Predisposing Factors for Any and Major Hypoglycemia With Saxagliptin Versus Placebo and Overall: Analysis From the SAVOR-TIMI 53 Trial

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OBJECTIVE

To analyze the impact of adding saxagliptin versus placebo on the risk for hypoglycemia and to identify predictors of any and major hypoglycemia in patients with type 2 diabetes included in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) study.

RESEARCH DESIGN AND METHODS

Patients with type 2 diabetes (*n* = 16,492) were randomized to saxagliptin or placebo and followed for a median of 2.1 years. Associations between any hypoglycemia (symptomatic or glucose measurement <54 mg/dL) or major hypoglycemia (requiring extended assistance) and patient characteristics overall and by treatment allocation were studied.

RESULTS

At least one hypoglycemic event was reported in 16.6% of patients, and 1.9% reported at least one major event. Patients allocated to saxagliptin versus placebo experienced higher rates of any (hazard ratio [HR] 1.16 [95% CI 1.08, 1.25]; *P* < 0.001) or major (HR 1.26 [1.01, 1.58]; *P* = 0.038) hypoglycemia. Hypoglycemia rates (any or major) were increased with saxagliptin in patients taking sulfonylureas (SURs) but not in those taking insulin. Rates were increased with saxagliptin in those with baseline HbA_{1c} ≤7.0% and not in those with baseline HbA_{1c} >7.0%. Multivariate analysis of the overall population revealed that independent predictors of any hypoglycemia were as follows: allocation to saxagliptin, long duration of diabetes, increased updated HbA_{1c}, macroalbuminuria, moderate renal failure, SUR use, and insulin use. Predictors of major hypoglycemia were allocation to saxagliptin, advanced age, black race, reduced BMI, long duration of diabetes, declining renal function, microalbuminuria, and use of short-acting insulin. Among SURs, glibenclamide was associated with increased risk of major but not any hypoglycemia.

CONCLUSIONS

The identification of patients at risk for hypoglycemia can guide physicians to better tailor antidiabetic therapy.

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The Diabetes Control and Complications Trial (DCCT) and UK Prospective Diabetes Study (UKPDS) demonstrated that tight glycemic control reduces the risk of microvascular complications (1,2). Hypoglycemia, a byproduct of treatment intensification with insulin and insulin secretagogues in particular, was generally viewed as justifiable, although rarely dangerous. Between the years 1999 and 2010, rates of hospitalization for hyperglycemia decreased, paralleled by an increase in the rates of hospitalization for hypoglycemia (3). The belief that "lower is better" was challenged by the publication of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial in 2008, which demonstrated increased mortality in patients assigned to a strategy of more intense glucose lowering (4). The rate of hypoglycemia was greater in the intensive versus control arm of the trial, although a conclusive link between hypoglycemic events and mortality has not yet been demonstrated. The Action in Diabetes and Vascular Disease (ADVANCE) study (5) published alongside the ACCORD, and the Veterans Affairs Diabetes Trial (VADT) published shortly thereafter (6), failed to demonstrate macrovascular and mortality benefits with tight glycemic control, thus further challenging the benefits of the intensive treatment approach. Moreover, post hoc analysis of the ADVANCE study showed that severe hypoglycemic events were associated with increased risk for mortality (7). Analysis of these trials and other epidemiological studies has demonstrated that frequent, recognized and unrecognized hypoglycemic events are associated with adverse outcomes (8), increased rates of dementia (9), increased cardiovascular morbidity (10,11), ventricular arrhythmias (12), mortality (13), and impaired quality of life (14).

Based on the accumulating data, practice guidelines now recognize that achieving a low HbA_{1c} is, by itself, not an end point and that good glycemic control should minimize the risk of hypoglycemia alongside HbA_{1c} reduction (15).

The incretin-based therapies, which have been available for nearly a decade, are of great value when aiming to reach this goal, as they are generally safe and are associated with low risk of hypoglycemia (16). Yet, even incretin-based therapies when prescribed in combination with glucose-lowering agents such as sulfonylureas (SURs) or insulins may increase the rates of hypoglycemia (17,18).

When considering if, and with what agent, to intensify glycemic control for the individual patient, study of the clinical predictors of the risk of hypoglycemia is important. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial was a cardiovascular outcome trial designed to assess the safety and efficacy of the addition of saxagliptin versus placebo to standard care (19). Hypoglycemia was one of the predefined safety end points of the study, and analysis of the predictors for hypoglycemia was a prespecified analysis in the trial. In this study we analyzed the effect of adding saxagliptin versus placebo to conventional care on the risk for hypoglycemia in the whole cohort and in subgroups of patients defined by demographic and clinical characteristics. We further identified the independent predictors of hypoglycemia in the overall study population.

RESEARCH DESIGN AND METHODS

In the SAVOR-TIMI 53 trial, a total of 16,492 patients with type 2 diabetes and cardiovascular disease (CVD) or risk factors were randomly assigned to receive saxagliptin or placebo and were followed for a median period of 2.1 years. All other therapies for the management of the patients' diabetes and CVD, including adding, discontinuing, or changing the dose of any antidiabetic drugs, were at the discretion of the treating physicians. The investigators were instructed to modify concomitant antihyperglycemic therapy as needed in order to achieve their patients' glycemic targets in accordance with local standards of care for diabetes. The design (20), baseline characteristics (21), and principal results of this study have been published (19).

