than in the placebo group were hospitalized for heart failure (3.5% vs. 2.8%; hazard ratio, 1.27; 95% CI, 1.07 to 1.51; P=0.007). Rates of adjudicated cases of acute and chronic pancreatitis were similar in the two groups (acute pancreatitis, 0.3% in the saxagliptin group and 0.2% in the placebo group; chronic pancreatitis, <0.1% and 0.1% in the two groups, respectively).

CONCLUSIONS

DPP-4 inhibition with saxagliptin did not increase or decrease the rate of ischemic events, though the rate of hospitalization for heart failure was increased. Although saxagliptin improves glycemic control, other approaches are necessary to reduce cardiovascular risk in patients with diabetes. (Funded by AstraZeneca and Bristol-Myers Squibb; SAVOR-TIMI 53 ClinicalTrials.gov number, NCT01107886.)

TYPE 2 DIABETES MELLITUS DOUBLES THE risk of major cardiovascular complications in patients with and in patients without established cardiovascular disease,[1-3] such that the majority of patients with diabetes die of cardiovascular diseases.[4] Although improved glycemic control has repeatedly been shown to reduce microvascular diabetic complications,[5] uncertainty remains regarding whether any particular glucose-lowering strategy, or specific therapeutic agent, is safe from a cardiovascular standpoint or can actually lower cardiovascular risk. With the possible exception of trials of metformin[6] and insulin,[7] most reported trials to date evaluating the effects on cardiovascular outcomes of specific glucose-lowering strategies or medications either have been insufficiently powered or have shown no significant cardiovascular benefit[8-10] or an increased risk of death[11] or heart failure.[12-15] Thus, there remains a strong clinical need to identify antihyperglycemic agents that are, at a minimum, safe and that can potentially reduce cardiovascular complications. Moreover, in 2008, the Food and Drug Administration and the European Medicines Agency simultaneously revised their approval processes for all new glucose-lowering therapies to require a demonstration of cardiovascular safety.[16]

Saxagliptin (Onglyza, AstraZeneca and Bristol-Myers Squibb) is a selective dipeptidyl peptidase 4 (DPP-4) inhibitor.[17] In phase 2–3 studies, treatment with saxagliptin improved glycemic control as compared with placebo and in pooled analyses reduced the risk of major cardiovascular events.[18] The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53 trial was designed to evaluate the safety and efficacy of saxagliptin with respect to cardiovascular outcomes in patients with diabetes mellitus who are at risk for cardiovascular events.

METHODS

STUDY OVERSIGHT

SAVOR-TIMI 53 was a multicenter, randomized, double-blind, placebo-controlled, phase 4 trial. We conducted the trial at 788 sites in 26 countries (see the Supplementary Appendix, available with the full text of this article at NEJM.org).[19] The trial was sponsored by AstraZeneca and Bristol-Myers Squibb and designed by the TIMI Study

Group and Hadassah Medical Organization in conjunction with the sponsors, who provided monitoring support and donated the drug. The protocol was approved by the relevant ethics committees at all participating centers. The raw database was provided to the TIMI Study Group, which, independently of the sponsor, performed the data analyses under the direction of one of the academic authors according to a prespecified statistical analysis plan (see the study protocol, available at NEJM.org). The first two authors wrote the first draft of the manuscript, and the TIMI Study Group drafted subsequent versions and made the decision to submit the manuscript for publication. The members of the TIMI Study Group and Hadassah Medical Organization assume responsibility for the accuracy and completeness of the data and all the analyses and for the fidelity of this report to the protocol.

