Efficacy and Safety of Saxagliptin in Older Participants in the SAVOR-TIMI 53 Trial

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OBJECTIVE

To examine the safety and cardiovascular (CV) effects of saxagliptin in the predefined elderly (≥65 years) and very elderly (≥75 years) subpopulations of the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial.

RESEARCH DESIGN AND METHODS

Individuals ≥40 years (*n* = 16,492; elderly, *n* = 8,561; very elderly, *n* = 2,330) with HbA_{1c} ≥6.5% (47.5 mmol/mol) and ≤12.0% (107.7 mmol/mol) were randomized (1:1) to saxagliptin (5 or 2.5 mg daily) or placebo in a double-blind trial for a median follow-up of 2.1 years.

RESULTS

The hazard ratio (HR) for the comparison of saxagliptin versus placebo for the primary end point (composite of CV mortality, myocardial infarction, or ischemic stroke) was 0.92 for elderly patients vs. 1.15 for patients <65 years (*P* = 0.06) and 0.95 for very elderly patients. The HRs for the secondary composite end points in the entire cohort, elderly cohort, and very elderly cohort were similar. Although saxagliptin increased the risk of hospitalization for heart failure in the overall saxagliptin population, there was no age-based treatment interaction (*P* = 0.76 for elderly patients vs. those <65 years; *P* = 0.34 for very elderly patients vs. those <75 years). Among saxagliptin-treated individuals with baseline HbA_{1c} ≥7.6% (59.6 mmol/mol), the mean change from baseline HbA_{1c} at 2 years was −0.69%, −0.64%, −0.66%, and −0.66% for those ≥65, <65, ≥75, and <75 years old, respectively. The incidence of overall adverse events (AEs) and serious AEs was similar between saxagliptin and placebo in all cohorts; however, hypoglycemic events were higher for saxagliptin versus placebo regardless of age.

CONCLUSIONS

The SAVOR-TIMI 53 trial supports the overall CV safety of saxagliptin in a robust number of elderly and very elderly participants, although the risk of heart failure hospitalization was increased irrespective of age category. AEs and serious AEs as well as glycemic efficacy of saxagliptin in elderly patients are similar to those found in younger patients.

Estimates place the global prevalence of diabetes in individuals between 60 and 79 years old at ~19%, with the number of these individuals projected to almost double by 2035 (1). Despite ongoing emphasis on the importance of practicing evidence-based medicine (2), older patients have been underrepresented in type 2 diabetes

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R.F. is currently retired from Bristol-Myers Squibb, Princeton, NJ.

**A complete list of the participating investigators of the SAVOR-TIMI 53 and the CONSORT (Consolidated Standards of Reporting Trials) diagram can be found in ref. 13. A complete list of the SAVOR-TIMI 53 Executive Committee members can be found in the APPENDIX.*

randomized controlled trials (RCTs) (3,4) often as a result of study entry criteria, including *1*) setting arbitrary caps on participant age and *2*) discouraging or disallowing participants with confounding comorbidities, frailty, or polypharmacy (common in the elderly). The justification for these criteria is a concern that including such subjects may complicate study interpretation (5). The resulting paucity of relevant data has culminated in a lack of definitive guidance on how to optimally manage glycemia in older patients with type 2 diabetes. Although many have begun to formally document recommendations for best care for the geriatric population with type 2 diabetes, these recommendations often are based on inadequate evidence (5–8). Given the increased cardiovascular (CV) risk in people with type 2 diabetes (9,10), current guidelines highlight the importance of a comprehensive, multifactorial approach to CV risk reduction, particularly among older individuals whose CV risk increases with age (5–8).

Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) is a recently completed CV outcome trial designed in accordance with the 2008 U.S. Food and Drug Administration (FDA) guidance for new antihyperglycemic agents (11). The study met its primary objective of demonstrating CV safety of the competitive dipeptidyl peptidase-4 (DPP-4) inhibitor saxagliptin in a large group of individuals with type 2 diabetes and either established CV disease or multiple CV risk factors, although superiority was not shown (12–14). Unlike many earlier studies, SAVOR-TIMI 53 had minimal exclusion criteria and did not exclude participation due to advanced age (individuals up to 99 years were randomized in the study). Accordingly, the large number of older participants in SAVOR-TIMI 53 (8,561 and 2,330 of the 16,492 participants were elderly [≥65 years] and very elderly [≥75 years], respectively) provided a unique opportunity to assess the safety and efficacy of saxagliptin in this important predefined population.

RESEARCH DESIGN AND METHODS

SAVOR-TIMI 53 was a multicenter, randomized, double-blind, placebo-controlled trial conducted at 788 sites in 26 countries spanning six continents (12–14). The study was performed according to the standards and principles of the Declaration of Helsinki. Ethics approval was site specific and always obtained before commencement at each study center. All participants provided written informed consent.