Reporting of Hypoglycemia

Each subject was provided with a diary in which to record symptoms of hypoglycemic episodes and any blood glucose values measured during the episode. A hypoglycemic event was defined as an episode with symptoms suggestive of hypoglycemia that resolved within 30 min of ingestion of carbohydrates. Glucose levels may or may not have been measured at the time. Additionally, regardless of the presence of symptoms, any recorded blood glucose $<$54 mg/dL ($<$3.0 mmol/L) was to be registered as a hypoglycemic event. A nocturnal event was considered as one that was reported to have occurred between midnight and 6:00 A.M.

A major hypoglycemic event was defined as one that required the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Plasma glucose measurements may not have been available during such an event, but restoration of consciousness and/or resolution of confusion attributable to carbohydrate ingestion or the restoration of plasma glucose to normal was considered sufficient evidence that the event was induced by hypoglycemia. Hospitalization due to hypoglycemia was recorded as well. In this analysis we refer to hypoglycemic events that were recorded in the case report forms and/or listed as adverse events.

Statistical Analysis

All analyses were conducted on an intent-to-treat basis. For subjects with multiple events, the analysis was based on the time to the earliest event, whereby each subject was counted only once.

The hazard ratio (HR) and *P* value for the overall risk for hypoglycemia with saxagliptin versus placebo were calculated from the Cox proportional hazards model (likelihood ratio test) stratified by baseline renal impairment category and baseline CVD risk group (subjects with a history of previous cardiovascular event), with treatment as a model term. The HR and 95% CI are reported. Unadjusted event rates are presented by incidence rates of the first event per 100 person-years.

The risk for hypoglycemia with saxagliptin versus placebo within each subgroup of interest was calculated from a bivariable Cox proportional hazards regression model that included treatment allocation, a single baseline variable, and their interaction. The models were calculated for baseline HbA_{1c} and medications and for updated values, i.e., by the most recent HbA_{1c} available prior to the event or last available HbA_{1c} if no event occurred, or by the last recorded medications during the occurrence of event or by medications at the end of treatment period. Predictors of the development of hypoglycemia were calculated by a multivariable Cox proportional hazards

regression model adjusting for age, sex, race, BMI, diabetes duration, baseline HbA_{1c}, estimated glomerular filtration rate (eGFR), albumin-to-creatinine ratio (ACR), baseline antidiabetic medications, and treatment allocation. An additional model was calculated by updated HbA_{1c} and medications, recorded as for above.

The multivariable analyses of hypoglycemia by type of SUR taken were calculated using Cox proportional hazards models adjusting for age, race, sex, BMI, eGFR, baseline HbA_{1c}, CVD versus multiple risk factors (MRF), disease duration, insulin use (in overall population only), and treatment allocation. Analysis was based upon last updated SUR/insulin use and last HbA_{1c} recorded prior to event. Patients using more than one type of SUR were excluded from analysis. The statistical software package SAS (version 9.3; SAS Institute, Cary, NC) was used for all analyses with a two-sided P value <0.05 considered to be statistically significant.

RESULTS

Frequency of Hypoglycemic Events

During a median follow-up of 2.1 years, at least one episode of hypoglycemia was reported by 2,739 (16.6%) of the 16,492 randomized patients and 317 (1.9%) patients reported at least one episode of major hypoglycemia. Hypoglycemic events were reported more often by patients allocated to saxagliptin (1,462 of 8,280 [17.7%]) versus those allocated to placebo (1,277 of 8,212 [15.6%]; HR 1.16 [95% CI 1.08, 1.25]; $P < 0.001$), with an estimated incidence of 10.06 vs. 8.63 initial event rate per 100 patient-years, respectively. At least one episode of major hypoglycemia was reported by 177 patients (2.1%) in the saxagliptin group and 140 (1.7%) in the placebo group (HR 1.26 [1.01, 1.58]; P = 0.038), with an estimated incidence of 1.08 vs. 0.85 initial episodes per 100 person-years at risk, respectively.

Nocturnal hypoglycemia also was more frequent among patients in the saxagliptin versus the placebo group (460 [5.6%] vs. 396 patients [4.8%]; HR 1.16 [95% CI 1.02, 1.33]; P = 0.028), with an estimated incidence of 2.87 vs. 2.47 initial event rate per 100 patient-years, respectively. Hospitalizations due to hypoglycemia were not increased with saxagliptin (53 [0.6%] vs. 43 events [0.5%]; HR 1.22 [0.82, 1.83]; P = 0.33), with an estimated incidence of 0.32 vs. 0.26 initial event rate per 100 patient-years, respectively. No mortality was reported by the investigators to be associated with hypoglycemia. There were nine cases of hypoglycemic coma in the saxagliptin group and five in the placebo group. Hypoglycemic seizures occurred in eight patients in the saxagliptin group and five in the placebo group. Kaplan-Meier curves of time to first hypoglycemia, major hypoglycemia, and hospitalization for hypoglycemia by treatment allocation are shown in Supplementary Fig. 1.

Unadjusted Associations of Patient Characteristics With Risk for Any or Major Hypoglycemia With Saxagliptin Versus Placebo

The risk for any hypoglycemic event with saxagliptin versus placebo was higher regardless of age, sex, race, BMI, cardiovascular risk status, renal function, ACR, and disease duration. The directional consistency remained across all subgroups examined. Major hypoglycemic events were numerically higher with saxagliptin versus placebo in nearly all of the above-mentioned subgroups, and with nominal P values <0.05 in male patients, in those aged >75 years, in patients with BMI >30 kg/m^2, in patients with MRF versus those with CVD, and in patients with moderate renal dysfunction (Table 1).

