**ORIGINAL ARTICLE** 

# Efficacy and Safety of Insulin Glargine 300 U/mL Versus Insulin Glargine 100 U/mL in High-Risk and Low-Risk Patients with Type 2 Diabetes Stratified Using Common Clinical Performance Measures

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# Abstract

**Background:** To determine whether previously reported reductions in hypoglycemia associated with insulin glargine 300 U/mL (Gla-300) compared with insulin glargine 100 U/mL (Gla-100) are impacted by patient risk category in type 2 diabetes (T2D), clinical performance measures based on the Healthcare Effectiveness Data and Information Set (HEDIS) were applied to patient-level data from the EDITION 2 and EDITION 3 clinical trials that compared Gla-300 and Gla-100.

*Methods:* In this post hoc analysis, patients were stratified as low risk (LR) if patients were <65 years old with no comorbidities derived from HEDIS (HbA1c target <7.0% [53 mmol/mol]), or as high risk (HR) if patients were either  $\geq$ 65 years old or had one or more HEDIS-defined comorbidities (HbA1c target <8.0% [64 mmol/mol]). Primary endpoint was a composite of patients achieving HbA1c target without confirmed or severe hypoglycemia over 6 months in the different treatment groups in each of the EDITION trials.

**Results:** There was a statistically nonsignificant trend of more patients treated with Gla-300 achieving the composite endpoint compared with Gla-100 in both the LR and HR patient cohorts, regardless of prior insulin experience. A similar trend was observed for the composite endpoint of HbA1c target without nocturnal hypoglycemia.

*Conclusions:* There is a consistent, nonsignificant trend suggesting that Gla-300 might reduce the burden of hypoglycemia compared with Gla-100 in patients with T2D irrespective of whether they are classed as LR or HR based on age- and National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set-derived comorbidities.

Keywords: Insulin glargine, Hypoglycemia, Quality measures, HEDIS, Type 2 diabetes.

# Introduction

**T**NSULIN GLARGINE 300 U/mL (Gla-300) is a newgeneration basal insulin formulation that delivers the same number of insulin units as insulin glargine 100 U/mL (Gla-100) but in a third of the injectable volume. Pharmacokinetic/ pharmacodynamic studies have shown that Gla-300 is released from the subcutaneous depot at the injection site more gradually than Gla-100, resulting in a prolonged and more constant pharmacokinetic profile with a duration of action that extends beyond 24 h.<sup>1–3</sup> As a result, Gla-300 is able to maintain blood glucose control for up to 36 h after administration.<sup>1,3</sup>

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The efficacy and safety of Gla-300 versus Gla-100 has been compared in six multinational, open-label studies in the EDITION phase 3a clinical program, which included trials evaluating patients with type 1 and type 2 diabetes and patients from different regions. For this analysis, data from the EDITION 2 and 3 trials were used, which included patients with type 2 diabetes (T2D) who were either uncontrolled on prior basal insulin therapy (EDITION 2) or were insulinnaive and inadequately controlled on oral antidiabetes drugs (OADs; EDITION 3). In both trials, glycemic control was comparable between Gla-300 and Gla-100 at 6 months, but patients treated with Gla-300 experienced fewer nocturnal confirmed ( $\leq 3.9 \text{ mmol/L}$ ) or severe hypoglycemia events compared with patients treated with Gla-100.<sup>4,5</sup> Furthermore, patients receiving Gla-300 gained less weight, a difference that reached statistical significance in EDITION 2.4,5

The National Committee for Quality Assurance (NCQA) Healthcare Effectiveness Data and Information Set (HEDIS) is a tool used by managed healthcare organizations to assess realworld performance of care and service, and to document health plan performance in diabetes care.<sup>6</sup> NCQA HEDIS 2014 diabetes criteria take patient age and comorbidities into account and are used to stratify patients as either low risk (LR) or high risk (HR); this can then be used to assign individualized HbA1c targets (<7.0% [53 mmol/mol)] for LR patients or <8.0% [64 mmol/mol] for HR patients) to assist in personalizing patient management, as recommended in the 2015 joint position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).<sup>7</sup>