STUDY POPULATION

Eligible patients had a history of documented type 2 diabetes mellitus, a glycated hemoglobin level of 6.5% to 12.0%, and either a history of established cardiovascular disease or multiple risk factors for vascular disease. To meet the criteria for established cardiovascular disease, patients had to be at least 40 years old and have a history of a clinical event associated with atherosclerosis involving the coronary, cerebrovascular, or peripheral vascular system. To meet the criteria for the multiple risk factors, patients had to be at least 55 years of age (men) or 60 years of age (women) with at least one of the following additional risk factors: dyslipidemia, hypertension, or active smoking. Patients were ineligible if they were currently receiving or had received within the previous 6 months an incretin-based therapy or if they had end-stage renal disease and were undergoing long-term dialysis, had undergone a renal transplantation, or had a serum creatinine level higher than 6.0 mg per deciliter (530 μmol per liter). The full eligibility criteria have been reported previously.[19] Written informed consent was obtained from all patients.

RANDOMIZATION AND STUDY TREATMENT

Eligible patients were randomly assigned, in a 1:1 ratio, to receive saxagliptin at a dose of 5 mg daily (or 2.5 mg daily in patients with an estimated glomerular filtration rate [GFR] of ≤50 ml per minute) or matching placebo. Randomization was performed by means of a central com-

puterized telephone or Web-based system in blocks of 4, with stratification according to the qualifying cardiovascular disease state (established cardiovascular disease vs. multiple risk factors only) and renal function (normal function or mild renal impairment [estimated GFR, >50 ml per minute] vs. moderate renal impairment [estimated GFR, 30 to 50 ml per minute] vs. severe renal impairment [estimated GFR, <30 ml per minute]).

Saxagliptin or placebo was administered in a blinded fashion until the end of the follow-up period. Patients in whom renal impairment (an estimated GFR of ≤50 ml per minute) developed during the study period had a single dose adjustment to 2.5 mg daily. All other therapy for the management of the patient's diabetes and cardiovascular disease — including adding, discontinuing, or changing the dose of concomitant antihyperglycemic drugs — was at the discretion of the responsible physician. Concomitant use of other DPP-4 inhibitors or glucagon-like peptide 1 agonists was not allowed.

END POINTS

The primary efficacy and safety end point was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke. The secondary efficacy end point included the primary composite end point plus hospitalization for heart failure, coronary revascularization, or unstable angina. Definitions of the end points, which are provided in the Supplementary Appendix, were developed to be consistent with the definitions in the Standardized Definitions for End Point Events in Cardiovascular Trials draft, which was created as an initiative of the Food and Drug Administration.[20] Pancreatitis was classified as acute (definite or possible) or chronic.

A clinical events committee comprising specialists in cardiovascular and pancreatic medicine, all of whom were unaware of the study-group assignments, adjudicated all components of the primary composite and secondary efficacy end points and all cases of pancreatitis.

Episodes of hypoglycemia were reported by the investigators and were classified as major if the events required a third party to intervene actively and minor if the patients had symptoms but recovered without assistance within 30 minutes after ingestion of carbohydrates. Investigators also reported any documented blood glucose

level lower than 54 mg per deciliter (3.0 mmol per liter), regardless of symptoms. Hypoglycemic events that required hospitalization were also classified separately.

STATISTICAL ANALYSIS

The primary safety and efficacy analyses were performed according to the intention-to-treat principle on data from all patients who underwent randomization, with the use of a Cox proportional-hazards model, with stratification according to baseline renal-impairment category and baseline cardiovascular risk group and with treatment as a model term. One planned interim analysis of efficacy was performed before completion of the study; therefore, a P value of less than 0.049 was considered to indicate statistical significance for the primary analysis. The trial was designed as a superiority trial, with a closed testing hierarchy to preserve the alpha level that prespecified that a test for noninferiority with respect to the primary composite end point should be performed first and a test for superiority performed thereafter. An on-treatment (modified intention-to-treat) analysis, which included events that occurred within 30 days after the last dose of study medication was administered, was performed as a sensitivity analysis. Further details of the statistical analysis have been reported previously[19] and are presented in the Supplementary Appendix.