Figure 1 shows the unadjusted rates of hypoglycemia by treatment allocation, use of SUR or insulin, and categorical HbA_{1c} levels. Patients allocated to saxagliptin versus placebo with a baseline HbA_{1c} $\leq$7.0% experienced increased rates of any or major hypoglycemia (HR 1.50 [95% CI 1.29, 1.76] and HR 1.99 [1.27, 3.19], respectively), unlike those with a baseline HbA_{1c} $>$7.0% (HR 1.06 [0.97, 1.15] and HR 1.05 [0.82, 1.37]; P for interaction <0.001 and 0.016, respectively) (Table 1).

The addition of saxagliptin versus placebo to conventional care enabled more patients, whose HbA_{1c} was not at target, to achieve their glycemic targets without hypoglycemia (Supplementary Fig. 2).

Assignment of saxagliptin versus placebo to patients with baseline use of SUR resulted in an increased risk of any hypoglycemia (HR 1.42 [95% CI 1.25, 1.61]) but no increase in risk in patients who were not taking SUR at baseline (HR 1.04 [0.95, 1.14]; P for interaction <0.001). Similarly, an increased risk of major hypoglycemia with saxagliptin versus placebo was observed in patients taking SUR at baseline (HR 1.73 [1.15, 2.64]), but no increase in risk in patients who were not taking SUR at baseline (HR 1.12 [0.86, 1.46]; P for interaction = 0.088). Analysis by updated SUR use revealed similar results (Table 1 and Supplementary Table 1).

Patients taking insulin at baseline did not experience increased rates of any or major hypoglycemia with saxagliptin versus placebo (HR 1.03 [95% CI 0.94, 1.13] and HR 1.07 [0.83, 1.40]). The risk of any hypoglycemia was increased with saxagliptin among insulin users with baseline HbA_{1c} $\leq$7 ($\leq$53 mmol/mol; HR 1.41 [1.13, 1.76]), and not in those with baseline HbA_{1c} $>$7.0% ($>$53 mmol/mol; HR 0.96 [0.86, 1.06]; P for interaction = 0.001). Analysis by updated insulin use revealed no increase in hypoglycemia rates with saxagliptin versus placebo among insulin users (Table 1 and Supplementary Table 1).

Adjusted Correlates of Hypoglycemia in the Overall Trial Population

Baseline demographic and clinical characteristics of patients presenting with no hypoglycemia, any hypoglycemia, or major hypoglycemia are shown in Table 2. Multivariate analysis showed that the risk of any hypoglycemia was increased with prolonged duration of diabetes, in patients with updated HbA_{1c} categories of 6.5–9.0% vs. $<$6.5%, in patients with moderate renal dysfunction, or in patients with macroalbuminuria. Additionally, rates of any hypoglycemia were independently increased with use of SURs or insulin-based treatment regimens and with allocation to saxagliptin (Supplementary Table 2). The independent predictors of major hypoglycemia were older age (age $>$75 years), black race, low BMI (BMI $\leq$30 vs. $>$30 kg/m^2), increased diabetes duration, renal dysfunction, microalbuminuria, use of short-acting insulin, and allocation to saxagliptin (Supplementary Table 2).

Analysis by baseline HbA_{1c} and medications revealed similar results, although notably baseline HbA_{1c} was not associated with the risk of any hypoglycemia (except for a decrease in those with baseline HbA_{1c} $\geq$9.0% vs. HbA_{1c} $<$6.5%) (Supplementary Table 3).

Table 1—Baseline characteristics of patients experiencing at least one any or major hypoglycemic event, by treatment allocation