In the present study, real-world diabetes performance measures based on ADA guidelines and selected NCQA HEDIS 2014 diabetes management criteria were applied to post hoc analyses of datasets from the EDITION 2 and 3 clinical trials to assess glycemic control and the incidence of hypoglycemia in patients with T2D. A composite endpoint of safety and efficacy outcomes was used to provide a measure of clinical effectiveness relevant to decision makers in a realworld healthcare context. This study used the NCQA HEDIS 2014 guidelines, which are part of quality of care assessments, to make the clinical trial results more applicable at the clinical level. Using these guidelines, patients were stratified into LR and HR cohorts, with the aim of the study to determine whether the previously observed benefit for Gla-300 compared with Gla-100 with regard to hypoglycemia was impacted by patient risk category.

### Subjects

The subjects and methods for the EDITION 2 and 3 trials have been previously published in full.<sup>4,5</sup> In this study, post hoc analyses of patient-level data from the EDITION 2 and 3 phase 3a studies were performed; the NCQA HEDIS 2014 and ADA diabetes performance measures were applied to stratify patients according to risk. Datasets from the EDI-TION 2 and 3 clinical trials were analyzed separately because the patient selection criteria were different for each trial in terms of insulin dosage, patient characteristics/background, and prior therapy.

### EDITION 2

EDITION 2 included adult patients with uncontrolled T2D (defined as HbA1c  $\geq$ 7.0% [53 mmol/mol] and  $\leq$ 10.0%

[86 mmol/mol] at screening) despite treatment with  $\geq$ 42 U of basal insulin plus OADs at baseline. Eligible patients were randomized in a 1:1 ratio to receive once daily Gla-300 or Gla-100, administered at the same time each evening; existing sulfonylurea treatment was discontinued.<sup>5,8</sup> Exclusion criteria included the use of premixed insulin, insulin detemir, or new glucose-lowering agents within the last 3 months, sulfonylurea use within the last 2 months, and recent use of recombinant human insulin or mealtime insulin (>10 days in the previous 3 months).

Insulin doses were switched unit-for-unit for patients previously on once-daily neutral protamine Hagedorn (NPH) or Gla-100, or reduced by  $\sim 20\%$  in those who were previously taking NPH insulin twice daily. Insulin doses were titrated weekly to a fasting plasma glucose (FPG) target of 4.4–5.6 mmol/L (80–100 mg/dL), based on the median of three self-monitored FPG readings.<sup>5,8</sup>

## EDITION 3

In EDITION 3, eligible patients had T2D for  $\geq 1$  year before screening, were insulin-naive, had been treated with OADs for  $\geq 6$  months, and had inadequate glycemic control (defined as HbA1c  $\geq 7.0\%$  [53 mmol/mol] at screening). Patients with HbA1c <7.0% (53 mmol/mol) or >11.0% (97 mmol/mol) were excluded. If patients were being treated with OADs not approved for combination with insulin, and/or sulfonylureas or glinide, these were discontinued at baseline.<sup>4</sup>

Patients were randomized in a 1:1 ratio to receive oncedaily Gla-300 or Gla-100 administered at the same time each evening, titrated to a FPG target of 4.4–5.6 mmol/L (80– 100 mg/dL) in the absence of hypoglycemia. The starting dose was 0.2 U/kg bodyweight for both insulins, rounded down to the closest whole number that was divisible by 3.<sup>4</sup>

#### Risk stratification

For the purposes of this secondary analysis of the EDI-TION 2 and 3 datasets, patients were stratified into one of two cohorts-LR or HR-based on age and the presence of NCQA HEDIS-defined comorbidities.<sup>6</sup> Patients were classified as LR if they were <65 years old and had none of the following comorbidities: evidence of coronary artery bypass surgery or percutaneous coronary intervention, ischemic vascular disease, thoracic aortic aneurysm, chronic heart failure, prior myocardial infarction, chronic renal failure or end-stage renal disease, dementia, blindness, or lowerextremity amputation. Patients classified as HR were either ≥65 years old or had at least one of the NCOA HEDISderived comorbidities listed above.<sup>6</sup> LR and HR patients were assigned HbA1c targets of <7.0% (53 mmol/mol) and <8.0% (64 mmol/mol), respectively, for the purposes of this analysis based on NCQA HEDIS-derived HbA1c targets appropriate for each risk category.