Inclusion and Exclusion Criteria

Study entry criteria have been described previously and were explicitly established to ensure that the final cohort closely reflected the real-life type 2 diabetes population (12–14). Briefly, participants had to have a documented type 2 diabetes diagnosis, a glycated hemoglobin (HbA_{1c}) level ≥6.5% (47.5 mmol/mol) and ≤12.0% (107.7 mmol/mol) at the last measurement during the 6 months before study initiation, and a history of either established CV disease or multiple risk factors (MRFs) for vascular disease (capped at 25% of the cohort size). The established CV disease criteria were ≥40 years of age with a documented atherosclerosis-associated event involving the coronary, cerebrovascular, or peripheral vascular system. The prerequisite MRF criteria were ≥55 and ≥60 years of age for men and women, respectively, with at least one of the following CV risk factors: dyslipidemia, hypertension, or active smoking. There was no upper limit on age at entry. Individuals who had been or were on current or previous (within 6 months) incretin-based therapy, were undergoing long-term dialysis, had a renal transplant, or had a serum creatinine level >6.0 mg/dL were excluded.

Conduct, Protocol, and Administration of Trial and Trial Procedure

From May 2010 through December 2011, 16,492 enrolled individuals were randomized in a 1:1 fashion to receive either placebo or saxagliptin (5 mg daily or 2.5 mg daily if they had an estimated glomerular filtration rate [eGFR] of ≤50 mL/min/1.73 m^2). Participants who developed renal impairment (eGFR ≤50 mL/min/1.73 m^2) during the study window underwent a single-dose adjustment to 2.5 mg daily. Stratification took into consideration the individual's qualifying CV disease versus MRFs and renal function (normal or mild insufficiency: eGFR >50 mL/min/1.73 m^2; moderate insufficiency: eGFR 30–50 mL/min/1.73 m^2; severe insufficiency: eGFR <30 mL/min/1.73 m^2). Pharmacotherapy for type 2 diabetes and CV disease management (i.e., addition, discontinuation, dose titration) was left entirely to the discretion of the attending physician. The use of other DPP-4 inhibitors and GLP-1 receptor agonists was not permitted.

End Points and Assessments

The primary efficacy outcome was a composite of CV mortality, nonfatal myocardial infarction (MI), or nonfatal ischemic stroke. The composite secondary end point included the primary composite end point plus hospitalization for heart failure, coronary revascularization, or unstable angina. All components of the primary composite and secondary efficacy end points were adjudicated by a central, blinded, and independent events committee. All hypoglycemic episodes were collected prospectively through patient diaries that were reviewed at each visit. Hypoglycemic episodes were classified as major if they necessitated a third party to actively intervene and minor if the patient had symptoms but recovered without assistance within 30 min of ingesting carbohydrates or documented blood glucose levels <54 mg/dL regardless of symptoms. Hypoglycemic events that required hospitalization were classified separately as hypoglycemic serious adverse events (AEs).

Statistical Analyses

Subgroup analyses by age were preplanned before unblinding this trial, and the primary hypothesis was to examine the degree of consistency of the overall treatment effect in the age groups. Thus, homogeneity of treatment effects was assessed using a Cox proportional hazards model (time to event) stratified by age groups, with treatment as the only covariate in the model and additional stratification by renal function category and baseline CV risk group. Comparisons between age groups for the demographic and baseline data and between treatments for treatment-emergent AEs for each age category were analyzed with either the χ^2 or *t* test. Cumulative incidence is reported using Kaplan-Meier event rate at the 2-year time point. Statistical significance was considered at an unadjusted α of 0.05.

RESULTS

Of the 16,492 participants randomized to either placebo (*n* = 8,212) or saxagliptin (*n* = 8,280) therapy, 51.9% (*n* = 8,561)

were elderly (median [interquartile range] 71 [67–75] years) and 14.1% (n = 2,330) very elderly (78 [76–80] years) at study entry. Baseline demographics, clinical history, laboratory values, and antihyperglycemic and CV pharmacotherapy are summarized in Table 1 and Supplementary Table 1.

Women comprised approximately one-third of the overall study population. Of note, however, nearly 40% of the very elderly participants were women. Elderly and very elderly participants had a lower mean weight than their younger counterparts (P = 0.0001); the percentage of individuals with a BMI >30 kg/m^2 was also lower in the elderly (P = 0.0001) and very elderly (P = 0.0001) groups. Although the mean duration of type 2 diabetes was longer in elderly individuals, the mean baseline fasting plasma glucose (FPG) level was higher among those <65 years old (P = 0.0001). Individuals ≤65 years old were also less likely (P = 0.0001) to have a baseline HbA_{1c} <8.0% (63.9 mmol/mol). Similarly, mean FPG levels (P = 0.0001) and percentage with HbA_{1c} >8.0% (63.9 mmol/mol) (P = 0.0001) at baseline were greater in the <75 years age group versus very elderly participants. Eighty percent of the participants had hypertension, and 70% had dyslipidemia. Elderly participants were less likely to be current smokers. Renal insufficiency (eGFR ≤50 mL/min/1.73 m^2) was documented more frequently among the elderly and very elderly participants (P = 0.0001). Use of antihyperglycemic and CV drugs was common in all groups. Approximately 40% of the entire study population was on insulin, and this distribution remained consistent regardless of whether the group was age stratified at the 65- or 75-year mark. At baseline, ~70% of those <75 years old were on metformin, whereas this was true for only 57% of the very elderly participants (P = 0.000).