	Any hypoglycemia				Major hypoglycemia			
	Saxagliptin (%)	Placebo (%)	HR (95% CI)	*P*+	Saxagliptin (%)	Placebo (%)	HR (95% CI)	*P*+
Overall	1,462/8,280 (17.7)	1,277/8,212 (15.6)	1.16 (1.08, 1.25)		177/8,280 (2.1)	140/8,212 (1.7)	1.26 (1.01, 1.58)	
Age (years)								
<65	671/3,990 (16.8)	560/3,941 (14.2)	1.20 (1.08, 1.35)	0.408	60/3,990 (1.5)	49/3,941 (1.2)	1.22 (0.84, 1.78)	0.368
≥65 to ≤75	629/3,336 (18.9)	555/3,314 (16.7)	1.16 (1.04, 1.30)		78/3,336 (2.3)	68/3,314 (2.1)	1.15 (0.83, 1.59)	
>75	162/954 (17.0)	162/957 (16.9)	1.02 (0.82, 1.27)		39/954 (4.1)	23/957 (2.4)	1.77 (1.07, 3.01)	
Sex								
Male	974/5,512 (17.7)	862/5,525 (15.6)	1.15 (1.05, 1.27)	0.815	118/5,512 (2.1)	88/5,525 (1.6)	1.33 (1.01, 1.76)	0.504
Female	488/2,768 (17.6)	415/2,687 (15.4)	1.18 (1.03, 1.34)		59/2,768 (2.1)	52/2,687 (1.9)	1.14 (0.79, 1.66)	
Race								
White	1,136/6,241 (18.2)	977/6,166 (15.8)	1.18 (1.08, 1.28)	0.860	130/6,241 (2.1)	104/6,166 (1.7)	1.24 (0.96, 1.61)	0.779
Black	53/278 (19.1)	56/290 (19.3)	1.03 (0.71, 1.50)		10/278 (3.6)	10/290 (3.4)	1.03 (0.42, 2.52)	
Asian	153/896 (17.1)	140/884 (15.8)	1.10 (0.88, 1.39)		18/896 (2.0)	10/884 (1.1)	1.83 (0.86, 4.12)	
Other*	120/865 (13.9)	104/872 (11.9)	1.18 (0.91, 1.54)		19/865 (2.2)	16/872 (1.8)	1.21 (0.62, 2.39)	
BMI (kg/m^2)								
≤30	664/3,829 (17.3)	567/3,821 (14.8)	1.20 (1.07, 1.34)	0.509	83/3,829 (2.2)	77/3,821 (2.0)	1.09 (0.80, 1.49)	0.195
>30	798/4,444 (18.0)	705/4,369 (16.1)	1.14 (1.03, 1.26)		94/4,444 (2.1)	63/4,369 (1.4)	1.47 (1.07, 2.04)	
CVD or MRF								
CVD	1,174/6,494 (18.1)	1,047/6,465 (16.2)	1.14 (1.05, 1.24)	0.287	137/6,494 (2.1)	124/6,465 (1.9)	1.11 (0.87, 1.42)	0.011
MRF	288/1,786 (16.1)	230/1,747 (13.2)	1.26 (1.06, 1.50)		40/1,786 (2.2)	16/1,747 (0.9)	2.45 (1.40, 4.51)	
Renal failure#								
Normal-mild	1,156/6,986 (16.5)	1,021/6,930 (14.7)	1.14 (1.05, 1.24)	0.667	105/6,986 (1.5)	94/6,930 (1.4)	1.11 (0.84, 1.47)	0.033
Moderate	266/1,122 (23.7)	221/1,118 (19.8)	1.25 (1.05, 1.49)		64/1,122 (5.7)	34/1,118 (3.0)	1.91 (1.27, 2.92)	
Severe	40/172 (23.3)	35/164 (21.3)	1.17 (0.74, 1.84)		8/172 (4.7)	12/164 (7.3)	0.65 (0.26, 1.58)	
ACR								
<30	813/4,867 (16.7)	731/4,829 (15.1)	1.12 (1.01, 1.24)	0.476	76/4,867 (1.6)	60/4,829 (1.2)	1.26 (0.90, 1.77)	0.988
≥30–300	426/2,217 (19.2)	356/2,209 (16.1)	1.24 (1.08, 1.43)		64/2,217 (2.9)	51/2,209 (2.3)	1.26 (0.87, 1.83)	
>300	165/832 (19.8)	151/806 (18.7)	1.09 (0.88, 1.37)		29/832 (3.5)	24/806 (3.0)	1.23 (0.71, 2.13)	
Diabetes duration (years)								
<5	170/1,975 (8.6)	139/1,941 (7.2)	1.23 (0.98, 1.54)	0.618	14/1,975 (0.7)	8/1,941 (0.4)	1.73 (0.74, 4.33)	0.734
≥5–10	269/1,957 (13.7)	228/1,968 (11.6)	1.20 (1.00, 1.43)		32/1,957 (1.6)	25/1,968 (1.3)	1.32 (0.78, 2.25)	
≥10–15	346/1,764 (19.6)	277/1,736 (16.0)	1.26 (1.07, 1.47)		40/1,764 (2.3)	26/1,736 (1.5)	1.46 (0.89, 2.42)	
≥15–20	260/1,027 (25.3)	257/1,084 (23.7)	1.10 (0.92, 1.30)		27/1,027 (2.6)	30/1,084 (2.8)	0.98 (0.58, 1.66)	
≥20	417/1,547 (27.0)	375/1,478 (25.4)	1.09 (0.94, 1.25)		64/1,547 (4.1)	51/1,478 (3.5)	1.20 (0.83, 1.74)	
Baseline HbA_{1c} (%)								
<6.5	73/590 (12.4)	66/673 (9.8)	1.28 (0.92, 1.79)	0.016	13/590 (2.2)	6/673 (0.9)	2.38 (0.94, 6.80)	0.072
≥6.5–7	234/1,442 (16.2)	157/1,414 (11.1)	1.53 (1.25, 1.87)		31/1,442 (2.1)	17/1,414 (1.2)	1.83 (1.02, 3.38)	
≥7–8	497/2,759 (18.0)	450/2,657 (16.9)	1.07 (0.94, 1.22)		58/2,759 (2.1)	51/2,657 (1.9)	1.06 (0.73, 1.55)	
≥8–9	347/1,577 (22.0)	304/1,562 (19.5)	1.16 (1.00, 1.35)		38/1,577 (2.4)	24/1,562 (1.5)	1.58 (0.95, 2.66)	
≥9	288/1,761 (16.4)	288/1,764 (16.3)	1.01 (0.86, 1.19)		34/1,761 (1.9)	42/1,764 (2.4)	0.83 (0.52, 1.30)	
≤7	384/2,374 (16.2)	268/2,393 (11.2)	1.50 (1.29, 1.76)	<0.001	54/2,374 (2.3)	28/2,393 (1.2)	1.99 (1.27, 3.19)	0.016
>7	1,055/5,755 (18.3)	997/5,677 (17.6)	1.06 (0.97, 1.15)		120/5,755 (2.1)	112/5,677 (2.0)	1.05 (0.82, 1.37)	
No baseline antidiabetic medications	21/370 (5.7)	17/417 (4.1)	1.43 (0.76, 2.75)		3/370 (0.8)	1/417 (0.2)	NA	
Metformin alone	76/1,588 (4.8)	81/1,554 (5.2)	0.92 (0.67, 1.26)		6/1,588 (0.4)	5/1,554 (0.3)	1.21 (0.36, 4.19)	
SUR + metformin	466/2,576 (18.1)	327/2,549 (12.8)	1.47 (1.27, 1.69)		47/2,576 (1.8)	22/2,549 (0.9)	2.13 (1.30, 3.61)	
Taking SUR	575/3,327 (17.3)	411/3,259 (12.6)	1.42 (1.25, 1.61)		61/3,327 (1.8)	35/3,259 (1.1)	1.73 (1.15, 2.64)	
HbA_{1c} ≤7%	185/849 (21.8)	107/838 (12.8)	1.80 (1.42, 2.30)	0.013	28/849 (3.3)	12/838 (1.4)	2.36 (1.23, 4.82)	0.179
HbA_{1c} >7%	377/2,415 (15.6)	298/2,372 (12.6)	1.27 (1.09, 1.48)		31/2,415 (1.3)	23/2,372 (1.0)	1.33 (0.78, 2.31)	
Not taking SUR	887/4,953 (17.9)	866/4,951 (17.5)	1.04 (0.95, 1.14)		116/4,953 (2.3)	105/4,951 (2.1)	1.12 (0.86, 1.46)	
HbA_{1c} ≤7%	199/1,525 (13.0)	161/1,555 (10.4)	1.31 (1.06, 1.61)	0.011	26/1,525 (1.7)	16/1,555 (1.0)	1.73 (0.94, 3.29)	0.117
HbA_{1c} >7%	678/3,340 (20.3)	699/3,305 (21.1)	0.96 (0.87, 1.07)		89/3,340 (2.7)	89/3,305 (2.7)	0.99 (0.74, 1.33)	
Taking insulin	930/3,423 (27.2)	904/3,364 (26.9)	1.03 (0.94, 1.13)		117/3,423 (3.4)	108/3,364 (3.2)	1.07 (0.83, 1.40)	
HbA_{1c} ≤7%	190/563 (33.7)	133/519 (25.6)	1.41 (1.13, 1.76)	0.001	27/563 (4.8)	14/519 (2.7)	1.76 (0.94, 3.46)	0.071
HbA_{1c} >7%	727/2,810 (25.9)	764/2,800 (27.3)	0.96 (0.86, 1.06)		89/2,810 (3.2)	94/2,800 (3.4)	0.95 (0.71, 1.27)	