#### Materials and Methods

#### Study design

EDITION 2 and 3 were multicenter, randomized, openlabel, two-arm, parallel-group phase 3a clinical trials. Both studies comprised a 2-week screening phase, followed by a 6-month treatment period and a 6-month safety extension period.<sup>4,5</sup> Data from the 6-month treatment period only are presented in this article.

#### Assessments and endpoints

The primary endpoint of this post hoc analysis was a composite of patients in each of the Gla-300 and Gla-100 treatment groups in the EDITION 2 and 3 trials who achieved HbA1c target without confirmed or severe hypoglycemia over the 6-month study period. Secondary endpoints included the proportion of patients who achieved HbA1c targets without nocturnal hypoglycemia, the change in HbA1c from baseline, the incidence of confirmed or severe hypoglycemia, and the incidence of nocturnal hypoglycemia. Additionally, response rate ratios (RRs) were calculated to assess the difference between Gla-300- and Gla-100-treated patients for the composite endpoints.

Confirmed or severe hypoglycemia was defined as all categories of hypoglycemia reported within the EDITION trials with symptomatic and asymptomatic events with self-monitored blood glucose (SMBG) level <3.9 mmol/L (<70 mg/dL) or severe hypoglycemic events; nocturnal hypoglycemia was defined as a confirmed or severe hypoglycemia event that occurred between the times of 00:01 and 05:59.

#### Statistical analyses

This was a post hoc analysis of patient-level data from the 6-month EDITION 2 and 3 studies. Efficacy endpoints were based on the modified intent-to-treat (mITT) population, which included all randomized patients who received at least one dose of study insulin and had both a baseline and at least one post-baseline assessment. A last observation carried forward analysis was applied to HbA1c and weight data from patients who discontinued treatment prematurely or did not have a 6-month efficacy assessment.

Descriptive statistics are presented for the baseline demographics and characteristics of patients in the LR and HR cohorts for the treatment arms (Gla-300 and Gla-100) in each study. For confirmed or severe hypoglycemia and nocturnal hypoglycemia, the proportion of patients experiencing events, and the rate per patient-year were calculated. Rate ratios (RRs) (percentage of patients receiving treatment with Gla-300 divided by percentage of patients receiving treatment with Gla-100) for each composite endpoint in both risk cohorts were plotted for a graphical display of the comparison between treatments.

*P* values were obtained using the Pearson  $X^2$  test to test for any association between the treatment groups, with *P* < 0.05 considered to represent statistical significance. *P* values for comparison of rate of hypoglycemia events (per patient-year) for patients in the different treatment arms were obtained by Poisson regression, with treatment as a fixed effect, and log of exposure as an offset variable. All statistical analyses were performed using SAS software version 9.2 (Cary, NC).

### Results

#### Patient population

Eligibility criteria (mITT population from each study) were met by a total of 609 patients classified as LR and 199 patients classified as HR from the EDITION 2 trial, and 629

