

Effect of Insulin Degludec Versus Insulin Glargine U100 on Hypoglycemia in Hispanic Patients With Type 2 Diabetes: Results From the SWITCH 2 Trial

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■ IN BRIEF Hispanic patients with type 2 diabetes have poorer glycemic control and are at higher risk of severe diabetes complications and mortality than non-Hispanic white patients. This post hoc analysis investigated the safety and efficacy of insulin degludec versus insulin glargine 100 units/mL (glargine U100) in the Hispanic patient subpopulation from the SWITCH 2 trial. In Hispanic patients, hypoglycemia was consistently lower and nocturnal hypoglycemia was significantly lower with degludec versus glargine U100 at similar levels of glycemic control. Overall, results in Hispanic patients in SWITCH 2 were consistent with those in non-Hispanic patients.

Diabetes is a major cause of morbidity and mortality. In 2012, the total cost of diagnosed diabetes in the United States was estimated at \$245 billion, with one in five U.S. health care dollars spent on caring for people with diabetes (1). Nearly twice as many Hispanic Americans have diabetes compared with their non-Hispanic white counterparts; the age-adjusted prevalence of diabetes (diagnosed and undiagnosed cases) in the 2011–2012 population has been estimated as 22.6% in Hispanics and 11.3% in non-Hispanic whites (2) and in the 2011–2014 population as 16.8% in Hispanics and 9.6% in non-Hispanic whites (3). The higher lifetime risk of developing diabetes in Hispanics compared with non-Hispanic whites (4) may be driven by biological factors, such as a predisposition to insulin resistance (5), augmented insulin secretion (6), and abdominal obesity (7), as well as complex socioeconomic and cultural factors (8). Hispanic individuals represent a sizeable group within the U.S. population; as of 2015, there were ~57 million, representing almost 18% of the total population (9). This

number is projected to rise, and by 2060, more than one in four people living in the United States (29%) will be of Hispanic origin (10). The terms “Hispanic” and “Latino” are interpreted differently by some but are often used interchangeably. In this article, we have used “Hispanic” to cover both “Hispanic” and “Hispanic/Latino” used in the literature and to cover patients of Spanish or Central/South/Latin American or Mexican ethnicity.

Current guidelines recommend A1C targets of <7.0% (53 mmol/mol [American Diabetes Association]) or ≤6.5% (48 mmol/mol [American Association of Clinical Endocrinologists]) for most patients to reduce the risk of diabetes-related complications (11,12). Hispanic patients are less likely to achieve adequate glycemic control compared with non-Hispanic white patients (13). In the U.S. data from 1999 to 2006, 37.8% of U.S.-born Hispanic patients with type 2 diabetes reached an A1C target of <7.0% (53 mmol/mol) compared with 58.1% of non-Hispanic white patients, with the difference between the two groups significantly increasing over time (14). This poorer

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glucose control results in a higher proportion of patients with complications associated with diabetes among Hispanics than among non-Hispanic whites, including retinopathy (29% higher) (15), nephropathy (31% higher) (16), and foot amputation (80% higher) (17). Hispanics are also 1.5-fold more likely to die from diabetes-related complications and associated conditions as their white non-Hispanic counterparts (18).

Insulin is currently recommended for the treatment of type 2 diabetes as the disease progresses and glycemic control fails to be achieved with oral antidiabetic drugs (11,12). Negative attitudes and fears about insulin therapy, so-called psychological insulin resistance (19), are common among Hispanics and constitute an important barrier to insulin therapy—with impacts on not only insulin initiation but also dosing and adherence (20). Commonly reported negative beliefs about insulin among Hispanics include a fear of hypoglycemia, concerns about adverse impacts on lifestyle, and a belief that blindness, amputation, and dialysis are direct consequences of insulin treatment (21,22). The barriers to insulin therapy in Hispanics include socioeconomic issues, language difficulties, poor health literacy, and cultural beliefs (20). An insulin that is associated with low rates of hypoglycemia may help to overcome one of the barriers to insulin therapy in Hispanic patients and contribute to improved care.