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Table 1—Continued

	Any hypoglycemia				Major hypoglycemia			
	Saxagliptin (%)	Placebo (%)	HR (95% CI)	*P*+	Saxagliptin (%)	Placebo (%)	HR (95% CI)	*P*+
Type of SUR§								
Glibenclamide	199/1,172 (17.0)	132/1,160 (11.4)	1.57 (1.26, 1.95)	0.482	34/1,172 (2.9)	15/1,160 (1.3)	2.28 (1.26, 4.30)	0.571
Glimepiride	169/959 (17.6)	112/932 (12.0)	1.50 (1.18, 1.91)		14/959 (1.5)	10/932 (1.1)	1.27 (0.56, 2.96)	
Glipizide	82/441 (18.6)	74/451 (16.4)	1.17 (0.86, 1.61)		9/441 (2.0)	5/451 (1.1)	1.91 (0.66, 6.21)	
Gliclazide	113/678 (16.7)	78/645 (12.1)	1.42 (1.07, 1.90)		4/678 (0.6)	4/645 (0.6)	0.88 (0.21, 3.76)	

+*P* values represent interaction between subgroups and treatment allocation. *Other: multiracial, Native Hawaiian, or other Pacific, American Indian, or Alaska native. #Renal function categories defined as normal function–mild impairment (eGFR >50 mL/min), moderate impairment (eGFR = 30–50 mL/min), and severe impairment (eGFR <30 mL/min). §Among patients taking SUR, excluding those taking more than one type of SUR, excluding tolbutamide and other SUR use.

Association of Subtype SUR Use With the Risk for Hypoglycemia

At baseline, 6,586 patients (39.9%) were taking SURs with or without concomitant insulin use; 2,332 were taking glibenclamide, 1,891 were taking glimepiride, 1,323 were taking gliclazide, and 892 were taking glipizide. The remaining patients were taking tolbutamide or other types of SURs and were not included in analysis due to their very small number. Throughout the trial, SUR therapy was initiated by 833 patients after baseline, 351 in the saxagliptin group and 482 in the placebo group. The risk of major hypoglycemia was increased with the use of glibenclamide versus the three other SURs. There was a borderline increase in the risk of any hypoglycemia with glibenclamide versus gliclazide or glimepiride that reached statistical significance in patients who were not taking insulin and were taking glibenclamide versus gliclazide (Fig. 2).