0	THE EDITION 2	2 AND EDITION 3	CLINICAL TRIAL	DATASETS (MOD	IFIED INTENTION-	TO-TREAT POPULA	ATION)	
		EDITION 2 (Pri	or basal insulin)			EDITION 3 (	Insulin-naive)	
	LR cohort (E	IbAIc < 7.0%	HR cohort (H	HbAIc < 8.0%	LR cohort (H	<i>IbA1c</i> <7.0%)	HR cohort (H	bAIc < 8.0%
	Gla-300 (n = 312)	Gla-100 $(n=297)$	Gla-300 $(n=91)$	Gla - I00 $(n = I08)$	Gla-300 (n = 312)	Gla-100 $(n = 317)$	Gla-300 (n = 120)	Gla-I00 $(n = 113)$
years	54.8 (7.6)	54.7 (7.0)	68.5 (4.8)	69.0 (5.9)	53.9 (7.6)	53.1 (8.0)	69.5 (4.8)	69.3 (5.2)
<65 years, n (%)	312(100)	297 (100)	5(5.5)	6(5.6)	312(100)	317(100)	7 (5.8)	4(3.5)
kg/m <sup>2</sup>	35.1(6.7)	35.2(6.4)	33.7 (6.4)	33.8(4.8)	33.1(6.9)	33.6(6.6)	32.0(6.6)	31.8(6.4)
ion of diabetes, years	11.8(3.2)	11.8 (6.4)	15.9(8.6)	14.6 (8.2)	9.2(6.0)	8.5 (5.3)	12.6 (7.0)	12.4 (7.2)
lc, %	8.3 (0.87)	8.3 (0.79)	8.2 (0.83)	8.1 (0.71)	8.6(1.08)	8.7 (1.08)	8.4 (0.96)	8.4 (1.03)

TABLE 1. BASELINE DEMOGRAPHICS AND PATIENT CHARACTERISTICS OF PATIENTS IN THE LOW-RISK AND HIGH-RISK COHORTS

Data are mean (standard deviation) unless indicated. BMI, body mass index; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; HbA1c, glycated hemoglobin; HR, high risk; LR, low risk.

Age, Age BMI Dura HbA



**FIG. 1.** Rate ratios for LR and HR patients achieving composite endpoint of HbA1c target without (**A**) confirmed or severe hypoglycemia and (**B**) nocturnal hypoglycemia. Rate ratio is the percentage of patients receiving treatment with Gla-300 divided by percentage of patients receiving treatment with Gla-100. CI, confidence interval; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; HbA1c, glycated hemoglobin; HR, high risk; LR, low risk.

LR and 233 HR patients from the EDITION 3 trial; in total, 26% of patients randomized in these studies met the criteria for HR.

Baseline demographics and patient characteristics are summarized according to trial, NCQA HEDIS-based risk cohort and treatment assignment (Table 1). Within each risk cohort, patients assigned to Gla-300 or Gla-100 were well balanced with respect to baseline characteristics. Compared with LR patients, HR patients were older (EDITION 2, 68.8 years vs. 54.7 years; EDITION 3, 69.4 years vs. 53.5 years), had a longer duration of T2D (EDITION 2, 15.0 years vs. 11.8 years; EDITION 3, 12.5 years vs. 8.8 years), and lower mean HbA1c level (EDITION 2, 8.1% [65 mmol/mol] vs. 8.3% [67 mmol/mol]; EDITION 3, 8.4% [68 mmol/mol] vs. 8.6% [71 mmol/mol]).

### Composite endpoints

Compared with Gla-100, in the LR cohort patients treated with Gla-300 had similar likelihood of achieving composite primary endpoint of target HbA1c without confirmed or severe hypoglycemia in EDITION 2 (EDITION 2, 6.1% vs. 5.7%, RR 1.06, 95% confidence interval [CI] 0.56–2.01, P=0.8483), but were more likely to achieve this composite primary endpoint in EDITION 3 (EDITION 3, 22.1% vs. 15.1%, RR 1.46 [1.05–2.04], P=0.0246). In the HR cohort, there were no statistically significant differences between

Gla-300 and Gla-100 treatments regarding primary composite endpoint achievement in either study (EDITION 2, 15.4% vs. 12.0%, RR 1.28 [0.63–2.58], P=0.4921; EDI-TION 3, 36.7% vs. 28.3%, RR 1.29 [0.89–1.89], P=0.1743) (Fig. 1A).