Insulin degludec is a basal insulin with a mean half-life of >25 hours and a flat glucose-lowering profile (23). The phase 3b SWITCH 2 trial was conducted in the United States in patients with type 2 diabetes to confirm the hypoglycemia benefit with degludec compared with insulin glargine 100 units/mL (glargine U100) observed in the phase 3a development program (24,25). In SWITCH 2, rates of overall symptomatic and nocturnal symptomatic hypoglycemia were significantly lower

with degludec versus glargine U100 in both the maintenance period (i.e., after titration had been completed) and the full treatment period, whereas rates of severe hypoglycemia were significantly lower during the full treatment period (24). The objective of these post hoc analyses was to assess the safety and efficacy of degludec versus glargine U100 in the Hispanic patient subpopulation from the SWITCH 2 trial.

Research Design and Methods

Study Design, Participants, and Study End Points

SWITCH 2 was a 2 × 32-week, double-blind, multicenter, treat-to-target, two-period crossover trial (ClinicalTrials.gov: NCT02030600). The design and primary results for the SWITCH 2 study have been reported previously (24). In brief, adults with type 2 diabetes for ≥26 weeks, A1C ≤9.5% (80 mmol/mol), BMI ≤45 kg/m², and treatment with a basal insulin with or without oral antidiabetic drugs for ≥26 weeks and at risk of developing hypoglycemia were included, reflecting the general type 2 diabetes population. When enrolling, patients were asked to self-identify as Hispanic/Latino, if applicable. Patients were randomized 1:1 to receive either degludec for 32 weeks followed by glargine U100 for a further 32 weeks or glargine U100 for 32 weeks followed by degludec for a further 32 weeks, all once daily. Each 32-week treatment period consisted of a 16-week titration period and a 16-week maintenance period (Supplementary Figure 1).

In the SWITCH 2 trial, overall symptomatic hypoglycemic episodes were defined according to the American Diabetes Association definition as those requiring the assistance of another person (severe [26]) and/or blood glucose-confirmed (<56 mg/dL [3.1 mmol/L]) episodes accompanied by typical symptoms of hypoglycemia. Symptomatic hypoglycemia with onset between 00:01 A.M. and 05:59 A.M. was classified as noc-

turnal. All reported episodes of severe hypoglycemia were adjudicated by an independent external committee (24).

Safety and Efficacy of Degludec Versus Glargine U100 in Hispanic Patients

In these post hoc analyses, the safety of degludec versus glargine U100 in Hispanic patients and non-Hispanic patients was assessed by comparing rates of overall symptomatic hypoglycemia, nocturnal symptomatic hypoglycemia, and severe hypoglycemia for degludec versus glargine U100 during the maintenance (weeks 17–32 and 49–64) and full (weeks 1–32 and 33–64) treatment periods. Rates of adverse events (AEs) were also analyzed for Hispanic and non-Hispanic patients. The efficacy of degludec versus glargine U100 was assessed by measuring the change from baseline in A1C, fasting plasma glucose (FPG), and prebreakfast self-measured plasma glucose (SMPG) levels for degludec versus glargine U100 in Hispanic and non-Hispanic patients. Baseline was defined as week 0 for treatment period 1 and week 32 for treatment period 2. Daily insulin dose with degludec versus glargine U100 was assessed at the end of treatment period 1 (week 32), the end of treatment period 2 (week 64), and over the total treatment period.

Statistical Analyses

Post hoc analyses of safety (hypoglycemia), efficacy, and insulin dose were based on the full analysis set (all randomized patients [except for one patient excluded due to an unsigned casebook]). Descriptive summaries of safety (hypoglycemia, AEs) and insulin dose were prepared for the safety analysis set (patients receiving at least one dose of investigational product or comparator), and efficacy summaries were prepared for the full analysis set. Differences between degludec and glargine U100 were analyzed statistically within each subpopulation (Hispanic or non-Hispanic), and the results were compared descriptively between subpopulations. The number

of hypoglycemic episodes and change from baseline in A1C were analyzed as per the prespecified primary models used in SWITCH 2 (24). Daily insulin dose was analyzed as per the post hoc analysis reported in Wysham et al. (24).

Results

Baseline Characteristics

In SWITCH 2, 36.4% (262/720) of patients were Hispanic, and 63.6% (458/720) were non-Hispanic. The disposition of Hispanic and non-Hispanic patients is shown in Supplementary Figure 2. Baseline

characteristics for Hispanic and non-Hispanic patients are summarized in Table 1. Sex, age, BMI, and A1C were generally comparable between Hispanic and non-Hispanic patients, whereas FPG tended to be higher for Hispanic patients at baseline.