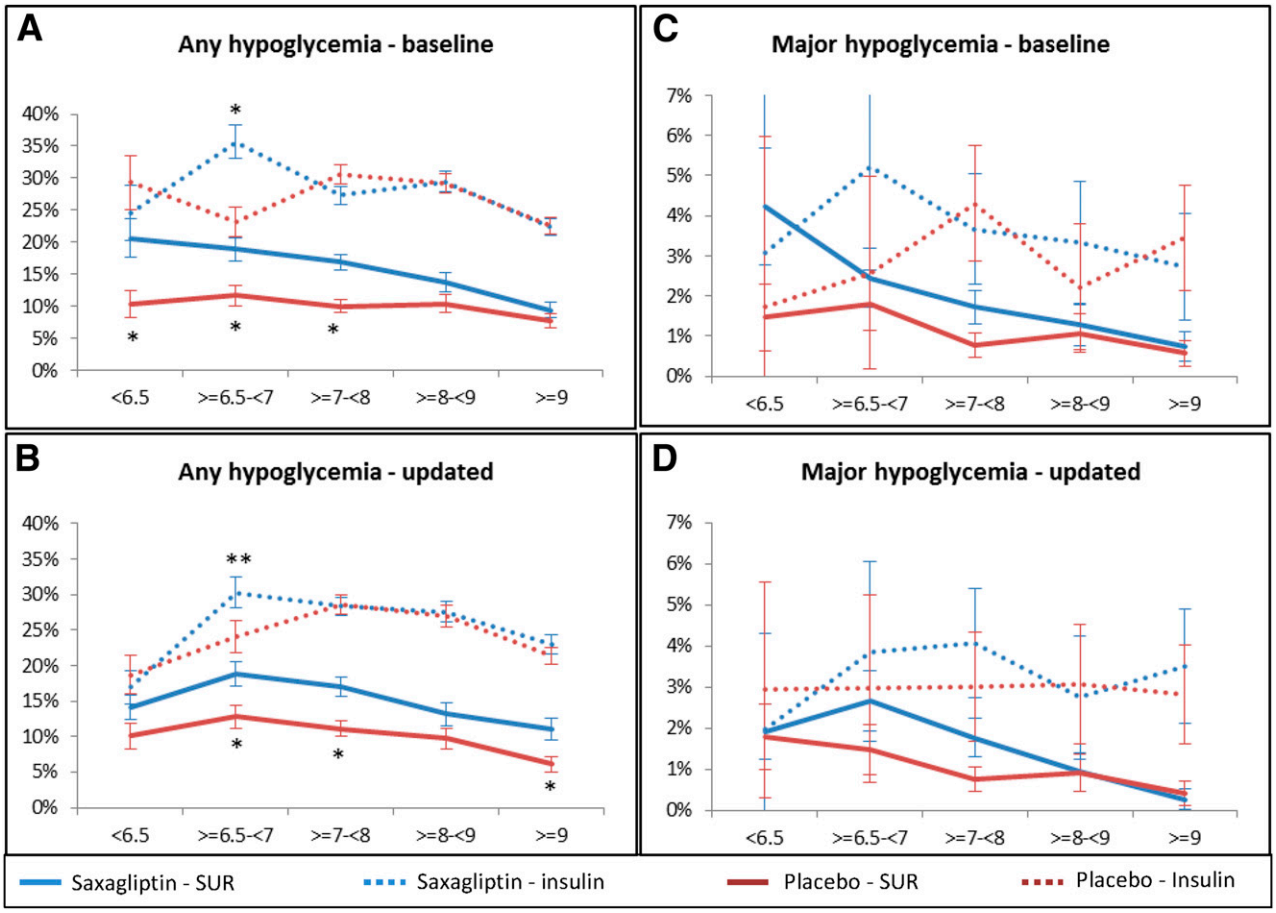

Figure 1—Percentages of patients experiencing "any" and "major" hypoglycemia by HbA_{1c} categories and baseline/updated use of SUR or insulin. Percentage of patients experiencing any hypoglycemia (*A* and *B*) and major hypoglycemia (*C* and *D*) with saxagliptin (blue lines), and placebo (red lines) with SUR and no insulin use (full lines) or with insulin (±oral hypoglycemic agent) use (dotted lines) by baseline and updated medications and HbA_{1c} categories. "Updated" is defined as recorded most prior to the event or at end of treatment period if no event occurred. *$P < 0.05$ and **$P = 0.0504$, for comparison of saxagliptin vs. placebo in the medication category. Vertical lines represent ± SE.

CONCLUSIONS

Analysis of the SAVOR- TIMI 53 trial data identified the predictors of any hypoglycemia and major hypoglycemia in a heterogeneous patient population with CVD or at high cardiovascular risk. Rates of any, major, and hospitalization for hypoglycemia reported in the trial were 10.06 vs. 8.63, 1.08 vs. 0.85, and 0.32 vs. 0.26 initial events per 100 person-years at risk, respectively, with saxagliptin versus placebo.

Rates of major hypoglycemia reported in the SAVOR-TIMI 53 trial were higher than those reported in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) (0.78 vs. 0.70 events per 100 patient-years [22]) or in the Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care (EXAMINE) trial (0.7% vs. 0.6% [23]), yet in these two studies, there was a less stringent collection of hypoglycemic events. Whereas in the SAVOR-TIMI 53 trial, patients were given diaries to record their hypoglycemic events, in the TECOS and EXAMINE trials, events were collected as reported by the investigators, based upon patient recall at the time of visit. This may have contributed to the trend of a higher incidence of these events in SAVOR-TIMI 53. Additionally, baseline insulin use was higher in the participants of the SAVOR-TIMI 53 trial compared with the other studies.

The excess risk of hypoglycemia introduced by saxagliptin was noted primarily when it was prescribed to patients who were taking an SUR (Fig. 1). The increased risk of hypoglycemia when prescribing saxagliptin on top of an SUR was observed in the early development program of saxagliptin and of other incretin-based therapies (17,18,24). It has been shown that the administration of the SUR tolbutamide uncouples the insulinotropic action of GLP-1 from its glucose dependence, resulting in increased insulin secretion in spite of low glucose levels (25). Additionally, patients with a baseline $HbA_{1c} \leq 7.0\%$ taking concomitant insulin or SUR who were allocated to saxagliptin versus placebo had increased rates of hypoglycemia. Of note, unlike the setting in this trial, saxagliptin is not indicated in patients who are at goal, so if prescribed in this specific population, caution should be exercised and dose adjustment of SUR and/or insulin is suggested.

