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ORIGINAL RESEARCH

Clinical Outcomes of Patients with Diabetes Who Exhibit Upper-Quartile Insulin Antibody Responses After Treatment with LY2963016 or Lantus® Insulin Glargine

Liza L. Ilag · Timothy M. Costigan · Mark A. Deeg · Robyn K. Pollom ·
Curtis L. Chang · Robert J. Konrad · Melvin J. Prince

ABSTRACT

Introduction: We compared insulin antibody response (IAR) profiles in patients with type 1 diabetes (T1D) or type 2 diabetes (T2D) who received LY2963016 insulin glargine (LY IGlar) or Lantus® insulin glargine (IGlar) and evaluated the potential relationship between higher IARs and clinical and safety outcomes with a focus on patients who exhibited antibody responses in the upper quartile.

Methods: Data from ELEMENT-1 (52-week open-label in T1D) and ELEMENT-2 (24-week, double-blind study in T2D) were analyzed. Maximum postbaseline IAR levels and proportions of patients in the upper quartile of maximum antibody percent binding (UQMAPB; patients with maximum postbaseline percent binding in the highest 25% of maximum values observed) were compared for differential treatment effects on clinical efficacy outcomes and incidence of adverse events. Continuous outcomes were analyzed by analysis of covariance. Categorical data were analyzed by the Cochran–Mantel–Haenszel or Breslow–Day test.

Results: In both studies ($N = 532$ evaluable patients with T1D; $N = 730$ with T2D), no statistically significant differences between LY IGlar and IGlar were observed for maximum antibody percent binding (MAPB) levels or for proportions of patients in the respective UQMAPB. No statistically significant differential treatment effects were observed in the relationship between MAPB and clinical efficacy and safety outcomes.

Conclusions: Maximum postbaseline IAR levels and the proportion of patients with high IAR levels were similar for LY IGlar and IGlar. High antibody levels did not affect clinical outcomes. These results add further evidence supporting similar IARs of LY IGlar and IGlar.

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L. L. Ilag (✉) · T. M. Costigan · M. A. Deeg ·
R. K. Pollom · C. L. Chang · R. J. Konrad ·
M. J. Prince
Lilly Corporate Center, Eli Lilly and Company,
Indianapolis, IN 46285, USA
e-mail: ilag_liza_l@lilly.com

C. L. Chang
Ditmanson Medical Foundation Chiayi Christian
Hospital, 539 Jhongsiao Road, Chiayi, Taiwan

INTRODUCTION

LY2963016 insulin glargine (LY IGlar; Eli Lilly and Company, Indianapolis, IN, USA) is the first biosimilar insulin approved in the European

Union [1] and Japan in 2014 [2] and was authorized as a follow-on biologic in the USA [3]. LY2963016 insulin glargine and Lantus® insulin glargine (IGlar; recombinant DNA origin; Sanofi-Aventis, Paris, France) have identical primary amino acid sequences, the same pharmaceutical form and strength, and the pharmacokinetic/pharmacodynamic, efficacy, and safety profiles of LY IGlar are highly similar to those of IGlar [4–7].

Insulin products can elicit the formation of insulin antibodies, often without clinical consequences [8, 9]. However, rare instances exist where the presence of insulin antibodies may have clinically relevant effects on efficacy and safety [9–11]. We have previously shown that the immunogenicity profile of LY IGlar is similar to that of IGlar [7], and that both LY IGlar and IGlar have comparable insulin antibody response (IAR) profiles, with no observed effect on efficacy and safety outcomes [7]. While the median antibody levels were low (i.e., less than 5%) and similar between treatment groups, there was variation in patient-to-patient IARs [7]. Because high IARs may provide additional insight into potential immune-mediated effects on efficacy or safety, and these effects may be diluted by looking at all patients, this study focuses on patients who elicited the highest quartile of maximum IARs observed in the LY IGlar phase 3 studies to determine how LY IGlar and IGlar compared in this subgroup of patients and assess whether their IARs were related to clinical outcomes. Thus, we assessed and compared IAR profiles of LY IGlar and IGlar treatment in patients with type 1 diabetes mellitus (T1D) or type 2 diabetes mellitus (T2D), assessed the frequencies of higher IARs among patients treated with either insulin glargine product, and evaluated the potential relationship between higher IARs and clinical and safety outcomes.