Mean follow-up duration was similar across age groups (Table 2). The hazard ratio (HR) for the primary end point between saxagliptin and placebo was 0.92 (95% CI 0.79, 1.06) for the elderly participants vs. 1.15 (95% CI 0.96, 1.37) for those <65 years old (P = 0.06) and 0.95 (95% CI 0.75, 1.22) for the very elderly participants vs. 1.01 (95% CI 0.89, 1.15) for those <75 years old (P = 0.67). The HR for the secondary composite outcome was well balanced and did not reveal

Table 1—Baseline demographics, clinical history, laboratory characteristics, and medications

	<65 years		≥65 years		P value§	<75 years		≥75 years		P value§
	Placebo (n = 3,941)	Saxagliptin (n = 3,990)	Placebo (n = 4,271)	Saxagliptin (n = 4,290)	(<65 vs. ≥65 years)	Placebo (n = 7,051)	Saxagliptin (n = 7,111)	Placebo (n = 1,161)	Saxagliptin (n = 1,169)	(<75 vs. ≥75 years)
Women	1,160 (29.4)	1,226 (30.7)	1,527 (35.8)	1,542 (35.9)	<0.0001	2,241 (31.8)	2,308 (32.5)	446 (38.4)	460 (39.3)	<0.0001
Age (years)	57.9 (5.2)	58.0 (5.2)	71.6 (5.2)	71.6 (5.1)	<0.0001	62.8 (7.0)	62.9 (7.0)	78.5 (3.3)	78.4 (3.2)	<0.0001
BMI (kg/m^2)										
Men	31.4 (5.6)	31.3 (5.3)	30.3 (5.0)	30.3 (4.9)	<0.0001	31.1 (5.4)	31.0 (5.2)	29.4 (4.9)	29.3 (4.5)	<0.0001
Women	32.7 (6.5)	32.7 (6.3)	31.4 (5.8)	31.1 (5.6)	<0.0001	32.3 (6.2)	32.2 (6.1)	30.1 (5.5)	30.1 (5.2)	<0.0001
Duration of diabetes (years)	10.5 (7.8)	10.5 (8.0)	13.2 (9.3)	13.4 (9.6)	<0.0001	11.4 (8.4)	11.6 (8.6)	14.7 (10.2)	14.9 (10.7)	<0.0001
HbA_{1c} (%)	7.9 (7.1–9.2)	7.9 (7.0–9.1)	7.4 (6.9–8.3)	7.5 (6.9–8.4)	<0.0001	7.7 (7.0–8.8)	7.7 (7.0–8.8)	7.3 (6.8–8.1)	7.3 (6.8–8.0)	<0.0001
HbA_{1c} (mmol/mol)	62.8 (54.1–77.1)	62.8 (53.0–76.0)	57.4 (51.9–67.2)	58.5 (51.9–68.3)	<0.0001	60.7 (53.0–72.7)	60.7 (53.0–72.7)	56.3 (50.8–65.0)	56.3 (50.8–63.9)	<0.0001
eGFR (mL/min/1.73 m^2)	79.3 (22.3)	78.7 (22.7)	66.5 (21.1)	66.6 (21.0)	<0.0001	74.7 (22.5)	74.4 (22.5)	60.2 (19.2)	60.5 (19.4)	<0.0001
Pharmacotherapy										
Insulin	1,662 (42.2)	1,681 (42.1)	1,701 (39.8)	1,742 (40.6)	0.012	2,965 (42.1)	2,985 (42.0)	398 (34.3)	438 (37.5)	0.000
Metformin	2,886 (73.2)	2,961 (74.2)	2,768 (64.8)	2,800 (65.3)	0.000	4,984 (70.7)	5,093 (71.6)	670 (57.7)	668 (57.1)	0.000
Metformin monotherapy	766 (19.4)	841 (21.1)	879 (20.6)	818 (19.1)	0.481	1,407 (20.0)	1,449 (20.4)	238 (20.5)	210 (18.0)	0.294
Statin	3,069 (77.9)	3,075 (77.1)	3,366 (78.8)	3,407 (79.4)	0.010	5,516 (78.2)	5,539 (77.9)	919 (79.2)	943 (80.7)	0.044
ACEi or ARB	3,090 (78.4)	3,103 (77.8)	3,427 (80.2)	3,375 (78.7)	0.032	5,610 (79.6)	5,557 (78.1)	907 (78.1)	921 (78.8)	0.664

Data are n (%), mean (SD), or median (Q1–Q3). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker. §χ^2 or t test.