RESULTS

STUDY PATIENTS

From May 2010 through December 2011, a total of 16,492 patients underwent randomization. The median follow-up period was 2.1 years (interquartile range, 1.8 to 2.3), and the maximum follow-up time was 2.9 years. The total observation time was 16,884 person-years in the saxagliptin group and 16,761 person-years in the placebo group. Details of the study assignment and patient disposition are presented in Figure S1 in the Supplementary Appendix. The study drug was discontinued prematurely less frequently among patients assigned to saxagliptin than among patients assigned to placebo (1527 patients [18.4%] vs. 1705 patients [20.8%], P<0.001). A final vital status was assessed in 99.1% of the patients. A total of 28 patients were lost to follow-up. The baseline characteristics of the patients who underwent randomization, which were

reported previously[21] and are shown in Table 1 and Table S1 in the Supplementary Appendix, were well balanced between the two groups.

The fasting plasma glucose levels were significantly lower in the saxagliptin group than in the placebo group at 2 years and at the end of the treatment period (P<0.001 for both comparisons), and glycated hemoglobin levels were significantly lower in the saxagliptin group than in the placebo group at 1 year (7.6% vs. 7.9%), at 2 years (7.5% vs. 7.8%), and at the end of the treatment period (7.7% vs. 7.9%) (P<0.001 for all comparisons). Specifically, significantly more patients in the saxagliptin group than in the placebo group had a glycated hemoglobin level of less than 7% by the end of the treatment period (36.2% vs. 27.9%, P<0.001) (Table S2 in the Supplementary Appendix). Fewer patients in the saxagliptin group than in the placebo group required an increase in the dose of antihyperglycemic medication or the addition of a new antihyperglycemic medication (1938 patients [23.7% according to 2-year Kaplan–Meier estimates] vs. 2385 patients [29.3% according to 2-year Kaplan–Meier estimates]; hazard ratio with saxagliptin, 0.77; 95% confidence interval [CI], 0.73 to 0.82; P<0.001) or the initiation of insulin therapy for more than 3 months (454 patients [5.5% according to 2-year Kaplan–Meier estimates] vs. 634 patients [7.8% according to 2-year Kaplan–Meier estimates];

Characteristic	Saxagliptin (N = 8280)	Placebo (N = 8212)
Table 1. Baseline Characteristics of the Patients.*		
Age		
Mean — yr	65.1±8.5	65.0±8.6
≥75 yr — no. (%)	1169 (14.1)	1161 (14.1)
Female sex — no. (%)	2768 (33.4)	2687 (32.7)
White race — no. (%)†	6241 (75.4)	6166 (75.1)
Hispanic ethnic group — no. (%)†	1778 (21.5)	1763 (21.5)
Weight‡		
Mean — kg	87.7±18.7	88.1±19.4
≥80 kg — no. (%)	5291 (63.9)	5265 (64.2)
Body-mass index§		
Mean	31.1±5.5	31.2 ±5.7
≥30 — no. (%)	4446 (53.7)	4370 (53.4)
Duration of diabetes — yr¶		
Median	10.3	10.3
Interquartile range	5.2–16.7	5.3–16.6
Established atherosclerotic disease — no. (%)	6494 (78.4)	6465 (78.7)
Hypertension — no. (%)	6725 (81.2)	6767 (82.4)
Dyslipidemia — no. (%)	5895 (71.2)	5844 (71.2)
Prior myocardial infarction — no. (%)	3147 (38.0)	3090 (37.6)
Prior heart failure — no. (%)	1056 (12.8)	1049 (12.8)
Prior coronary revascularization — no. (%)	3566 (43.1)	3557 (43.3)
Glycated hemoglobin‖		
Mean — %	8.0±1.4	8.0±1.4
Distribution — no. (%)		
<6.5%	590 (7.3)	673 (8.3)
6.5 to <7.0%	1442 (17.7)	1414 (17.5)
7.0 to <8.0%	2759 (33.9)	2657 (32.9)
8.0 to <9.0%	1577 (19.4)	1562 (19.4)
≥9%	1761 (21.7)	1764 (21.9)