METHODS

Data from the ELEMENT-1 and ELEMENT-2 studies were analyzed. Both trials were registered at Clinical Trials.gov (NCT01421147 and NCT01421459). Detailed study methods and results for the primary endpoints for both

studies have been previously described [5, 6]. Briefly, ELEMENT-1 was a 52-week (24-week treatment period plus 28-week extension period), open-label study of patients with T1D being treated with basal and bolus insulin [5]. ELEMENT-2 was a 24-week, double-blind study of patients with T2D who were insulin-naïve or previously treated with IGlar [6]. In both studies, patients were randomized to receive an LY IGlar or IGlar dose that was equivalent to their prestudy insulin dose except for patients with T2D who were insulin-naïve and started with 10 units of LY IGlar or IGlar. The LY IGlar or IGlar dose was titrated on the basis of daily blood glucose levels [5, 6]. The primary efficacy outcome in both studies was to demonstrate the non-inferiority (0.4% and then 0.3% margin) of LY IGlar to IGlar as measured by change in HbA1c from baseline to 24 weeks [5, 6]. Both of these studies were done in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki [12], and written informed consent was obtained from all patients [5, 6].

Antibody determination methods have been described in greater detail previously [5–7]. Briefly, samples used in this study for antibody determination were those collected before randomization (baseline) and at study endpoint. Insulin antibodies were quantified as percent binding using a classic radioimmunoassay format. The anti-LY IGlar antibody assay has cross-reactivity to IGlar and human insulin; hence, antibodies to LY IGlar and IGlar were measured using the same assay [5–7]. Insulin antibody testing was conducted by Millipore (St. Charles, MO, USA).

In each study, patients in the upper quartile of maximum antibody percent binding (UQMAPB) were determined as follows: among all patients with postbaseline insulin antibodies, the maximum postbaseline insulin antibody level (percent binding) per patient was identified. Patients whose maximum postbaseline percent binding belonging to the highest 25% of the maximum values observed comprised the UQMAPB. Patients in the lower 75% and patients who did not have any detectable antibodies postbaseline comprised those patients

not in the UQMAPB. Postbaseline maximum antibody percent binding (MAPB) levels and the proportions of patients who exhibited IARs in the UQMAPB with either treatment were evaluated to compare the IAR profiles of LY IGlar and IGlar. Separate analyses for each study also compared LY IGlar to IGlar for clinical outcomes [changes in glycated hemoglobin (HbA1c) (%), basal insulin dose (U/kg/day), weight (kg), incidence of adverse events, and incidence of total hypoglycemia] among patients who did or did not exhibit IARs in the UQMAPB. The potential differential treatment effects of UQMAPB status on clinical and safety outcomes were also assessed by interaction tests. Hypoglycemia was defined in accordance with American Diabetes Association [13] and European Medicine Agency [14] guidelines as having a blood glucose no greater than 3.9 mmol/L (70 mg/dL) or signs or symptoms attributable to low blood glucose levels. Analyses were also performed with hypoglycemia defined as having a blood glucose of less than 3.0 mmol/L (54 mg/dL), a cutoff that had been recommended in the past [15].

Statistical Analysis

The analysis population was comprised of all randomized patients who took at least one dose of study drug (full analysis set) and also had a baseline and at least one postbaseline insulin antibody level assessment. Fisher's exact test was used to analyze binary data.

Relationships between UQMAPB status (UQMAPB or not UQMAPB) and continuous outcomes were analyzed by an analysis of covariance model with adjustments for design factors—with baseline HbA1c serving as a covariate; and country, time of basal insulin injection (daytime vs. evening/bedtime), sulfonylurea use (ELEMENT-2 only), treatment, UQMAPB status, and treatment-by-UQMAPB interaction as fixed effects. Relationships between UQMAPB status and categorical outcomes for adverse events were analyzed. The Cochran–Mantel–Haenszel test was used for between-treatment comparisons of odds ratios within UQMAPB status subgroups. The

Breslow–Day test was used to assess the homogeneity of odds ratios for the interaction between treatment and UQMAPB status. Data were analyzed using SAS version 9.1.3 (SAS Drug Development, Cary, NC, USA).