Hypoglycemia has been identified as the limiting factor in the treatment of diabetes, preventing patients from achieving their desirable glycemic control. Understanding which patients are at risk for hypoglycemia has been defined by the Workgroup of the American Diabetes Association and the Endocrine Society as one of the prevailing research goals (26). Better characterization of the patients at high risk for hypoglycemia may aid us in deciding in which patient populations treatment intensification is safe (27).

Table 2—Characteristics of patients reporting at least one any or major hypoglycemic event

	No hypoglycemia (n = 13,753)	Any hypoglycemia (n = 2,739)	Major hypoglycemia (n = 317)
Age (years)	64.9 ± 8.6	65.6 ± 8.2‡	67.9 ± 8.7‡
Male sex	9,201 (66.9)	1,836 (67.0)	206 (65.0)
Race			
White	10,294 (74.8)	2,113 (77.1) (for overall category‡)	234 (73.8) (for overall category*)
Black	459 (3.3)	109 (4.0)	20 (6.3)
Asian	1,487 (10.8)	293 (10.7)	28 (8.8)
Other	1,513 (11.0)	224 (8.2)	35 (11.0)
BMI (kg/m^2)	31.1 ± 5.5	31.4 ± 5.7	30.9 ± 5.9
Duration of diabetes	11.3 ± 8.6	15.4 ± 9.2‡	17.4 ± 9.7‡
HbA_{1c} (%)	8.0 ± 1.4	8.1 ± 1.3‡	8.1 ± 1.5
HbA_{1c} (%)			
<6.5	1,124 (8.3)	139 (5.1) (for overall category‡)	19 (6.1)
6.5–<7.0	2,465 (18.3)	391 (14.5)	48 (15.3)
7.0–<8.0	4,469 (33.1)	947 (35.0)	109 (34.7)
8.0–<9.0	2,488 (18.4)	651 (24.1)	62 (19.7)
≥9.0	2,949 (21.9)	576 (21.3)	76 (24.2)
eGFR (mL/min)	73.3 ± 22.7	68.7 ± 22.0‡	60.6 ± 22.5‡
eGFR (mL/min)			
<30	261 (1.9)	75 (2.7) (for overall category‡)	20 (6.3) (for overall category‡)
30–≤50	1,753 (12.7)	487 (17.8)	98 (30.9)
>50	11,739 (85.4)	2,177 (79.5)	199 (62.8)
ACR (mg/gr)			
<30	8,152 (62.1)	1,544 (58.4) (for overall category‡)	136 (44.7) (for overall category‡)
≥30–300	3,644 (27.8)	782 (29.6)	115 (37.8)
>300	1,322 (10.1)	316 (12.0)	53 (17.4)
Established CVD	10,738 (78.1)	2,221 (81.1)‡	261 (82.3)
β-Blockers	8,378 (60.9)	1,784 (65.1)‡	202 (63.7)
ACE inhibitors	7,422 (54.0)	1,518 (55.4)	179 (56.5)
Sulfonylurea	5,600 (40.7)	986 (36.0)‡	96 (30.3)‡
Insulin	4,953 (36.0)	1,834 (67.0)‡	225 (71.0)‡

Data are mean ± SD or n (%). *$P < 0.05$; ‡$P < 0.001$, for differences between any hypoglycemia and no hypoglycemia or between major hypoglycemia and no major hypoglycemia (column of no major hypoglycemia not shown).

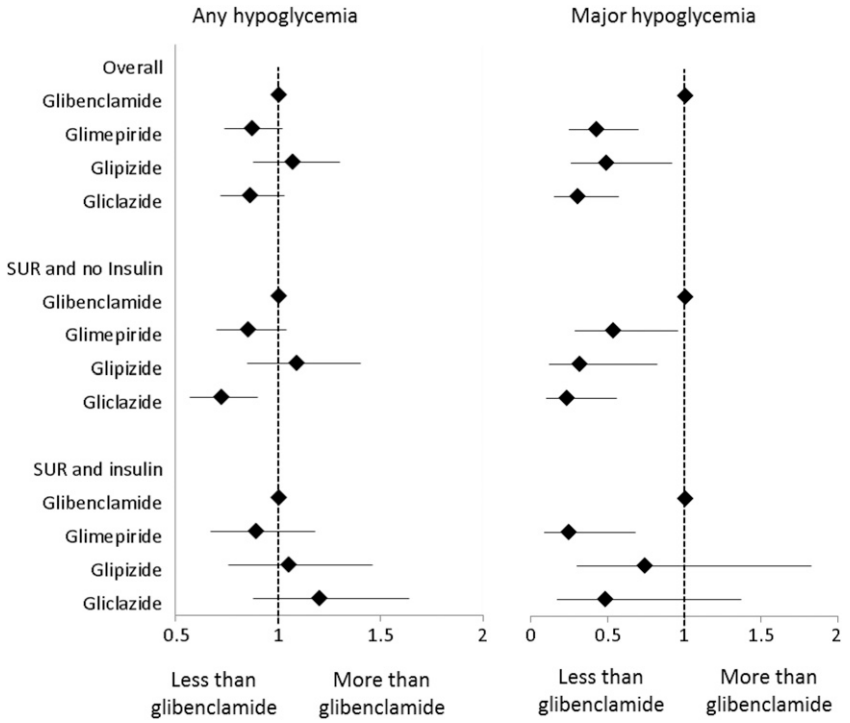

Figure 2—Adjusted HR and 95% CI of "any" and "major" hypoglycemia by updated type of SUR. Adjusted HR for experiencing at least one "any" or "major" hypoglycemic episode: glibenclamide vs. other SUR, in the overall population of SUR users and without/with concomitant insulin use. Horizontal bar indicates 95% CIs from the adjusted model.