Safety

Hypoglycemia

In Hispanic patients, the rate of overall symptomatic hypoglycemia was numerically lower with degludec compared with glargine U100, but differences were not statistically

significant (Figure 1 and Table 2). The rate of nocturnal symptomatic hypoglycemia was significantly lower with degludec compared with glargine U100 in the maintenance (51.7 vs. 84.2 episodes/100 patient-year exposure [PYE]; estimated rate ratio [ERR] = 0.63 [95% CI 0.41–0.99]; $P = 0.043$) and total treatment period (56.0 vs. 71.3 episodes/100 PYE; ERR = 0.71 [95% CI 0.51–0.98]; $P = 0.035$) (Figure 1 and Table 2). ERRs for severe hypoglycemia during the maintenance period could not be calculated because of the small number of events reported. Rates of severe hypoglycemia were numerically lower with degludec compared with glargine U100 during the full treatment period, but differences were not statistically significant (Figure 1).

In non-Hispanic patients, there were statistically significant reductions in the rates of both overall and nocturnal symptomatic hypoglycemia with degludec versus glargine U100 during the maintenance period (overall symptomatic hypoglycemia 195.8 vs. 312.3 episodes/100 PYE; ERR = 0.63 [95% CI 0.53–0.74]; $P < 0.001$; nocturnal symptomatic hypoglycemia 57.2 vs. 98.9 episodes/100 PYE; ERR = 0.57 [95% CI 0.42–0.77]; $P < 0.001$). These results were consistent with the full treatment period (Figure 1 and Table 2). Rates of severe hypoglycemia were numerically lower with degludec versus glargine U100 during both treatment periods, but differences were not statistically significant (Figure 1). Rates of hypoglycemia appeared to be lower in Hispanic versus non-Hispanic patients, in both treatment groups, and across hypoglycemia definitions (Table 2).

AEs

During the trial, AEs were reported in 137 (53.1%) Hispanic patients and 364 (80.0%) non-Hispanic patients, at rates of 225.9 events/100 PYE in Hispanic patients and 414.1 events/100 PYE in non-Hispanics. A similar pattern was observed for serious AEs, with rates of 14.4 versus

TABLE 1. Baseline Characteristics in the Full Analysis Set According to Hispanic Ethnicity

	Hispanic Patients (n = 262)	Non-Hispanic Patients (n = 458)
Male	141 (53.8)	241 (52.6)
Race		
White	238 (90.8)	340 (74.2)
Black or African American	16 (6.1)	90 (19.7)
American Indian or Alaska Native	4 (1.5)	3 (0.7)
Other	4 (1.5)	2 (0.4)
Asian	0 (0)	22 (4.8)
Native Hawaiian or other Pacific Islander	0 (0)	1 (0.2)
Age, years	60.4 ± 10.7	61.9 ± 10.4
Weight, kg	87.8 ± 18.8	94.0 ± 19.5
Height, m	1.66 ± 0.11	1.70 ± 0.10
BMI, kg/m ²	32.0 ± 5.7	32.3 ± 5.6
Duration of diabetes, years	13.9 ± 8.0	14.1 ± 8.2
A1C		
%	7.7 ± 1.2	7.5 ± 1.0
mmol/mol	61 ± 13	59 ± 11
FPG		
mmol/L	8.1 ± 3.2	7.3 ± 2.7
mg/dL	146 ± 57	132 ± 49
eGFR (mL/min/1.73 m ²)	81 ± 20.4	76.7 ± 21.7
Smoking status		
Never smoked	155 (59.2)	209 (45.6)
Previous smoker	69 (26.3)	176 (38.4)
Current smoker	38 (14.5)	73 (15.9)

Reported for the full analysis set. Values are mean ± SD or n (%). eGFR, estimated glomerular filtration rate.