RESULTS

IAR Profiles of LY IGlar and IGlar Treatment

Of the 535 patients with T1D (ELEMENT-1), 265 LY IGlar and 267 IGlar patients were evaluable. Of the 756 patients with T2D (ELEMENT-2), 365 LY IGlar and 365 IGlar patients were evaluable. No significant differences were observed in either study between the medians for MAPB levels for LY IGlar vs. IGlar or for the proportions of patients in the respective UQMAPB with either treatment (Table 1).

Relationship Between IAR and Clinical and Safety Outcomes

There were no significant between-treatment differences in baseline and endpoint values for HbA1c, basal insulin dose, and body weight among patients in UQMAPB or not in UQMAPB (Table 2). Baseline-to-endpoint changes in HbA1c and basal insulin dose were similar between LY IGlar and IGlar irrespective of UQMAPB status (Fig. 1a–d). While significant treatment-by-UQMAPB interactions were noted for the change from baseline to endpoint in total (basal + prandial) insulin dose ($p = 0.008$) and in prandial insulin dose ($p = 0.027$) in ELEMENT-1, there were no significant treatment-by-UQMAPB interactions for endpoint values of total insulin dose ($p = 0.105$) or prandial insulin dose ($p = 0.143$) in ELEMENT-1. More importantly there were no between-treatment differences in total insulin or in prandial insulin dose among patients in UQMAPB or not in UQMAPB (Table 2) which is consistent with the absence of between-treatment differences in basal insulin dose among patients by UQMAPB subgroups (Fig. 1c, d). Although IGlar-treated patients who demonstrated UQMAPB showed a greater weight

Table 1 Maximum antibody percent binding (MAPB) characteristics of evaluable patients

Outcome	ELEMENT-1 (T1D)		ELEMENT-2 (T2D)	
	LY IGlar	**IGlar**	**LY IGlar**	**IGlar**
Evaluable patients, N	265	267	365	365
MAPB levels, %	($n = 107$)	($n = 105$)	($n = 56$)	($n = 40$)
Minimum	0.26	0.27	0.27	0.26
25th percentile	0.46	0.50	0.39	0.44
Mean (SD)	2.11 (3.71)	1.83 (3.15)	3.94 (7.75)	3.59 (5.78)
Median	0.84[a]	0.90[a]	0.56[b]	0.78[b]
75th percentile	2.13	1.66	3.29	3.90
Maximum	30.41	20.20	37.70	24.11
Patients in the upper quartile of MAPB, n (%)	29 (10.9)[c]	24 (9.0)[c]	14 (3.8)[d]	10 (2.7)[d]
Patients in the lower 3 quartiles of MAPB, n (%)	236 (89.1)	243 (91.0)	351 (96.2)	355 (97.3)

IGlar insulin glargine, *LY IGlar* LY2963016 insulin glargine, *MAPB* maximum antibody percent binding, *SD* standard deviation, *T1D* type 1 diabetes, *T2D* type 2 diabetes

[a] Wilcoxon rank sum, $p = 0.959$

[b] Wilcoxon rank sum, $p = 0.489$

[c] Treatment comparison for the proportion of patients in the UQMAPB, $p = 0.472$

[d] Treatment comparison for the proportion of patients in the UQMAPB, $p = 0.534$

gain than LY IGlar-treated patients or IGlar-treated patients who exhibited lower MAPB, this trend was not found to be statistically significant in either study (Fig. 1e, f).

In both studies, both treatment groups exhibited similar frequencies of allergic reactions, injection site reactions, and serious adverse events irrespective of UQMAPB status (Table 3). Likewise, the overall incidence of hypoglycemia events was similar between both treatment groups irrespective of patient UQMAPB status (Fig. 2).

DISCUSSION

This study shows that patients with T1D or T2D who received LY IGlar or IGlar exhibited similar levels and frequencies of IARs. The number of patients exhibiting IARs in the UQMAPB was similar for LY IGlar and IGlar. Median antibody levels of those patients in the UQMAPB were comparable between both treatment groups and

low (i.e., less than 5%). No significant differential treatment effects were observed between LY IGlar and IGlar for clinical efficacy or safety outcomes among patients who did or did not exhibit UQMAPBs for IARs. Clinical efficacy and safety outcomes were similar among patients treated with LY IGlar or IGlar regardless of IAR levels.