Table 2—Incidence of primary, secondary, and other prespecified end points

	<65 years (placebo *n* = 3,941; saxagliptin *n* = 3,990)				≥65 years (placebo *n* = 4,271; saxagliptin *n* = 4,290)				
	KM event rate (%)				KM event rate (%)				Interaction
End point	Placebo	Saxagliptin	HR (95% CI)	*P* value	Placebo	Saxagliptin	HR (95% CI)	*P* value	*P* value
Primary* Interaction *P* value 0.06	5.7	6.8	1.15 (0.96, 1.37)	0.128	8.6	7.8	0.92 (0.79, 1.06)	0.243	0.058
Secondary* Interaction *P* value 0.09	10.8	12.3	1.11 (0.98, 1.27)	0.104	13.9	13.3	0.96 (0.85, 1.07)	0.447	0.087
MI	2.7	3.1	1.09 (0.84, 1.41)	0.521	4.0	3.3	0.86 (0.69, 1.07)	0.186	0.179
CV mortality	1.9	2.7	1.33 (0.99, 1.79)	0.056	3.9	3.7	0.92 (0.74, 1.13)	0.420	0.047
Non-CV mortality	0.7	1.1	1.41 (0.91, 2.22)	0.123	1.8	2.3	1.22 (0.92, 1.63)	0.169	0.568
All-cause mortality	2.6	3.7	1.36 (1.06, 1.74)	0.014	5.6	5.9	1.01 (0.86, 1.20)	0.869	0.057
Nonfatal ischemic stroke	1.4	1.7	1.12 (0.78, 1.62)	0.529	1.6	1.8	1.17 (0.85, 1.61)	0.344	0.904
Hospitalization for/due to									
Coronary revascularization	5.7	5.5	0.96 (0.80, 1.16)	0.670	5.5	4.9	0.87 (0.73, 1.05)	0.160	0.492
Heart failure	2.0	2.8	1.32 (0.99, 1.77)	0.062	3.5	4.2	1.25 (1.01, 1.56)	0.042	0.759
Hypoglycemia	0.4	2.4	1.12 (0.57, 2.21)	0.748	0.6	0.8	1.29 (0.78, 2.14)	0.323	0.720
Unstable angina	1.0	1.6	1.50 (1.01, 2.26)	0.043	0.9	0.9	0.89 (0.56, 1.39)	0.594	0.082
Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dL (530 mmol/L)	1.6	2.2	1.19 (0.88, 1.60)	0.257	2.3	2.2	0.99 (0.75, 1.31)	0.936	0.368

	<75 years (placebo *n* = 7,051; saxagliptin *n* = 7,111)				≥75 years (placebo *n* = 1,161; saxagliptin *n* = 1,169)				
	KM event rate (%)		HR	*P*	KM event rate (%)				Interaction
End point	Placebo	Saxagliptin	(95% CI)	value	Placebo	Saxagliptin	HR (95% CI)	*P* value	*P* value
Primary* Interaction *P* value 0.67	6.6	6.9	1.01 (0.89, 1.15)	0.840	11.3	10.0	0.95 (0.75, 1.22)	0.710	0.673
Secondary* Interaction *P* value 0.57	11.9	12.2	1.01 (0.92, 1.11)	0.857	15.7	16.4	1.08 (0.88, 1.32)	0.469	0.573
MI	3.3	3.0	0.9 (0.75, 1.09)	0.289	4.1	4.2	1.17 (0.79, 1.74)	0.437	0.246
CV mortality	2.4	2.8	1.10 (0.90, 1.35)	0.344	6.4	5.5	0.88 (0.63, 1.21)	0.421	0.247
Non-CV mortality	1.1	1.4	1.21 (0.91, 1.61)	0.191	2.2	3.8	1.43 (0.91, 2.29)	0.120	0.531
All-cause mortality	3.4	4.2	1.14 (0.96, 1.34)	0.127	8.5	9.1	1.03 (0.80, 1.34)	0.804	0.563
Nonfatal ischemic stroke	1.5	1.7	1.12 (0.86, 1.45)	0.414	1.5	2.1	1.38 (0.76, 2.57)	0.294	0.53
Hospitalization for/due to									
Coronary revascularization	5.7	5.2	0.90 (0.78, 1.04)	0.167	5.1	5.1	0.98 (0.69, 1.41)	0.924	0.685
Heart failure	2.4	3.0	1.21 (0.99, 1.48)	0.064	4.9	6.8	1.47 (1.05, 2.08)	0.026	0.342
Hypoglycemia	0.5	0.6	1.12 (0.72, 1.77)	0.607	0.7	0.9	1.73 (0.70, 4.65)	0.241	0.415
Unstable angina	1.0	1.3	1.23 (0.90, 1.68)	0.192	0.7	0.7	0.87 (0.31, 2.42)	0.788	0.521
Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dL (530 mmol/L)	1.8	2.1	1.13 (0.90, 1.41)	0.288	2.8	2.3	0.87 (0.52, 1.46)	0.610	0.34