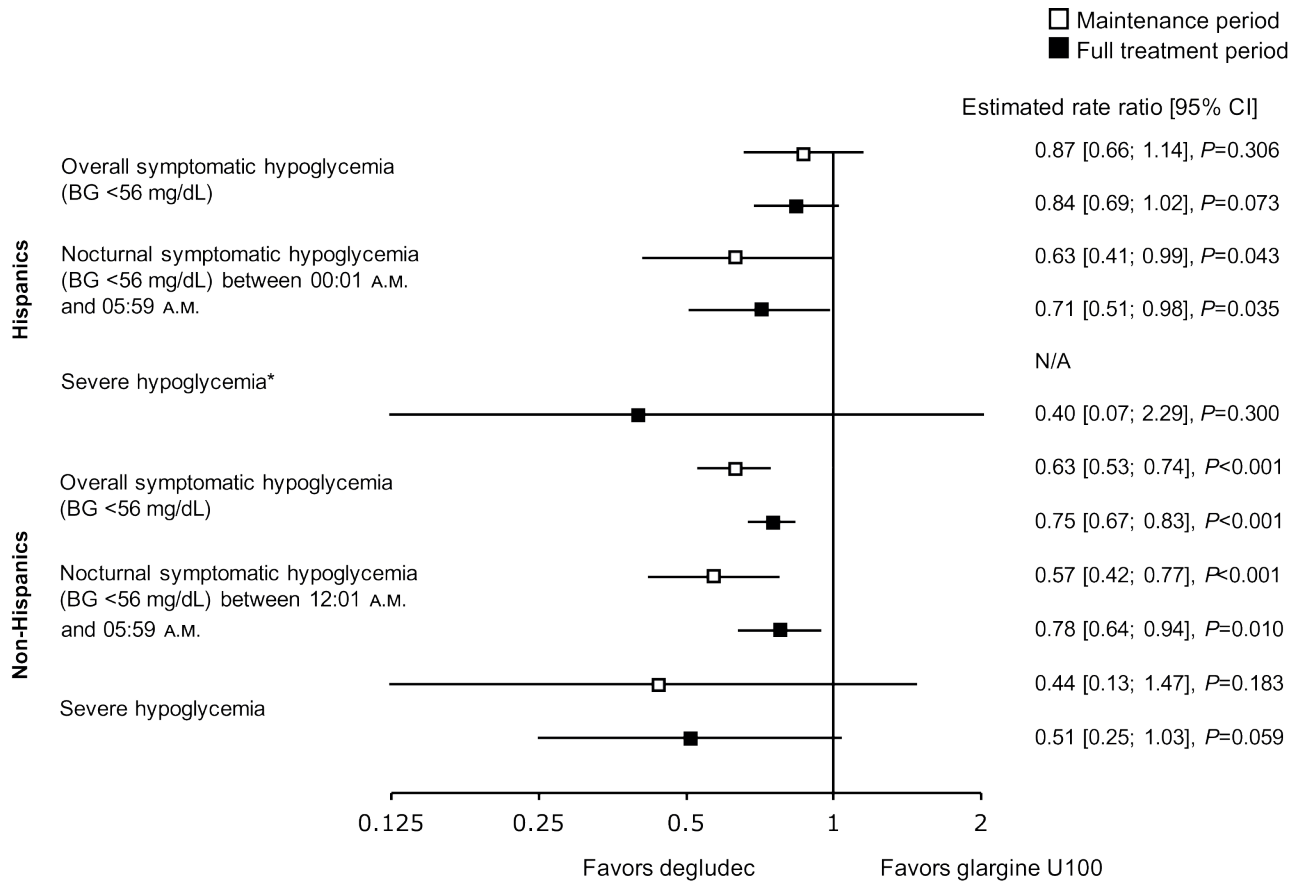


FIGURE 1. ERRs (degludec/glargine U100) of hypoglycemia in Hispanic and non-Hispanic patients during the SWITCH 2 trial. Full analysis set. *Only four episodes of severe hypoglycemia were reported in the maintenance period, which precluded statistical analysis. P values derived using a Poisson Model with logarithm of the exposure time (100 years) as offset; estimates adjusted for treatment, period, sequence, and dosing time as fixed effects and patient as random effects. BG, blood glucose.