LY IGlar has an identical primary amino acid sequence, similar pharmacokinetic/pharmacodynamic, efficacy, and safety profiles as IGlar [4–6] and is considered a biosimilar insulin in certain jurisdictions. In previous studies, IGlar has been shown to exhibit a low immunogenic potential compared to neutral protamine Hagedorn (NPH) insulin. In a 28-week study that compared IGlar to NPH insulin, 1–2% of patients with T1D in either group exhibited clinically relevant [at least 20 U, % bound/total (B/T)] antibodies [16]. Similarly, IGlar was significantly less immunogenic than NPH insulin in a 52-week study of patients with T2D [17].

Table 2 Baseline and endpoint values for HbA1c, insulin dose, and body weight by treatment-by-upper quartile of the maximum antibody percent binding

	UQMAPB–yes			UQMAPB–no		
	LY IGlar	IGlar	p value	LY IGlar	IGlar	p value
ELEMENT-1 (T1D)						
Evaluable patients[a]	N = 265	N = 267		N = 265	N = 267	
Patients in UQMAPB	(Yes) n = 29	(Yes) n = 24		(No) n = 236	(No) n = 243	
Baseline HbA1c (%)	7.71 (0.20)	7.84 (0.22)	0.663	7.75 (0.07)	7.78 (0.07)	0.722
Endpoint HbA1c (%)	7.58 (0.14)	7.62 (0.15)	0.834	7.49 (0.06)	7.48 (0.06)	0.844
Baseline basal insulin dose (U/kg/day)	0.36 (0.03)	0.31 (0.03)	0.277	0.32 (0.01)	0.31 (0.01)	0.305
Endpoint basal insulin dose (U/kg/day)	0.39 (0.03)	0.34 (0.03)	0.158	0.38 (0.01)	0.36 (0.01)	0.321
Baseline basal insulin lispro dose (U/kg/day)	0.37 (0.04)	0.38 (0.04)	0.833	0.40 (0.01)	0.40 (0.02)	0.790
Endpoint basal insulin lispro dose (U/kg/day)	0.45 (0.04)	0.38 (0.04)	0.181	0.36 (0.02)	0.37 (0.02)	0.530
Baseline total insulin dose (U/kg/day)	0.69 (0.05)	0.69 (0.05)	0.956	0.72 (0.02)	0.71 (0.02)	0.664
Endpoint total insulin dose (U/kg/day)	0.84 (0.05)	0.71 (0.06)	0.081	0.74 (0.02)	0.74 (0.02)	0.908
Baseline body weight (kg)	77.5 (3.0)	74.1 (3.3)	0.453	75.7 (1.05)	74.8 (1.0)	0.547
Endpoint body weight (kg)	77.6 (2.8)	72.2 (3.1)	0.179	74.2 (1.2)	73.3 (1.2)	0.506
ELEMENT-2 (T2D)						
Evaluable patients[a]	N = 365	N = 365		N = 365	N = 365	
Patients in UQMAPB	(Yes) n = 14	(Yes) n = 10		(No) n = 351	(No) n = 355	
Baseline HbA1c (%)	8.86 (0.29)	8.38 (0.34)	0.285	8.33 (0.06)	8.33 (0.06)	0.969
Endpoint HbA1c (%)	7.04 (0.24)	6.94 (0.28)	0.786	7.07 (0.07)	7.02 (0.07)	0.377
Baseline basal insulin dose (U/kg/day)	0.12 (0.06)	0.02 (0.08)	0.298	0.16 (0.01)	0.14 (0.01)	0.184
Endpoint basal insulin dose (U/kg/day)	0.52 (0.10)	0.51 (0.11)	0.921	0.50 (0.03)	0.48 (0.03)	0.437
Baseline body weight (kg)	79.9 (5.2)	84.9 (6.2)	0.540	90.8 (1.1)	90.3 (1.1)	0.744
Endpoint body weight (kg)	80.2 (5.1)	87.6 (5.9)	0.324	85.7 (1.4)	85.0 (1.4)	0.611

Data are least squares mean ± standard error

HbA1c glycated hemoglobin, *IGlar* insulin glargine, *LY IGlar* LY2963016 insulin glargine, *UQMAPB* upper quartile of maximum antibody percent binding, *T1D* type 1 diabetes, *T2D* type 2 diabetes