Mean follow-up duration is 2.0 years. KM, Kaplan-Meier. *Primary end point: CV death, MI, or stroke. Secondary end point: CV death, MI, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization.

any treatment-by-age interaction (Table 2). Event rates for MIs, CV mortality, and non-CV mortality were similar for placebo versus saxagliptin whether the study population was examined in its entirety or by age stratification (Table 2). Although the HR for overall all-cause mortality was balanced, the data suggest a higher risk for the <65-year-old subcohort of the saxagliptin arm (Table 2). Similarly, unstable angina–associated hospitalization was modestly greater among participants in the saxagliptin arm who were <65 years old (Table 2). Risk of hospitalization as a consequence of heart failure was a component of the overall balanced secondary end point, which was increased in the saxagliptin-treated participants in the overall SAVOR-TIMI 53 cohort. The analysis indicates that although the incidence of hospitalization for heart failure in all four age groups was numerically higher in the saxagliptin versus placebo group, the risk of heart failure–associated hospitalization did not demonstrate any treatment-by-age interaction (*P* = 0.76 for the elderly

participants vs. those <65 years; P = 0.34 for the very elderly participants vs. those <75 years). There was no overall or age-related difference in the incidence of hypoglycemia-associated hospitalization between placebo and saxagliptin (Table 2).

The 2009 position statement of the American Association of Clinical Endocrinologists and American College of Endocrinology recommended the consideration of dual therapy in individuals on monotherapy who continue to have an HbA_{1c} of ≥7.6% (59.6 mmol/mol) (15). Among individuals with a baseline HbA_{1c} of ≥7.6% (59.6 mmol/mol), the mean change from baseline HbA_{1c} associated with the use of saxagliptin at 2 years was −0.69%, −0.64%, −0.66%, and −0.66% for those ≥65, <65, ≥75, and <75 years old, respectively. Temporal achievements of HbA_{1c} <7.0% (53.0 mmol/mol) and HbA_{1c} ≤6.5% (47.5 mmol/mol) among participants with a baseline HbA_{1c} >8.0% (63.9 mmol/mol) are shown in Fig. 1. Saxagliptin and placebo produced modest changes in body weight (<1% from baseline), and similar to the overall study population, the elderly and very elderly participants showed less deteriorations and greater improvements in their albumin-to-creatinine ratio with saxagliptin versus placebo (data not shown).

There were no differences detected for AE-associated discontinuations when the cohort was divided into the <65 vs. ≥65 year and <75 vs. ≥75 year groups, although serious AE–associated discontinuations were more common among the elderly participants treated with placebo (vs. saxagliptin) (Table 3). The incidence of overall AEs and serious AEs for saxagliptin versus placebo was comparable between age-stratified groups. The imbalance for treatment-related AEs observed in the very elderly participants treated with saxagliptin versus placebo was also noted in the overall population. Incidence of hypoglycemic occurrences, mostly minor in nature, was greater in the saxagliptin arm. The risk for pancreatitis was low and similar between saxagliptin- and placebo-treated groups in all age strata (Table 3). There was no difference in the incidence of cancer, including pancreatic cancer, between the two study arms, but participants <75 years randomized to saxagliptin reported the occurrence of significantly less cancer of all types than the corresponding placebo arm. In the very elderly group, more patients on saxagliptin versus placebo reported cancer, but this difference was not statistically significant (Table 3).