Table 1. (Continued.)		
Characteristic	Saxagliptin (N=8280)	Placebo (N=8212)
Fasting serum glucose — mg/dl**	156±56	157±57
Estimated glomerular filtration rate		
Mean — ml/min	72.5±22.6	72.7±22.6
Distribution — no. (%)		
<30 ml/min	172 (2.1)	164 (2.0)
30 to ≤50 ml/min	1122 (13.6)	1118 (13.6)
>50 ml/min	6986 (84.4)	6930 (84.4)
Albumin-to-creatinine ratio††		
Median	1.8	1.9
Interquartile range	0.7–7.5	0.7–7.9
Distribution — no. (%)		
<3.4	4867 (61.5)	4829 (61.6)
3.4 to 33.9	2217 (28.0)	2209 (28.2)
>33.9	832 (10.5)	806 (10.3)

* Plus–minus values are means ±SD. There were no significant differences between the two groups in any of the characteristics listed here. To convert the values for glucose to millimoles per liter, multiply by 0.05551.
† Race and ethnic group were self-reported.
‡ Data were available for 8277 patients in the saxagliptin group and 8197 in the placebo group.
§ Body-mass index is the weight in kilograms divided by the square of the height in meters. Data were available for 8273 patients in the saxagliptin group and 8190 in the placebo group.
¶ Data were available for 8270 patients in the saxagliptin group and 8207 in the placebo group.
‖ Data were available for 8129 patients in the saxagliptin group and 8070 in the placebo group.
** Data were available for 7892 patients in the saxagliptin group and 7805 in the placebo group.
†† Albumin was measured in milligrams, and creatinine was measured in millimoles. Data were available for 7916 patients in the saxagliptin group and 7844 in the placebo group.

hazard ratio, 0.70; 95% CI, 0.62 to 0.79; P<0.001). (Table S1 in the Supplementary Appendix provides details on the actual medication use over time.) Patients treated with saxagliptin were significantly more likely than patients receiving placebo to have an improved albumin-to-creatinine ratio and less likely to have a worsening ratio (Table S3 in the Supplementary Appendix).

CARDIOVASCULAR END POINTS

A primary end-point event of cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke occurred in 613 patients in the saxagliptin group (7.3%, according to 2-year Kaplan–Meier estimates; 3.7 per 100 person-years) and in 609 patients in the placebo group (7.2%, according to 2-year Kaplan–Meier estimates; 3.7 per 100 person-years) (hazard ratio, 1.00; 95% CI, 0.89 to 1.12; P=0.99 for superiority and P<0.001 for noninferiority) (Table 2 and Fig. 1A). Similar results were seen in the modified intention-to-treat (on-treatment) population (6.8% with saxagliptin vs. 6.4% with placebo, according to

2-year Kaplan–Meier estimates; hazard ratio with saxagliptin, 1.03; 95% CI, 0.91 to 1.17; P=0.60) (Table S5 in the Supplementary Appendix).

A major secondary end-point event of cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, hospitalization for unstable angina, coronary revascularization, or heart failure occurred in 1059 patients in the saxagliptin group (12.8%, according to 2-year Kaplan–Meier estimates; 6.6 per 100 person-years) and in 1034 patients in the placebo group (12.4%, according to 2-year Kaplan–Meier estimates; 6.5 per 100 person-years) (hazard ratio, 1.02; 95% CI, 0.94 to 1.11; P=0.66) (Table 2 and Fig. 1B). Individual components of these composite end points are shown in Table 2. More patients in the saxagliptin group than in the placebo group were hospitalized for heart failure (3.5% vs. 2.8%, according to 2-year Kaplan–Meier estimates; hazard ratio, 1.27; 95% CI, 1.07 to 1.51; P=0.007).