27.5 events/100 PYE. The most common AEs in both populations were infections and infestations (Hispanic patients 71/258, 27.5%; non-Hispanic patients 234/455, 51.4%), whereas the most common serious AE in both populations was hypoglycemia (Hispanic patients 3/258, 1.2%; non-Hispanic patients: 8/455, 1.8%). Five treatment-emergent AEs had a fatal outcome in three Hispanic patients and two non-Hispanic patients, all during treatment with glargine U100. There were a further two deaths resulting from nontreatment-emergent AEs during follow-up. All but one of the fatal AEs were judged by the investigator as unlikely to be related to the trial product; the remaining fatal AE, sepsis in a 60-year-old Hispanic female, was judged possibly related to glargine

U100. An overview of AEs is presented in Supplementary Table 1.

Efficacy

Reductions in A1C over time are shown for each patient population in Figure 2A and B. There were no significant differences between the change in A1C achieved with degludec or glargine U100 in either patient group or treatment period (Supplementary Table 2). At baseline and throughout the trial, FPG values tended to be higher in Hispanic patients compared with non-Hispanic patients, but reductions in FPG with degludec were similar to those with glargine U100 (Figure 2C and D). In Hispanic and non-Hispanic patients, mean prebreakfast SMPG level decreased in both degludec and glargine U100 groups during the first 16 weeks of the SWITCH 2 trial and remained

stable for the remainder of the trial (Supplementary Figure 3A and B).

Insulin Dose

Over the total treatment period, insulin dose was lower with degludec versus glargine U100 across patient groups (estimated treatment ratio [ETR] = 0.97 [95% CI 0.94–1.00]; P = 0.046 and ETR = 0.95 [95% CI 0.94–0.98]; P < 0.001 for Hispanic patients and non-Hispanic patients, respectively) (Supplementary Tables 3 and 4). A pattern of a higher insulin dose for both degludec and glargine U100 was observed in Hispanic patients compared with non-Hispanic patients as the trial progressed (Supplementary Tables 3 and 4).

Discussion

In these post hoc analyses of the SWITCH 2 trial, the lower risk of

TABLE 2. Hypoglycemia in Hispanic and Non-Hispanic Patients During the SWITCH 2 Trial

	Degludec			Glargine U100			Total		
	Patients, n (%)	Episodes, n	Episodes, n/100 PYE	Patients, n (%)	Episodes, n	Episodes, n/100 PYE	Patients, n (%)	Episodes, n	Episodes, n/100 PYE
Maintenance period									
Hispanic patients	n = 231			n = 219			n = 236		
Overall symptomatic hypoglycemia	33 (14.3)	117	168.0	47 (21.5)	120	180.4	61 (25.8)	237	174.1
Nocturnal symptomatic hypoglycemia	18 (7.8)	36	51.7	25 (11.4)	56	84.2	32 (13.6)	92	67.6
Severe hypoglycemia	1 (0.4)	1	1.4	2 (0.9)	3	4.5	3 (1.3)	4	2.9
Non-Hispanic patients	n = 401			n = 399			n = 417		
Overall symptomatic hypoglycemia	109 (27.2)	236	195.8	148 (37.1)	376	312.3	195 (46.8)	612	254.0
Nocturnal symptomatic hypoglycemia	43 (10.7)	69	57.2	66 (16.5)	119	98.9	93 (22.3)	188	78.0
Severe hypoglycemia	9 (2.2)	9	7.5	3.3 (13)	14	11.6	19 (4.6)	23	9.6
Full treatment period									
Hispanic patients	n = 241			n = 241			n = 258		
Overall symptomatic hypoglycemia	55 (22.8)	225	160.0	64 (26.6)	237	172.4	87 (33.7)	462	165.9
Nocturnal symptomatic hypoglycemia	32 (13.3)	79	56.0	39 (16.2)	98	71.3	49 (19.0)	177	63.6
Severe hypoglycemia	2 (0.8)	2	1.4	5 (2.1)	7	5.1	6 (2.3)	9	3.2
Non-Hispanic patients	n = 430			n = 424			n = 455		
Overall symptomatic hypoglycemia	188 (43.7)	630	254.3	213 (50.2)	818	332.4	279 (61.3)	1448	293.2
Nocturnal symptomatic hypoglycemia	84 (19.5)	201	81.1	106 (25.0)	241	97.9	143 (31.4)	442	89.5
Severe hypoglycemia	13 (3.0)	15	6.1	21 (5.0)	29	11.8	30 (6.6)	44	8.9

Reported for the safety analysis set.