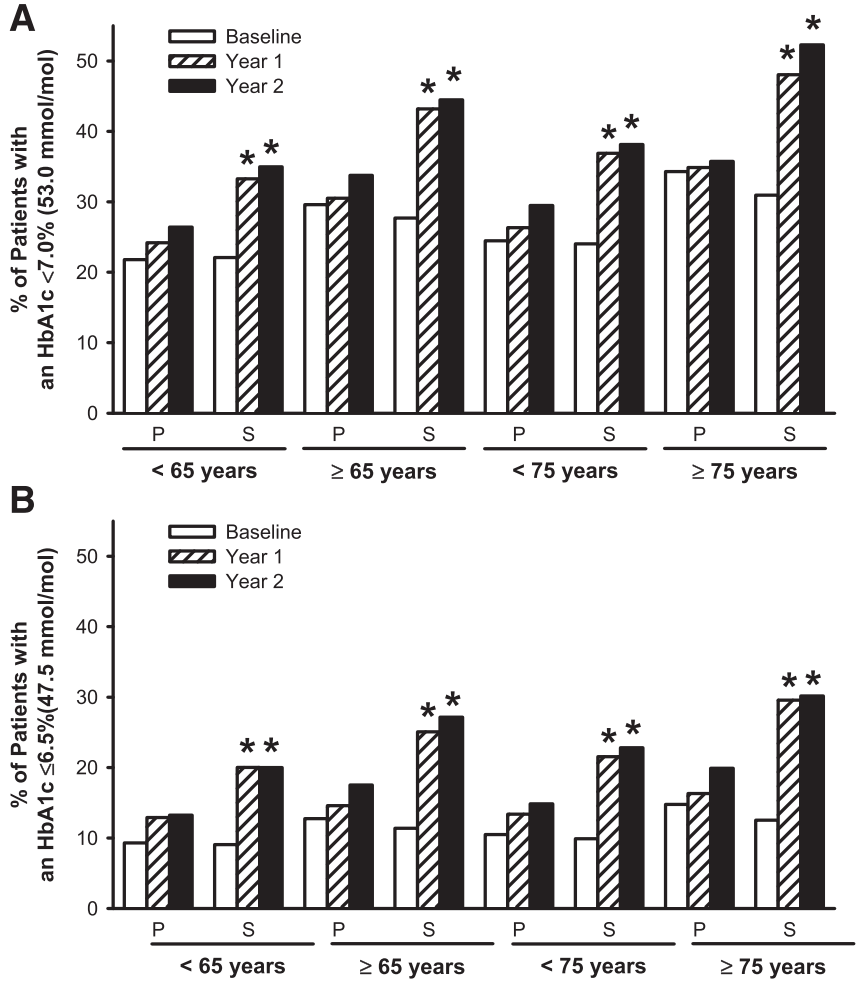

Figure 1—Saxagliptin improves glycemic control in younger and older individuals with type 2 diabetes. Temporal achievement rates for HbA_{1c} <7.0% (53.0 mmol/mol) (*A*) and HbA_{1c} ≤6.5% (47.5 mmol/mol) (*B*). Participants randomized to the saxagliptin arm received either 5 mg daily or 2.5 mg daily if they had an eGFR ≤50 mL/min/1.73 m^2. Median follow-up was 2.1 years. *P < 0.001 vs. corresponding placebo group. P, placebo; S, saxagliptin.

CONCLUSIONS

These data demonstrate that in elderly and very elderly individuals with type 2 diabetes, similar to the entire SAVOR-TIMI 53 cohort, the use of the DPP-4 inhibitor saxagliptin was associated with no increased risk of ischemic events, but without superiority relative to placebo, as well as with enhanced glycemic control with no weight gain. The observed increased risk of hospitalization for heart failure and hypoglycemic episodes with saxagliptin was similar, regardless of age.

The number of type 2 diabetes cases globally continues to soar, with the aging population contributing to this growth (1). Nonetheless, clinical trial evidence in older populations with diabetes is relatively limited. A recent descriptive analysis reported that of the 2,484 interventional diabetes–relevant trials registered at ClinicalTrials.gov, 31% excluded individuals >65 years, most excluded those >75 years, and 0.6% included only elderly participants (4). These findings were echoed in a review of the World Health Organization Clinical Trials Registry Platform where of the 440 studies examining type 2 diabetes therapies, nearly 66% excluded individuals based on an arbitrary upper age limit (3). This worrisome evidence gap has led to the question of whether it is sound clinical practice to extrapolate the findings derived from type 2 diabetes