The results of additional analyses of efficacy in prespecified subgroups, including subgroups defined according to status with respect to car-

Table 2. Prespecified Clinical End Points.*

End Point	Saxagliptin (N=8280)	Placebo (N=8212)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Cardiovascular death, myocardial infarction, or stroke: primary efficacy end point	613 (7.3)	609 (7.2)	1.00 (0.89–1.12)	0.99
Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization: secondary efficacy end point	1059 (12.8)	1034 (12.4)	1.02 (0.94–1.11)	0.66
Death from any cause	420 (4.9)	378 (4.2)	1.11 (0.96–1.27)	0.15
Death from cardiovascular causes	269 (3.2)	260 (2.9)	1.03 (0.87–1.22)	0.72
Myocardial infarction	265 (3.2)	278 (3.4)	0.95 (0.80–1.12)	0.52
Ischemic stroke	157 (1.9)	141 (1.7)	1.11 (0.88–1.39)	0.38
Hospitalization for unstable angina	97 (1.2)	81 (1.0)	1.19 (0.89–1.60)	0.24
Hospitalization for heart failure	289 (3.5)	228 (2.8)	1.27 (1.07–1.51)	0.007
Hospitalization for coronary revascularization	423 (5.2)	459 (5.6)	0.91 (0.80–1.04)	0.18
Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dl (530 μmol/liter)	194 (2.2)	178 (2.0)	1.08 (0.88–1.32)	0.46
Hospitalization for hypoglycemia	53 (0.6)	43 (0.5)	1.22 (0.82–1.83)	0.33

* Event rates and percentages are 2-year Kaplan–Meier estimates.

diovascular risk and baseline renal function, are shown in Figures S2 and S3 in the Supplementary Appendix. The adjudicated causes of death are shown in Table S4 in the Supplementary Appendix.

SAFETY END POINTS

The prespecified safety end points are listed in Table 3. The numbers of patients with thrombocytopenia, lymphocytopenia, infections, cancers, hypersensitivity or skin reactions, bone fractures, or liver abnormalities were similar in the saxagliptin and placebo groups. Hospitalization for hypoglycemia occurred infrequently, and the rate was similar in the two groups: 0.6% according to 2-year Kaplan–Meier estimates (53 patients) in the saxagliptin group and 0.5% according to 2-year Kaplan–Meier estimates (43 patients) in the placebo group (hazard ratio with saxagliptin, 1.22; 95% CI, 0.82 to 1.83; P=0.33). However, significantly more patients in the saxagliptin group than in the placebo group reported at least one hypoglycemic event (1264 patients [15.3%] vs. 1104 patients [13.4%], P<0.001); major hypoglycemic events occurred in 177 patients (2.1%) in the saxagliptin group as compared with 140 patients (1.7%) in the placebo group (P=0.047), and minor hypoglycemic events in 1172 patients (14.2%) in the saxagliptin group, as compared

with 1028 patients (12.5%) in the placebo group (P=0.002). Pancreatitis occurred infrequently, and the number of patients with acute or chronic pancreatitis was similar in the two groups (24 patients [0.3%] in the saxagliptin group and 21 patients [0.3%] in the placebo group, P=0.77). Definite or possible acute pancreatitis occurred in 22 patients (0.3%) in the saxagliptin group and in 16 patients (0.2%) in the placebo group (P=0.42), definite acute pancreatitis in 17 patients (0.2%) and 9 patients (0.1%) in the two groups, respectively (P=0.17), and chronic pancreatitis in 2 patients (<0.1%) and 6 patients (0.1%), respectively (P=0.18). There were 5 cases of pancreatic cancer in the saxagliptin group and 12 in the placebo group (P=0.095). There were no cases of fatal angioedema; nonfatal angioedema occurred in 8 patients in the saxagliptin group and 1 in the placebo group (P=0.04).