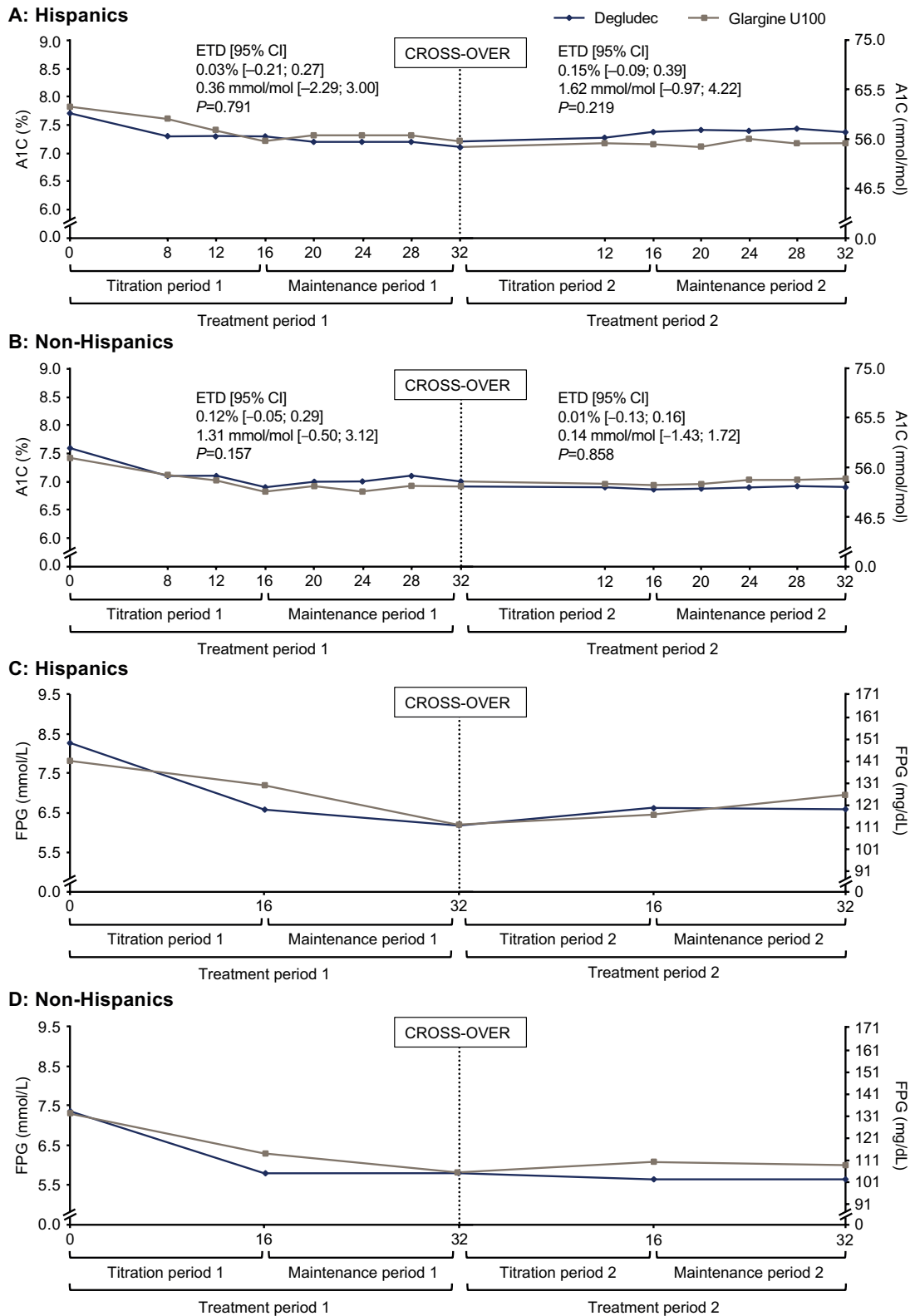


FIGURE 2. Glycemic control in Hispanic and non-Hispanic patients during the SWITCH 2 trial. Full analysis set. *A* and *B*: A1C. *C* and *D*: FPG. Estimated treatment differences (ETDs; degludec – glargine U100) for change in A1C after 32 weeks of treatment are derived from a mixed model for repeated measures with an unstructured covariance matrix including sex, antidiabetic therapy at screening, visit and dosing time as fixed effects, and age and baseline A1C as covariates. FPG, fasting plasma glucose.