Table 3—Adverse events

	<65 years			≥65 years			<75 years			≥75 years		
	P (*n* = 3,941)	S (*n* = 3,990)	*P* value*	P (*n* = 4,271)	S (*n* = 4,290)	*P* value*	P (*n* = 7,051)	S (*n* = 7,111)	*P* value*	P (*n* = 1,161)	S (*n* = 1,169)	*P* value*
% AEs (including hypoglycemia)												
≥1 AE	71.4	70.6	0.446	75.7	76.5	0.368	73.2	73.1	0.971	76.4	76.9	0.774
≥1 treatment-related AE	8.6	9.3	0.259	10.6	12.2	0.015	9.5	10.5	0.054	10.0	12.7	0.042
Death due to AE	0.8	1.2	0.129	2.0	2.4	0.251	1.2	1.5	0.212	2.8	3.8	0.171
≥1 SAE	21.4	22.4	0.287	29.4	29.2	0.895	24.2	24.5	0.675	33.9	34.9	0.624
≥1 treatment-related SAE	0.3	0.8	0.007	0.6	0.6	0.987	0.6	0.7	0.259	0.1	0.7	0.020
Discontinued due to SAE(s)	1.2	1.2	0.951	2.6	1.9	0.026	1.8	1.4	0.043	2.8	2.7	0.878
Discontinued due to AE(s)	3.9	3.9	0.903	6.0	5.8	0.676	4.7	4.5	0.554	6.6	7.3	0.544
% AEs (excluding hypoglycemia) reported by ≥5% of patients												
Hypertension	3.8	4.8	0.032	4.5	4.3	0.641	4.0	4.6	0.103	5.1	4.3	0.358
Nausea	2.4	2.3	0.703	2.0	2.6	0.066	2.3	2.3	0.883	1.9	3.4	0.022
Peripheral edema	3.4	3.2	0.632	5.2	5.1	0.962	4.3	4.0	0.321	4.4	5.6	0.166
Renal impairment	1.4	1.8	0.144	2.4	2.3	0.861	1.7	2.0	0.191	3.1	2.5	0.364
Urinary tract infection	3.5	3.3	0.772	5.3	4.8	0.349	3.7	3.8	0.835	8.4	5.9	0.021
% Hyperglycemia	4.4	3.7	0.110	3.7	2.7	0.008	4.1	3.3	0.011	3.6	2.4	0.084
% Hypoglycemia	12.4	14.5	0.006	14.4	16.0	0.043	13.3	15.4	0.001	14.1	14.5	0.774
Major	1.2	1.5	0.319	2.1	2.7	0.073	1.6	1.9	0.306	2.2	3.9	0.017
Only minor	11.2	13.1	0.011	12.4	13.4	0.161	11.8	13.7	0.001	12.0	10.9	0.376
% Pancreatitis												
Acute	0.2	0.4	0.078	0.2	0.2	0.479	0.2	0.3	0.405	0.1	0.1	1.000
Chronic	0.1	0.1	0.450	0.0	0.0	0.499	0.1	0.0	0.451	0.1	0.0	0.498
% Neoplasms												
All cancers	3.3	2.4	0.012	5.4	5.4	0.999	4.2	3.4	0.020	5.7	7.0	0.188
Pancreatic cancer	0.1	0.1	0.405	0.2	0.1	0.130	0.2	0.0	0.012	0.1	0.3	0.320

P, placebo; S, saxagliptin; SAE, serious adverse event. *χ^2 test.

RCTs that enroll younger, less vulnerable, and typically healthier individuals to the geriatric population with type 2 diabetes. In response, recent FDA (11) and European Medicines Agency (16) guidance has mandated that late-phase type 2 diabetes RCTs focusing on emerging antihyperglycemic agents must also include meaningful numbers of older participants representative of the entire diabetes spectrum and enumerate key CV outcomes in addition to other potential AEs to provide a comprehensive safety profile. Recently, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) investigators reported that although elderly adults had more hypoglycemia than younger participants, those in the intensively treated group did not exhibit elevated risk for the CV end point (17). These findings clearly underscore the significance of personalizing therapy.

The DPP-4 inhibitors are among the first antihyperglycemic agents to be assessed under the new FDA regulations. Until now, their demonstrated glycemic efficacy along with low rates of hypoglycemic episodes, weight neutrality, and good tolerability in people of all ages have perhaps been the most attractive and desirable features (18–29). Two meta-analyses suggested that the DPP-4 inhibitors are associated with reduced CV risk (23,24). Importantly, however, these data were obtained predominantly from relatively small and/or short-term investigations (18,19,30), systematic reviews (21,28,29), and pooled analyses (20,22,25–27,31,32) in by-and-large younger and healthier study participants with very limited, and generally unadjudicated, CV safety information.

The SAVOR-TIMI 53 trial was a large, multinational RCT designed to demonstrate the safety (overall and CV) and efficacy of saxagliptin beyond glucose lowering. Per the 2008 FDA guidance (11), the SAVOR-TIMI 53 cohort included a robust number of persons >40 years old and into their 90s with a broad duration of type 2 diabetes, with renal function ranging from normal to poor, and on a spectrum of antihyperglycemic and CV medications. It is notable that baseline and in-study glycemic control were better in the elderly group despite little difference in insulin usage across the age-stratified groups. Whether these observations resulted from differential management practices is beyond the scope of this article.