There were no statistically significant differences between Gla-300 and Gla-100 treatment groups in either EDITION 2 or EDITION 3 regardless of risk cohort with regards to achieving target HbA1c without nocturnal hypoglycemia (LR: EDITION 2, 17.9% vs. 17.2%, RR 1.07 [0.75–1.51], P=0.7491; EDITION 3, 36.5% vs. 32.5%, RR 1.14 [0.91–1.41], P=0.2751; HR: EDITION 2, 44.0% vs. 39.8%, RR 1.10 [0.80–1.53], P=0.5672; EDITION 3, 62.5% vs. 59.3%, RR 1.06 [0.86–1.30], P=0.6883) (Fig. 1B).

#### Change in HbA<sub>1c</sub> from baseline

The mean (standard deviation) change in HbA1c from baseline to the 6-month endpoint was comparable between the treatment groups in the LR cohort in EDITION 2 (Gla-300 vs. Gla-100, -0.7 [1.03]% vs. -0.6 [1.02]%) and EDITION 3 (Gla-300 vs. Gla-100, -1.3 [1.21]% vs. -1.5 [1.24]%) (Table 2). This was also seen in the HR cohorts in EDITION 2 (Gla-300 vs. Gla-100, -0.6 [1.29]% vs. -0.6 [0.92]%) and EDITION 3 (Gla-300 vs. Gla-100, -1.2 [1.16]% vs. -1.2 [1.12]%) (Table 2).

TABLE 2. CHANGE IN  $HBA_{1c}$  FROM BASELINE TO THE 6-MONTH ENDPOINT IN THE LOW-RISK AND HIGH-RISK COHORTS OF EDITION 2 AND 3

	ED	ITION 2 (Pri	or basal insi	ılin)		EDITION 3 (	Insulin-naive	)
	LR c	ohort	HR a	cohort	LR c	ohort	HR c	cohort
	<i>Gla-300</i> (n=312)	<i>Gla-100</i> (n = 297)	<i>Gla-300</i> (n=91)	Gla-100 (n = 108)	<i>Gla-300</i> (n=312)	<i>Gla-100</i> (n=317)	Gla-300 (n = 120)	<i>Gla-100</i> (n = 113)
Change in HbA1c from baseline to 6 months	-0.7 (1.03)	-0.6 (1.02)	-0.6 (1.29)	-0.6 (0.92)	-1.3 (1.21)	-1.5 (1.24)	-1.2 (1.16)	-1.2 (1.12)

Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; HbA1c, glycated hemoglobin; HR, high risk; LR, low risk.

OF EDITION 2	TABLE AND 3 WITH	2 3. NUMBER CONFIRMED	and Perc (<70 mg/d	ENTAGE OF L) OR SEVEI	PATIENTS IN RE, OR NOCT	n the Lov 'urnal Hy	v-Risk and F ypoglycemia	High-Risk Cc During 6-N	horts Ionth Tr	eatment Pi	ERIOD	
		EDITIO	N 2 (Prio	r basal insu	(in)			EDI	ION 3 (In	tsulin-naive)		
		LR cohort			HR cohort			LR cohort		1	HR cohort	
	Gla-300 $(n=312)$	Gla-100 (n = 297)	Ь	Gla-300 $(n=91)$	Gla-I00 $(n = 108)$	Ч	Gla-300 $(n=312)$	Gla-I00 $(n=317)$	Ь	Gla-300 (n = 120)	Gla-I00 $(n = 113)$	Р
Patients with confirmed or severe hypoglycemia,	213 (68.3)	227 (76.4)	0.0245	69 (75.8)	87 (80.6)	0.4192	136 (43.6)	157 (49.5)	0.136	65 (54.2)	73 (64.6)	0.105
Patients with nocturnal hypoglycemia, $n$ (%)	93 (29.8)	124 (41.8)	0.002	23 (25.3)	41 (38.0)	0.0678	52 (16.7)	69 (21.8)	0.1069	29 (24.2)	37 (32.7)	0.1903
Gla-100, insulin glargine 100	U/mL; Gla-300	0, insulin glarg	ine 300 U/1	nL; HbA1c, g	dycated hemo	globin; HR	, high risk; LR	, low risk.				