hypoglycemia with degludec versus glargine U100 observed in Hispanic patients was generally consistent with that observed in non-Hispanic patients. All ERRs were numerically or significantly in favor of degludec versus glargine U100 during the maintenance and full treatment periods across different types of hypoglycemia in Hispanic and non-Hispanic patients. These new analyses support the overall findings of the SWITCH 2 trial, where treatment with degludec compared with glargine U100 resulted in significant reductions in the rates of overall symptomatic hypoglycemia and nocturnal symptomatic hypoglycemia over the 16-week maintenance period and the full treatment period (24). These new analyses provide more evidence of the favorable safety profile of degludec in various populations of patients with type 2 diabetes (27–29). In SWITCH 2, noninferiority of degludec compared with glargine U100 for A1C levels was confirmed for both treatment periods in the overall trial population (24). We report similar findings in these post hoc analyses of the Hispanic and non-Hispanic patient populations. Treatment with degludec versus glargine U100 resulted in similar improvements in glycemic control, but at a lower daily insulin dose over the total treatment period in favor of degludec, regardless of Hispanic or non-Hispanic ethnicity.

There have been numerous reports in the literature on the differences between Hispanics and non-Hispanics with respect to risk factors for diabetes (5,7,30), with guidelines including Hispanic/Latino ethnicity as a risk factor for prediabetes and type 2 diabetes (11). In addition, negative attitudes toward the use of diabetes therapy, in particular insulin, are common among Hispanics (20,22). In the current study, differences in the outcomes between Hispanic and non-Hispanic patients were compared descriptively, and some patterns were noted.

The mean rate of hypoglycemic episodes tended to be lower in

Hispanics versus non-Hispanics across all hypoglycemia types, despite a trend toward a higher insulin dose/kg of body weight in Hispanic patients. Observed rates of AEs were consistently lower in Hispanic patients compared with non-Hispanic patients across system organ classes. A slightly higher proportion of patients in the Hispanic group had a history of hypoglycemia unawareness at baseline (20.2 vs. 16.6% in the Hispanic and non-Hispanic groups, respectively); this may have resulted in fewer reports of symptomatic hypoglycemia in this group. Alternatively, lower rates of hypoglycemia in Hispanic versus non-Hispanic patients could be a consequence of their slightly poorer glycemic control. Improvements in A1C tended to be smaller in Hispanic patients in comparison to their non-Hispanic counterparts after 32 weeks of treatment with degludec or glargine U100. Higher FPG values were also observed in Hispanics compared with non-Hispanics throughout the trial, although change from baseline was similar between the two groups. In contrast to a pattern of higher FPG values in Hispanic patients during the trial, self-reported prebreakfast SMPG values tended to be lower in Hispanic patients compared with non-Hispanic patients as the trial progressed, which would align well with intensive insulin titration but is puzzling.

Previous reports have indicated that Hispanic patients have poorer glycemic control than non-Hispanic patients (13,14) and that they are less likely to adhere to insulin therapy than their non-Hispanic white counterparts (20). Reports have suggested that lower adherence may be related to fear of hypoglycemia or to an inability to afford insulin (20). In the current analyses, however, observed mean doses/kg of both degludec and glargine U100 appeared to be higher in Hispanic versus non-Hispanic patients at the end of treatment; thus, it seems unlikely that a failure to intensively titrate insulin could have

accounted for the lower reported rates of hypoglycemia. However, treatment adherence to diabetes medications is reported to be lower in Hispanics versus non-Hispanic white patients (31), highlighting the potential for differences in adherence rates between patient groups during the trial.