DISCUSSION

In this randomized, placebo-controlled trial, the DPP-4 inhibitor saxagliptin neither reduced nor increased the risk of the primary composite end point of cardiovascular death, myocardial infarction, or ischemic stroke, when added to the standard of care in patients at high risk for cardiovascular events, thus meeting the criterion for

noninferiority[16] to placebo but not providing any cardioprotective benefit. Saxagliptin was associated with significantly improved glycemic control and reduced the development and progression of microalbuminuria; however, it increased the risk of hospitalization for heart failure and the risk of hypoglycemic events. Taken together, our findings provide data to evaluate both the benefits and risks of saxagliptin in patients at high risk for cardiovascular events.

Saxagliptin, together with several other DPP-4 inhibitors, represents a class of oral antihyperglycemic agents that are approved for glycemic control. Pooled data from the phase 2b–3 studies of saxagliptin showed that patients treated with saxagliptin had a significantly lower rate of major adverse cardiovascular events than did control patients.[18] Moreover, pooled analyses from other development programs for DPP-4 inhibitors showed similar trends toward improved cardiovascular outcomes with active therapy.[22,23] The apparent discordance between the findings of the phase 2b–3 trials and this larger, postmarketing trial highlights the importance of performing properly powered studies with appropriate follow-up and formalized adjudication procedures to provide a full evaluation of the long-term risks and benefits of therapy.

There are several potential explanations for the finding that a median of 2 years of therapy with saxagliptin did not reduce the rate of ischemic events, despite improved glycemic indexes. First, exposure to the study drug may not have been long enough to reverse the effects of years of pro-atherosclerotic processes in patients with a median duration of diabetes mellitus of more than 10 years; therefore, the study does not exclude the possibility of either benefit or risk with a longer duration of saxagliptin therapy. The United Kingdom Prospective Diabetes Study (UKPDS), for example, required 10 years of follow-up after the actual intervention period was complete to show a beneficial effect of intense glucose control on reducing the risk of myocardial infarction, though that study included low-risk patients who were enrolled soon after the diagnosis of diabetes.[6]

Second, the actual difference in glycated hemoglobin levels between the study groups was relatively small because additional antihyperglycemic therapy was prescribed at the discretion of the treating physician and was used more frequently in the control group than in the saxa-
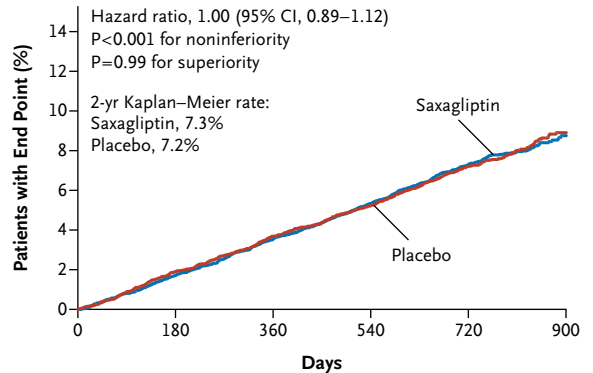
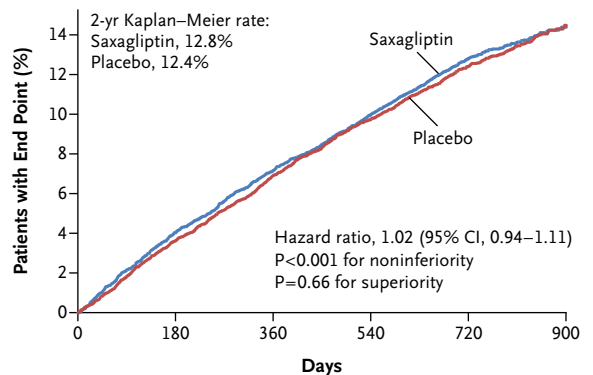**Figure 1. Kaplan–Meier Rates of the Primary and Secondary End Points.**

The primary end point (Panel A) was a composite of death from cardiovascular causes, myocardial infarction, or ischemic stroke. The secondary end point (Panel B) was a composite of death from cardiovascular causes, myocardial infarction, ischemic stroke, hospitalization for unstable angina, coronary revascularization, or heart failure.