# Incidence and rate of hypoglycemia regardless of HbA1c goal achievement

Confirmed or severe hypoglycemia. At 6 months, fewer patients in the LR cohort who were treated with Gla-300 had confirmed or severe hypoglycemia compared with those treated with Gla-100, a difference that was significant in EDITION 2 (68.3% vs. 76.4%; P=0.0245), but not in EDITION 3 (43.6% vs. 49.5%; P=0.136) (Table 3). In the HR cohorts, although numerically lower, there was no significant difference in the proportion of patients experiencing confirmed or severe hypoglycemia when treated with Gla-300 compared with Gla-100 in either study (Table 3).

There were significant reductions in rates (events per patient-year) of confirmed or severe hypoglycemia for patients treated with Gla-300 compared with Gla-100 in both the LR and HR cohorts of EDITION 2, although a significantly lower rate was only observed for the LR cohort in EDITION 3 (LR: EDITION 2, 13.4 vs. 17.1 events per patient-year, P < 0.0001; EDITION 3, 5.13 vs. 7.62 events per patient-year, P < 0.001; HR: EDITION 2, 16.2 vs. 21.2 events per patient-year, P < 0.0001; EDITION 3, 9.78 vs. 10.9 events per patient-year, P = 0.0664) (Table 4).

Nocturnal hypoglycemia. Similar results were seen for the incidence of nocturnal hypoglycemia at 6 months. Patients in the LR cohort who were treated with Gla-300 had a lower incidence of nocturnal hypoglycemia than those treated with Gla-100 in EDITION 2 (29.8% vs. 41.8%, respectively; P=0.002), but differences were not significant in EDITION 3 (16.7% vs. 21.8%, respectively; P=0.107). In the HR cohort, patients treated with Gla-300 showed a nonsignificant trend toward lower nocturnal hypoglycemia compared with those treated with Gla-100 (EDITION 2, 25.3% vs. 38.0%, P=0.0678; EDITION 3, 24.2% vs. 32.7%, P=0.1903) (Table 3).

In EDITION 2, the rate of nocturnal hypoglycemia in both cohorts was significantly lower for those treated with Gla-300 than with Gla-100 (LR: 1.99 vs. 3.62 events per patient-year; HR: 1.54 vs. 3.86 events per patient-year; both P < 0.0001) but was comparable in EDITION 3 (LR: 1.11 vs. 1.21 events per patient-year, P = 0.4245; HR: 1.82 vs. 1.68 events per patient-year, P = 0.5943) (Table 4).

## Discussion

In this exploratory post hoc analysis of the EDITION 2 and 3 trials, we classified patients into LR and HR cohorts using NCQA HEDIS 2014 and ADA/EASD guidelines and applied the NCQA HEDIS HbA1c target levels of <7% (53 mmol/ mol) for the LR cohort and <8% (64 mmol/mol) for the HR cohort. The percentage of patients who achieved the primary composite endpoint of target HbA1c without confirmed or severe hypoglycemia at 6 months was higher in the Gla-300treated group compared with Gla-100, however, this only reached statistical significance in the LR group of the EDI-TION 3 study. Similarly, a higher percentage of LR and HR patients treated with Gla-300 achieved the composite endpoint of target HbA1c without nocturnal hypoglycemia than those treated with Gla-100, but neither comparison reached statistical significance. Changes in HbA1c from baseline were similar in both LR and HR patients treated with either Gla-300 or Gla-100, regardless of prior insulin experience.