[a] Defined as patients having "detected" or "nondetected" insulin antibody levels at baseline and postbaseline visit (patients at risk of treatment-emergent antibody response)
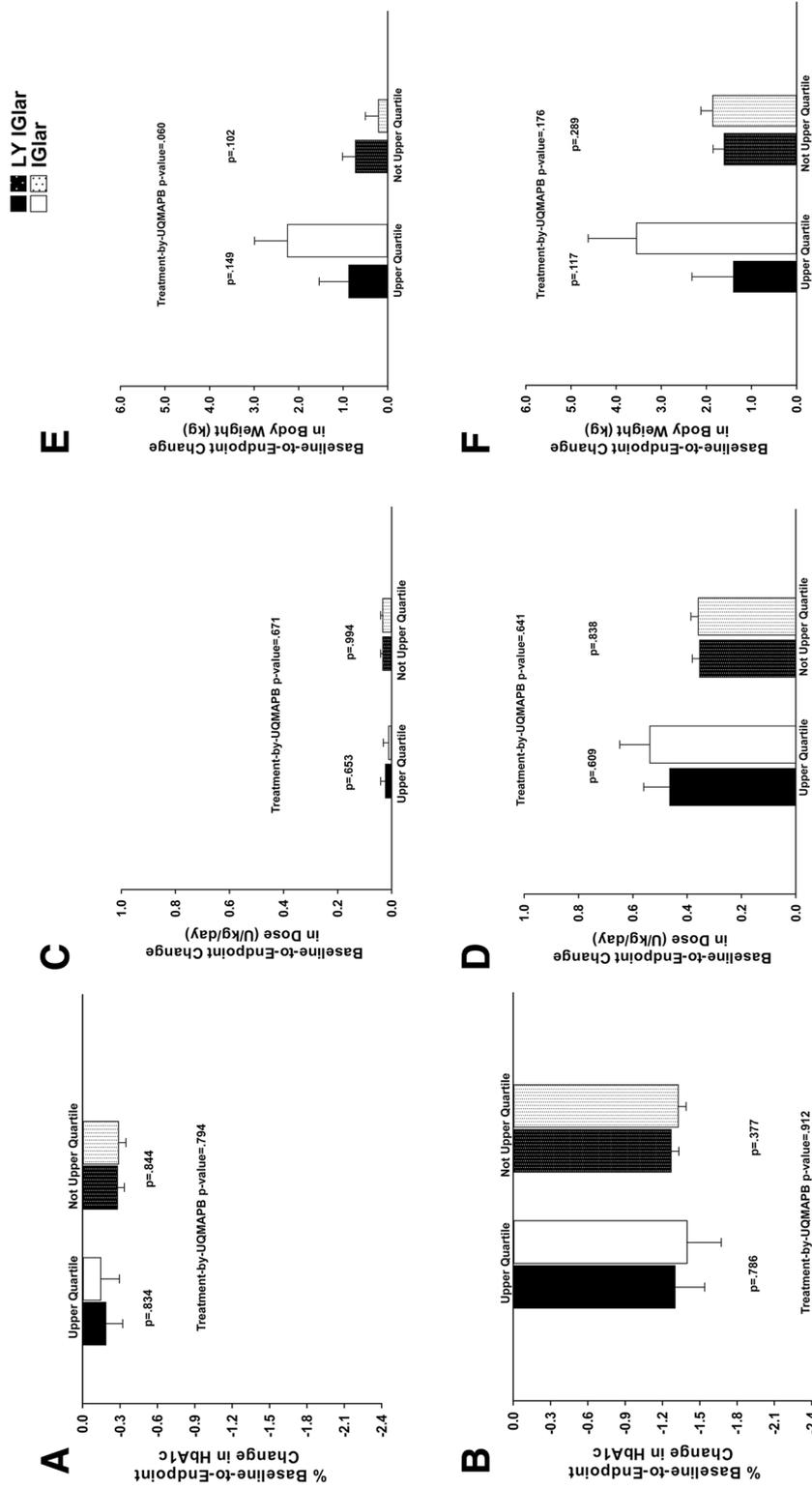
Fig. 1 Baseline-to-endpoint changes in glycated hemoglobin (HbA1c) in patients with a type 1 diabetes (T1D) or b type 2 diabetes (T2D), basal insulin dose in patients with c T1D or d T2D, weight in patients with e T1D or f T2D. Data are least squares mean ± standard error. *HbA1c* glycated hemoglobin, *IGlar* insulin glargine, *LY IGlar* LY2963016 insulin glargine, *UQMAPB* upper quartile of maximum antibody percent binding