gliptin group. However, other studies in which there was greater glycemic differentiation over a longer period have also not individually shown definitive macrovascular benefit with more intense glycemic control,[9-11] and therefore, the overall hypothesis that improved glycemic control will reduce macrovascular events remains in question. Moreover, a large proportion of patients in our trial received statins, antiplatelet therapy, and blood-pressure–lowering agents — therapies that may have mitigated the cardiovascular risk and blunted potential differences between the study groups.[21,24]

End Point	Saxagliptin (N=8280)	Placebo (N=8212)	P Value*
	no. (%)		
Thrombocytopenia	55 (0.7)	65 (0.8)	0.36
Lymphocytopenia	49 (0.6)	40 (0.5)	0.40
Severe infection	590 (7.1)	576 (7.0)	0.78
Opportunistic infection	21 (0.3)	35 (0.4)	0.06
Hypersensitivity reaction	93 (1.1)	89 (1.1)	0.82
Bone fracture	241 (2.9)	240 (2.9)	1.00
Skin reaction	228 (2.8)	232 (2.8)	0.81
Renal abnormality	483 (5.8)	418 (5.1)	0.04
Any hypoglycemia†	1264 (15.3)	1104 (13.4)	<0.001
Major	177 (2.1)	140 (1.7)	0.047
Minor	1172 (14.2)	1028 (12.5)	0.002
Cancer	327 (3.9)	362 (4.4)	0.15
Any liver abnormality†	55 (0.7)	67 (0.8)	0.28
AST >3× ULN	60 (0.7)	61 (0.7)	0.93
AST >10× ULN	12 (0.1)	15 (0.2)	0.57
ALT or AST >3× ULN and total bilirubin >2× ULN	13 (0.2)	23 (0.3)	0.097
Any pancreatitis†	24 (0.3)	21 (0.3)	0.77
Acute: definite or possible	22 (0.3)	16 (0.2)	0.42
Acute: definite	17 (0.2)	9 (0.1)	0.17
Acute: possible	6 (0.1)	7 (0.1)	0.79
Chronic	2 (<0.1)	6 (0.1)	0.18

Table 3. Safety End Points.

* P values were calculated with the use of a chi-square test or Fisher's exact test. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and ULN upper limit of the normal range.
† Patients may have had more than one type of event.

The observation of a higher incidence of hospitalization for heart failure among patients treated with saxagliptin was unexpected and should be considered within the context of multiple testing that may have resulted in a false positive result. This finding merits further investigation and needs to be confirmed in other ongoing studies, and a class effect should not be presumed.[25,26] The increased risk of heart failure has been observed with other antihyperglycemic agents, including thiazolidinediones[13,27] and dual peroxisome-proliferator–activated receptor α−γ agonists,[15] with divergent results in trials of intensive glucose management.[28,29]

Saxagliptin reduced the development and progression of microalbuminuria, though it is unclear whether the degree of change observed in our study would be associated with a subsequent decrease in cardiovascular or renal complications.[30,31] We found no differences between saxa-gliptin and placebo with respect to the prespecified adverse events of special interest, including acute or chronic pancreatitis. We also found no excess of pancreatic cancer with saxagliptin, despite observational reports of a potential association between DPP-4 inhibitors and these events.[32-35]

Numerous studies, even those involving patients with advanced cardiovascular disease, have shown that improved glycemic control reduces microvascular complications. Thus, there remains a strong clinical need for antihyperglycemic drugs that can improve glycemic control without increasing the risk of cardiovascular complications. Few antihyperglycemic agents have been evaluated as extensively as saxagliptin was in this trial; the findings point to likely but unproven benefit with respect to microvascular disease without adverse macrovascular outcomes. Together with ongoing trials of other DPP-4 inhibitors and novel antihyperglycemic agents,

these data will provide a more rigorous and robust evidence base than is currently available to guide the future care of patients with diabetes.

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