;		EDITI	ON 2 (Pric	or basal in	sulin)			ED	ITION 3 (I	nsulin-naive	()	
		LR cohort			HR cohort			LR cohort		1	HR cohort	
	Gla-300 (n=312)	Gla-100 $(n=297)$	Ч	Gla-300 $(n=91)$	Gla-I00 $(n = 108)$	Ч	Gla-300 (n = 312)	Gla-I00 (n = 317)	Ь	Gla-300 (n = 120)	Gla-I00 $(n = 113)$	Р
Rate of confirmed or severe	13.4	17.1	<0.0001	16.2	21.2	<0.0001	5.13	7.62	<0.001	9.78	10.9	0.0664
nypogrycernia, event/pauent-year Rate of nocturnal hypoglycernia, events/patient-year	1.99	3.62	<0.0001	1.54	3.86	<0.0001	1.11	1.21	0.4245	1.82	1.68	0.5943
Gla-100, insulin glargine 100 U/mL; G	3la-300, insul	in glargine 3(	00 U/mL; H	bA1c, glyca	ted hemoglob	oin; HR, higl	h risk; LR, lo	ow risk.				

Table 4. Rate Of Hypoglycemia (Events per Patient-Year) for Patients in the Low-Risk and High-Risk Cohorts

Since the improvement in glycemic control was similar in all cohorts, these findings were driven by the difference in hypoglycemia. Hypoglycemia rates, of confirmed or severe, and nocturnal hypoglycemia, tended to be lower in patients treated with Gla-300 in both risk cohorts of EDITION 2 and EDITION 3 trials.

Although large clinical trials have improved our clinical understanding of the potential benefits and risks associated with intensive glycemic control,<sup>9-12</sup> and the current ADA/ EASD guidelines for T2D recommend individualizing glycemic targets,<sup>7</sup> there are limited data to guide patients and clinicians in both the clinical trial and real-world settings. The NCQA HEDIS quality care measures have been designed to determine appropriate HbA1c targets based on age and the presence of comorbidities, and can therefore be used as a tool to classify patients according to risk, and consequently, to set individual target levels for glycemic control a priori. A recent cross-sectional, observational study modeling a similar stratification technique based on age and comorbidities found that up to one-third of patients with diabetes in a primary care setting would be reclassified from having uncontrolled to controlled glycemia using this approach, without differentially affecting vulnerable patient subgroups (e.g., patients with low socioeconomic status) who may potentially benefit greatly from early intervention to achieve good glycemic control early in the disease process.<sup>13</sup>

The individualization of patient glycemic targets is in line with the "Triple Aim" concept of the U.S. Patient Protection and Affordable Care Act of 2010. This aims to simultaneously improve the health of the U.S. population, improve the individual experience of care, and reduce the per capita cost of healthcare.<sup>14</sup> The use of less stringent HbA1c targets (8.0% [64 mmol/mol]) for patients who are older, or who have comorbidities as indicated by the NCOA HEDIS performance criteria, is particularly relevant to this. Reducing hypoglycemia in HR groups, while maintaining sufficient glycemic control, is likely to improve overall population health and individual care experience, and minimize management costs.

Importantly, the principal costs of care associated with insulin use are due not only to costs of the medicine, but also to the high cost of treating diabetes treatment-related complications such as hypoglycemia.<sup>15</sup> Thus, healthcare costs may be reduced by adopting insulin treatment and dosing strategies associated with a lower risk of hypoglycemia.<sup>16,17</sup> Furthermore, patients at HR of hypoglycemia, such as the elderly and those with multiple comorbidities, are at significant risk of further complications (falls, fractures, and vascular disease) as a consequence of repeat hypoglycemia episodes and therefore more likely to benefit from reducing the risk of a hypoglycemia event.<sup>18</sup>