In the SAVOR-TIMI 53 trial, the highest rates of any hypoglycemia (29.3%) or major hypoglycemia (3.7%), regardless of treatment allocation, were observed in patients taking insulin (including short-acting insulin), and this observation remained significant after adjustment for relevant clinical confounders.

Declining renal function and increasing levels of urinary microalbumin have been shown to be predictors of hypoglycemia (28,29) and probably represent both an independent effect of decreased insulin clearance associated with reduced GFR and the vulnerability of the population with impaired renal function (28,29). Low BMI and increased duration of diabetes had been similarly reported as well. The increased vulnerability of the elderly population is an additional finding of our study, yet only rates of major hypoglycemia were significantly increased and rates of any hypoglycemia were nonsignificantly increased. Contrariwise, in the Outcome Reduction With an Initial Glargine Intervention (ORIGIN) study, older age increased the risk of severe hypoglycemia, yet younger age increased the risk of nonsevere events (29). The recording of nonsevere hypoglycemia is more open to subjective interpretation, possibly explaining the discrepant observation in both studies.

Association of HbA_{1c} levels with hypoglycemia has varied in different studies (30–32). Viewing the analysis by updated data in our study, an inverted U-shaped curve was observed for any hypoglycemia by HbA_{1c} categories in patients with use of insulin or of SUR without insulin. Major hypoglycemia rates by HbA_{1c} categories showed a slightly different trend, with a decline in the high end of HbA_{1c} levels in SUR users and a relatively stable rate in insulin users. The excess risk of hypoglycemia with saxagliptin was observed in the lower HbA_{1c} levels (Fig. 1).

Of note is the increased adjusted rate of major hypoglycemia observed with the use of glibenclamide. A recent meta-analysis of the risk of hypoglycemia in randomized controlled trials with SURs versus comparators indicated an increase in rates of any hypoglycemia in all four SUR subtypes to a similar extent, although a direct comparison was not reported (33). A meta-analysis of trials directly comparing the different SURs reported an increased risk of any hypoglycemia and a trend for an increase in the risk of major hypoglycemia with glibenclamide versus other SURs (34). The increased hypoglycemia rates observed with glibenclamide relative to other SURs may be explained by the relatively long terminal half-life of the drug in chronic dosing compared with other SURs, owing to its high affinity for the β-cell SUR receptor (34).

The detailed collection of hypoglycemic events from a large heterogeneous population with antidiabetic treatment adjusted by standard of care reflects one of the major strengths of our analysis. However, there are several limitations to the study. First, hypoglycemic events were ascertained by patient diaries that were collected at study visits, and it is possible that patients neglected to note all events in their diary; thus, it is possible that there is under-reporting, particularly of minor hypoglycemic events. Second, as self-monitoring of blood glucose was not a mandatory study procedure, many asymptomatic events of hypoglycemia may not have been registered, particularly in those patients with glucose unawareness. Third, glucose measuring during the hypoglycemic episode was not mandatory and symptoms that resolved with the ingestion of carbohydrates were considered hypoglycemic episodes as well. This may have led to misclassification and/or overestimation of hypoglycemic events. Fourth, rates of hypoglycemia observed in randomized clinical trials may be lower than those obtained from real world data (35). Although not a formal exclusion criteria in our trial, physicians may have chosen to exclude patients with recurrent hypoglycemic events or hypoglycemia unawareness, thus resulting in lower hypoglycemia rates compared with the "real world" population with diabetes. Finally, although hypoglycemia was a prespecified end point of the study, multivariable analyses of the predictors of hypoglycemia may be confounded by unmeasured factors such as cognitive function and patient adherence to lifestyle, self-monitoring of blood glucose, and medication regimens.

In conclusion, the excess hypoglycemic risk posed by saxagliptin is relatively small in absolute terms and observed primarily in those receiving SURs. This combination should be prescribed with caution, and lowering the dose of SURs

when initiating saxagliptin should be considered, as recommended in the prescribing information. Our study confirmed the high prevalence of hypoglycemia in the elderly and in patients with long-standing disease duration, renal insufficiency, albuminuria, or low BMI. The association of hypoglycemia and HbA_{1c} is complex and depends upon the treatment regimen. Among SURs, glibenclamide conferred an increased risk of hypoglycemia, and its use should be carefully considered in vulnerable patients.

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Author Contributions. A.C. acquired, analyzed, and interpreted the data; drafted the manuscript; reviewed the manuscript for important intellectual content; and approved the final version of the manuscript submitted. I.R., B.H., C.S., B.M.S., D.L.B., and E.B. conceived and designed the study; helped to acquire, analyze, and interpret the data; reviewed the manuscript for important intellectual content; and approved the final version of the manuscript submitted. O.M., G.L., I.Y., A.R., N.I., M.S., K.I., and E.K. helped to acquire, analyze, and interpret the data; reviewed the manuscript for important intellectual content; and approved the final version of the manuscript submitted. A.C., I.R., B.H., C.S., B.M.S., and D.L.B. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented at the 74th Scientific Sessions of the American Diabetes Association, San Francisco, CA, 13–17 June 2014, and at the 50th Scientific Sessions of the European Association for the Study of Diabetes, Vienna, Austria, 15–19 September 2014.

Appendix

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 Gabriel Steg.

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