Table 3 Treatment reactions and serious adverse events

	UQMAPB–yes			UQMAPB–no			INT
	LY IGlar	IGlar	*p* value[b]	LY IGlar	IGlar	*p* value[c]	*p* value[d]
ELEMENT-1 (T1D)							
Evaluable patients[a]	*N* = 265	*N* = 267		*N* = 265	*N* = 267		
Patients in UQMAPB	(Yes) *n* = 29	(Yes) *n* = 24		(No) *n* = 236	(No) *n* = 243		
Allergic reactions, *n* (%)	2 (6.9)	1 (4.2)	0.672	18 (7.6)	10 (4.1)	0.102	0.927
Injection site reactions, *n* (%)	0 (0.0)	0 (0.0)	NA	7 (3.0)	3 (1.2)	0.186	NA
Serious adverse events n (%)	3 (10.3)	1 (4.2)	0.401	17 (7.2)	23 (9.5)	0.372	0.282
ELEMENT-2 (T2D)							
Evaluable patients[a]	*N* = 365	*N* = 365		*N* = 365	*N* = 365		
Patients in UQMAPB	(Yes) *n* = 14	(Yes) *n* = 10		(No) *n* = 351	(No) *n* = 355		
Allergic reactions, *n* (%)	1 (7.1)	1 (10.0)	0.807	19 (5.4)	25 (7.0)	0.371	0.954
Injection site reactions, *n* (%)	2 (14.3)	1 (10.0)	0.759	11 (3.1)	10 (2.8)	0.804	0.830
Serious adverse events n (%)	0 (0.0)	0 (0.0)		14 (4.0)	17 (4.8)	0.604	NA

p values are not shown if the total number of patients with events for the combined subgroups and treatments is <10. If the total number of events within a subgroup is 0, the interaction test is not performed. Patients may be counted in more than one category of reaction or event

IGlar insulin glargine, *INT* interaction, *LY IGlar* LY2963016 insulin glargine, *NA* not assessed, *T1D* type 1 diabetes, *T2D* type 2 diabetes, *UQMAPB* upper quartile of maximum antibody percent binding

[a] Defined as patients having "detected" or "nondetected" insulin antibody levels at baseline and postbaseline visit (patients at risk of treatment-emergent antibody response)

[b] *p* values are from the Mantel–Haenszel test for comparison of LY IGlar (yes) vs. IGlar (yes)

[c] *p* values are from the Mantel–Haenszel test for comparison of LY IGlar (no) vs. IGlar (no)