Thus, in the context of both the "Triple Aim" strategy and the current guidelines on diabetes management from the ADA/EASD, the reduction of hypoglycemia, along with HbA1c control, is clearly an important component in the management of T2D. In this study, notwithstanding the similar glycemic control achieved with Gla-300 and Gla-100, a consistent trend toward lower rates of confirmed or severe hypoglycemia, and nocturnal hypoglycemia, was observed with Gla-300 compared with Gla-100 in both LR and HR patients, regardless of prior insulin experience. The consistency in the findings between LR and HR patients also

indicates that the benefit associated with Gla-300 persists at stringent (<7% [53 mmol/mol] for LR) and more conservative target HbA1c levels (<8% [64 mmol/mol] for HR). Although the post hoc arbitrary separation of patients into LR and HR cohorts does not represent real-world management practices, and the advantages in terms of a reduction in hypoglycemia with Gla-300 did not reach significance for the HR patients, the data from this analysis may be used to inform prospective real-world trials currently in progress for Gla-300. Such real-world studies include the ongoing ACHIEVE CONTROL,<sup>19</sup> REACH CONTROL, and REGAIN CON-TROL studies that aim to compare the clinical effectiveness of Gla-300 with other basal insulins in a standard care setting and to capture additional measures relating to healthcare resource utilization and patient-reported outcomes.

This study presented several limitations. Most importantly, the subdivision of each study population in EDITION 2 and EDITION 3 into LR and HR cohorts and the overall relatively low rate of both confirmed or severe hypoglycemia and nocturnal hypoglycemia resulted in very limited power to detect clinically relevant differences in outcomes between groups. Additionally, the treat-to-target design used in the EDITION 2 and EDITION 3 trials may have contributed to limited power due to small differences in glycemic outcomes as a result of the design. Furthermore, there would have been a bias toward patients largely being classified as LR because of the inclusion/exclusion criteria in the EDITION 2 and EDITION 3 trials (e.g., EDITION 2 and 3 excluded patients with a history of myocardial infarction, heart failure, and endstage renal disease; patients with stroke were also excluded from EDITION 2).

Sample sizes were relatively small because of variation within the populations. Indeed, numbers of patients in each category separated by both study and risk group were small. Although the decision to analyze subgroups within each of the two EDITION trials separately (rather than pooling data for the EDITION 2 and 3 populations as a whole) was justified because of the differences in patient characteristics and treatment backgrounds between the two trials, it may be an important factor contributing to the reduced power of the study. The combination of these factors may have affected the statistical power of this analysis. This exploratory post hoc analysis also involved retrospective reassignment of HbA1c goals for the HR group. These patients were still treated to meet a "stringent" goal during the study, thus hypoglycemia rates could have been even lower if they had been treated to reach this more "liberal" goal.

The study was also designed to show noninferiority. In clinical practice, there is always a trade-off between glycemic control and avoidance of hypoglycemia, but this balance may not have been implemented in a trial setting. Hypoglycemic events may have been under-reported if patients treated their symptoms without confirmation of hypoglycemia through the measurement of blood glucose levels. Moreover, the incidence of patient-reported hypoglycemia symptoms without SMBG confirmation was not reported in this post hoc analysis.

In conclusion, the assessment of diabetes performance measures to guide treatment strategy in a real-world setting is an important consideration for healthcare decision makers in diabetes management. The findings from this retrospective analysis of phase 3a data point to a nonsignificant but consistent trend, suggesting that Gla-300 might reduce the clinical and economic burden of hypoglycemia compared with Gla-100 in patients with T2D irrespective of whether they are classed as LR or HR based on age- and NCQA HEDISderived comorbidities. Future planned or ongoing real-world studies are required to confirm this potential clinical advantage of Gla-300, which has important implications for diabetes management. In the meantime, current evidence suggests that basal insulin treatment with Gla-300 is effective and safe for use in LR and HR patients alike, with the potential to reduce the risk of hypoglycemia compared with Gla-100.

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#### Authors' Contribution

I.L. contributed to the data analysis, interpretation of the data, and drafting and critically revising the article. J.C. contributed to the study conception and design, acquisition and analysis of data, interpretation of data, and drafting of the article as the guarantor of this work and takes responsibility for the integrity of the data and the accuracy of the data analysis. M.D. contributed to the study conception and design, acquisition and analysis of data, interpretation of data, and drafting and critically revising the article. L.M. contributed to the data analysis, interpretation of the data, and drafting and critically revising the article. All authors had full access to all the data in the study and agree to be accountable for all aspects of the work.

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