The present data represent the first from a large-scale multinational study population demonstrating that saxagliptin, at a dose that improves glycemic control in older individuals with type 2 diabetes, is not accompanied by an increase in CV ischemic events among very elderly patients. As previously reported (13), hospitalization for heart failure showed a nominal statistically significant excess in the overall saxagliptin population, but there was no heterogeneity as a function of age. Weight gain, an unwelcomed side effect of several traditional antihyperglycemic agents, did not occur with saxagliptin therapy. Hypoglycemia was only slightly higher in those randomized to saxagliptin, although this excess has been shown to have occurred in those on background sulphonylureas and with a baseline HbA_{1c} <7.0% (53.0 mmol/mol) (33). This finding is important because age is an independent risk factor for hypoglycemia (10,34,35). Furthermore, age-related comorbidities and severe oscillations in glucose levels in elderly patients due to poor or noncompliant management may increase the risk for hypoglycemia and may contribute to cognitive disorders and physical debilitation (35,36). Importantly, the results from this work indicate that the overall safety and efficacy profiles of saxagliptin at the doses studied are age independent. In addition, the present findings demonstrating that saxagliptin produces better glycemic control and is associated with AE incidence that is no worse in older versus younger individuals extend those previously reported (20,22). This study provides evidence regarding the safety and efficacy of saxagliptin as both monotherapy and add-on therapy to a wide variety of antihyperglycemic agents, including insulin, in individuals of all ages, including elderly and very elderly.

Linagliptin has been reported in subjects ≥70 years to also have similar safety, tolerability, and hypoglycemic profiles (18). However, the short 24-week follow-up meant that it was not possible to collect more clinically relevant long-term data, although these data will likely be forthcoming from the ongoing CAROLINA (Cardiovascular Outcomes Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes) (ClinicalTrials.gov identifier NCT01243424) (37) and CARMELINA (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus) (ClinicalTrials.gov identifier NCT01897532) trials. There is also published geriatric experience with vildagliptin. Two pooled analysis investigations found that elderly (n = 238) (26) and very elderly (n = 301) (27) individuals treated with vildagliptin experienced comparable benefits with similar or fewer AEs than younger individuals, regardless of renal function being either normal or mildly insufficient. Recently, a retrospective analysis reported greater HbA_{1c} <7.0% (53.0 mmol/mol) achievement, better compliance, and lower incidences of hypoglycemia with vildagliptin (vs. sulfonylurea/glitazone) add-on to metformin in elderly individuals (38). Impending reports from TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) will undoubtedly shed additional insight on the use of this class of drugs in elderly patients with diabetes (39).

Although the numerical change in HbA_{1c} and FPG levels in SAVOR-TIMI 53 was relatively modest, this efficacy was observed despite the study being designed to minimize any glycemic differences between the two arms by encouraging the blinded study investigators to treat glycemia per local guidelines. The fact that the HbA_{1c} levels in both arms remained above target is not surprising given the consistent demonstration that guidelines-recommended HbA_{1c} goals are rarely achieved in practice (40–42). Furthermore, newer guidelines now endorse personalizing diabetes management for the elderly patient in whom the general HbA_{1c} goal of <7.0% (53 mmol/mol) may or may not be appropriate (5–8).

This study has several strengths and limitations. The study entry conditions and CV end points were in line with those recently published by the FDA (11). Specifically, this was a rigorously conducted large-scale, multinational study. Older individuals (elderly and, importantly, very elderly patients) at various stages along the type 2 diabetes continuum, with varying degrees of renal insufficiency, and on multiple combinations of antihyperglycemic and CV medications comprised a significant

percentage of the cohort. The median follow-up of 2.1 years facilitated valuable assessments of CV safety but was probably not sufficiently long to assess CV efficacy. Internal validity was further ensured by encouraging participating physicians to establish HbA_{1c} goals and manage glycemia per local guidelines. Limitations include absence of cognitive function and frailty examinations at entry and as outcome measures as well as only having a 40% female representation while the majority of elderly individuals with type 2 diabetes are women. Furthermore, because all participants had to possess sufficient cognitive ability to provide informed consent to participate in the study and had to be sufficiently functional to attend regular study visits, this limited the number of frail and cognitively impaired elderly participants.

In conclusion, the SAVOR-TIMI 53 trial provides safety and efficacy data from an RCT with a robust number of elderly and very elderly participants. Overall safety, CV safety, and efficacy of saxagliptin in this subset of patients are similar to those found in younger patients, supporting the use of saxagliptin in elderly people.

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Author Contributions. L.A.L. contributed to the data acquisition, analysis, and interpretation; drafting and revision of the manuscript for important intellectual content; and approval of the final manuscript. H.T. contributed to the data analysis and interpretation, drafting and revision of the manuscript for important intellectual content, and approval of the final manuscript. E.B., B.H., R.F., B.M.S., D.L.B., and I.R. contributed to the study concept and design; data acquisition, analysis, and interpretation; revision of the manuscript for important intellectual content; and approval of the final manuscript. O.M., A.C., K.M.P.K., A.S., C.S., and F.B. contributed to the data acquisition, analysis, and interpretation; revision of the manuscript for important intellectual content; and approval of the final manuscript. L.A.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix

SAVOR-TIMI 53 Executive Committee. Eugene Braunwald (Study Chair), Deepak L. Bhatt (Co-Principal Investigator), Itamar Raz (Co-Principal Investigator), Jaime A. Davidson, Robert Frederich (nonvoting), Boaz Hirshberg (nonvoting), and Ph. Gabriel Steg.

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