[d] Interaction *p* value assessed using the Breslow–Day test

Our finding of no relationship between immune response and efficacy or safety with LY IGlar or IGlar is also consistent with previous studies of IGlar. Although some of these studies comparing IGlar and NPH insulin did not specifically analyze any relationship between anti-IGlar antibodies and clinical outcomes, IGlar exhibited similar or greater glycemic control than NPH [15–17]. In addition, treatment-related adverse events were comparable between IGlar and NPH insulin [17, 18]. A recent retrospective analysis of seven published registration studies that evaluated the immunogenicity of IGlar and NPH in relation to clinical outcomes found that the proportion of patients with clinically relevant changes in anti-IGlar antibody levels (at least 20 U, %B/T) was low. In addition, antibody levels were not associated with any clinically relevant effects on HbA1c, insulin dose, and hypersensitivity [19].
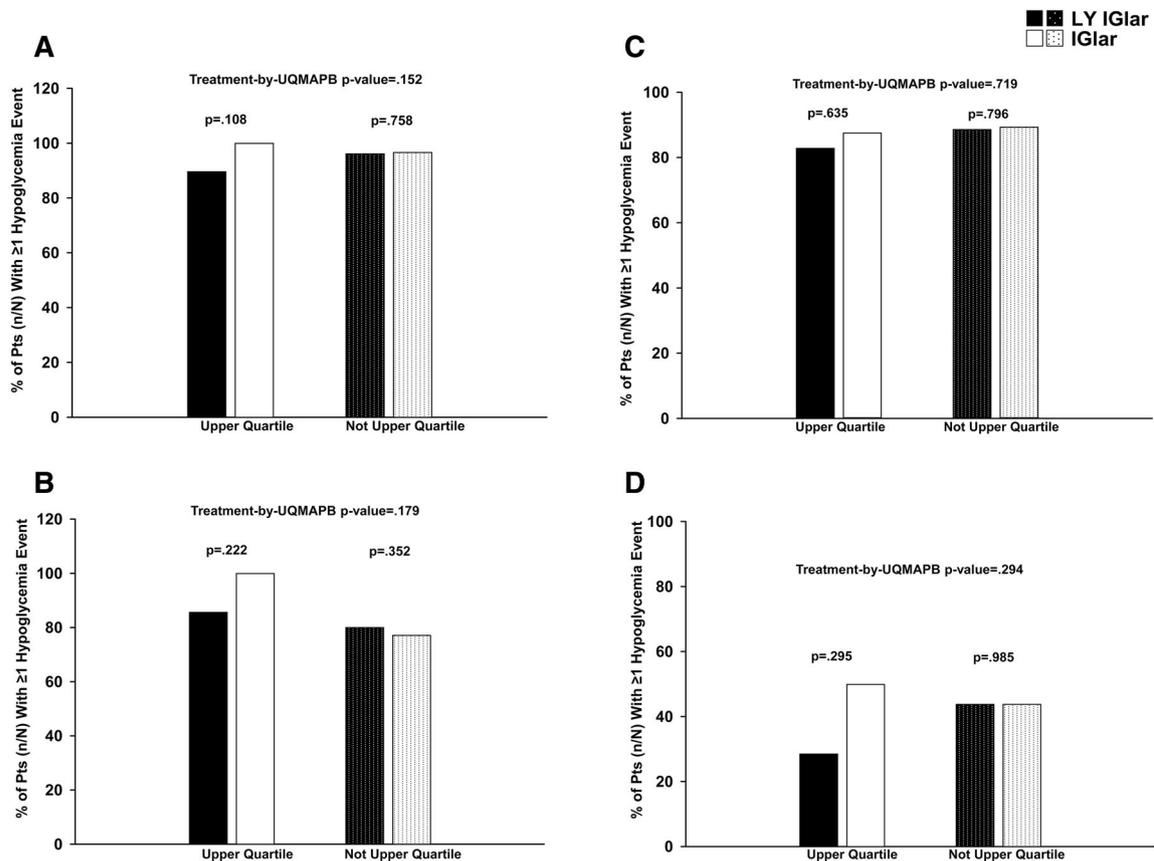
Fig. 2 Overall incidence of hypoglycemia (blood glucose no greater than 3.9 mmol/L) in patients with **a** type 1 diabetes (T1D) or **b** type 2 diabetes (T2D), hypoglycemia (blood glucose less than 3.0 mmol/L) in patients with **c** T1D or **d** T2D. *IGlar* insulin glargine, *LY IGlar* LY2963016 insulin glargine, *Pts* patients, *UQMAPB* upper quartile of maximum antibody percent binding

One study limitation is the sample size; because the registration studies were originally designed to demonstrate noninferiority in HbA1c change [5, 6], some may argue that the sample is relatively small to detect differences in rare events, such as immune reactions. Notably, the parent studies included 535 patients with T1D and 756 patients with T2D, and the findings in this study are consistent with what was shown in analyses including the total study populations [7]. Furthermore, no relationship between UQMAPB status and clinical outcomes was observed for patients with the highest IARs. A second limitation is the study length which limits our findings to anti-insulin antibody formation for up to 24 or 52 weeks. However, it should be noted that a previous 52-week study

has shown that the level of antibodies against insulin glargine plateaus after approximately 20 weeks of treatment [17], a time frame covered by both studies in this analysis.

CONCLUSIONS

Patients treated with LY IGlar and IGlar had similar maximum antibody responses, with similar proportions of patients having high IARs. High antibody levels were not associated with effects on clinical outcomes. These findings reduce concerns of immunogenicity responses that may affect efficacy and safety with insulin glargine treatment and provide additional support for the similarity between LY IGlar and IGlar.

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Compliance with Ethics Guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

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