Taken together, the higher FPG values throughout the trial, smaller improvement in A1C after 32 weeks of treatment, and higher mean dose/kg of degludec and glargine U100 at the end of treatment observed in Hispanic versus non-Hispanic patients highlight the potential for greater insulin resistance in Hispanic patients. Ferrannini et al. (5) reported a 27% lower insulin sensitivity of glucose uptake in Mexican American versus Caucasian patients with normal glucose tolerance. Although speculative, there is the potential for increased insulin resistance in Hispanic patients with type 2 diabetes in comparison to their non-Hispanic white counterparts, which may have been reflected in the lower incidence of hypoglycemia observed in Hispanics during the trial. This contrasts with data on U.S. emergency department visits for hypoglycemia (1993–2005), where rates per 1,000 people with diabetes were almost twice as high in Hispanic versus non-Hispanic patients (32). In the United States, Hispanics face socioeconomic barriers to health care access, i.e., national data from 2011 to 2013 indicate that 41.5% of Hispanics were found to be lacking health insurance, compared with 15.1% of non-Hispanic whites (18). Hispanics are over two times more likely to live under the U.S. poverty line than non-Hispanic whites (18), with an increased incidence of severe hypoglycemia previously reported for patients of lower economic status (32).

Albeit from a large study population, these are post hoc analyses. This limits the interpretation of the findings, as the Hispanic and non-Hispanic patients were not two randomized groups. The small number of severe hypoglycemic events

reported precluded the calculation of ERRs (degludec/glargine U100) for this definition during the maintenance period.

Hypoglycemia has negative effects on patient health and quality of life (33), while posing a significant economic burden through loss of productivity and increased health care costs (34,35). Fear of hypoglycemia has been reported as a significant barrier to the initiation of insulin therapy for Hispanic patients (21,22) and contributes to psychological resistance to initiating insulin (19). The evidence from the current analyses showing that lower rates of hypoglycemia with degludec versus glargine U100 are seen in both Hispanic and non-Hispanic patients could help to counteract this fear.

Conclusion

In conclusion, safety and efficacy results from the Hispanic subpopulation of SWITCH 2 were generally consistent with those from the non-Hispanic subpopulation. In Hispanic patients, there was a numerically lower risk of overall hypoglycemia and a significantly lower risk of nocturnal hypoglycemia with degludec versus glargine U100, and both degludec and glargine U100 led to similar improvements in glycemic outcomes. Evidence of lower rates of hypoglycemia with degludec versus glargine U100 may help to counteract psychological insulin resistance in Hispanics with type 2 diabetes, thereby removing a barrier to insulin therapy and improving care.

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Duality of Interest

L.C. has served on an advisory panel for Intarcia Therapeutics and on a speaker's bureau for Novo Nordisk. A.B. has served on advisory panels for Abbott, Janssen, and Sanofi and speaker's bureau for Abbott, Sanofi, and AstraZeneca and received research support from Boehringer Ingelheim, Bristol-Myers Squibb, Novo Nordisk, Eli Lilly and Company, Dexcom, Medtronic, Sanofi, Mylan, Duke Clinical Research Institute, Janssen, Jaeb Center for Health Research, GlaxoSmithKline, Orexigen Therapeutics, Hygieia Research, University of Oxford, and AbbVie. R.D.I.R. has received speaking honoraria from Novo Nordisk, Boehringer Ingelheim, and Sanofi and clinical trial support from Novo Nordisk, Janssen Pharmaceuticals, Sanofi, GlaxoSmithKline, Elcelyx Therapeutics, and Merck. C.H.W. has served as a speaker and/or an advisor for Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Insulet, Janssen, Novo Nordisk, and Sanofi. L.N.T. and S.H.Ø. are employees of Novo Nordisk. A.P.-T. has served on advisory panels for AstraZeneca, Dexcom, Lilly, Merck, Novo Nordisk, and Sanofi and received research support from Dexcom, Janssen, Lilly, Mylan, and Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

Author Contributions

L.C., A.B., R.D.I.R., C.H.W., and A.P.-T. contributed to the analysis and manuscript writing for this study. L.N.T. and S.H.Ø. contributed to the design, analysis, and manuscript writing for this study. L.C. 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.

Prior Presentation

Some of the data included in the manuscript have been previously presented in poster form at the International Diabetes Federation Congress, 4–8 December 2017, Abu Dhabi, United Arab Emirates.

Author's Note

There are changes between this version of the manuscript and the version initially posted online on 26 September 2018. After this paper was accepted for publication and published online, it came to our attention that there was an error in Figure 2. In this updated version of the paper, the secondary y-axis labels have been corrected in Figure 2A and B to display values in mmol/mol rather than %. Data for Hispanics and non-Hispanics have also been clearly identified. The caption for Figure 2 has been updated to clearly detail ETDs.

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