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ORIGINAL ARTICLE

Effectiveness of insulin glargine U-300 versus insulin glargine U-100 on nocturnal hypoglycemia and glycemic control in type 1 and type 2 diabetes: a systematic review and meta-analysis

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Abstract

Aims To assess the effectiveness of insulin glargine 300 ui/ml (Gla-300) compared with insulin glargine 100 ui/ml (Gla-100) on reducing nocturnal hypoglycemia and improving glycemic control in type 1 and type 2 diabetes patients.

Methods We systematically searched in Medline, Embase, Web of Science, and Cochrane Central Register of Controlled Trials until July 4th, 2018. This study was registered with PROSPERO (CRD42017080134). We included randomized clinical trials comparing Gla-300 versus Gla-100 reporting the rate ratio or number of events of nocturnal hypoglycemia and HbA_{1c} levels percentage or $mmol/mol^{-1}$. The main outcome was the incidence rate ratio (RR) of nocturnal hypoglycemia events. The heterogeneity of results across studies was assessed using the I^2 statistic. Fixed- and random-effect models were used to estimate pooled RRs.

Results Nine studies were included in the meta-analysis, including 3977 adult patients. Compared with Gla-100, the use of Gla-300 reduced confirmed nocturnal hypoglycemia [RR = 0.81 (0.69, 0.95)] and clinically significant nocturnal hypoglycemia [RR = 0.75 (0.63, 0.91)]. Reductions in clinically significant nocturnal hypoglycemia events [RR = 0.64 (0.42, 0.97)] in type 1 diabetes patients were found. A small decrease in HbA_{1c} levels in favor of Gla-300 in the pooled sample was identified [ES = − 0.08 (95% CI − 0.14, − 0.01)].

Conclusions The best current evidence indicates that Gla-300 reduces the incidence of nocturnal hypoglycemia with slight improvements in glycemic control compared with Gla-100 in both type 1 and type 2 diabetes adult patients.

Keywords Type 2 diabetes · Type 1 diabetes · Insulin glargine · Hypoglycemia · HbA1c; meta-analysis

Introduction

Optimal glycemic control in diabetes mellitus (DM) patients, considering $HbA_{1c} < 7\%$ (< 53 $mmol/mol^{-1}$) as the most common reference level is, despite all technological advances, a significant barrier to overcome for these patients [1].

Basal insulins have significantly improved the treatment of both type 1 and type 2 diabetes patients, because they have responded to the need of achieving optimal glycemic control in patients [2]. However, clinicians are also concerned about episodes of hypoglycemia, especially nocturnal hypoglycemia, since these affect health-related quality of life, fear, suboptimal glycemic control [3, 4], may produce impaired awareness of hypoglycemia and can have negative effects on cognitive function, leading to a significant morbidity and mortality in insulin-treated DM patients [5].

Managed by Massimo Porta.

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Insulin glargine 300 units/mL (Gla-300) is a new formulation which provides the same insulin dose as extended insulin glargine 100 units/mL (Gla-100), but the volume that is injected in the subcutaneous tissue is reduced by a third [6]. This results in a more gradual and prolonged release of insulin, which reflects in a more steady-state pharmacokinetics (PK) and pharmacodynamics (PD), and a longer duration of action compared with Gla-100 [7, 8].

Several randomized clinical trials (RCTs) have assessed the clinical efficacy of Gla-300 versus Gla-100 in different patient populations and different reviews have addressed the clinical impact of this new insulin glargine formulation [9, 10]. Nevertheless, to our knowledge, no systematic review or meta-analysis of clinical trials has been conducted in this field.

Therefore, the objective of this study was to determine whether the use of Gla-300 compared with Gla-100 in type 1 and type 2 diabetes patients resulted in a reduction of nocturnal hypoglycemia events and in improved glycemic control (measured by HbA_{1c} levels).

Materials and methods

This study is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [11] (Fig. 1), and follows the recommendations of the Cochrane Collaboration Handbook [12]. This systematic review and meta-analysis was registered through PROSPERO (registration number: CRD42017080134).

Data sources and searches

We systematically searched MEDLINE (via PubMed), EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Web of Science databases from their inception until July 4th, 2018. The search strategy included the following terms: ("U-300" OR "Toujeo" OR "insulin glargine 300 units/ml" OR "Glargine 300 units" OR "Gla-300") AND ("HbA_{1c}" OR "glycosylated hemoglobin" OR "glycated hemoglobin" OR "hemoglobin A1c") AND ("hypoglycemia" OR "hypoglycaemia"). The

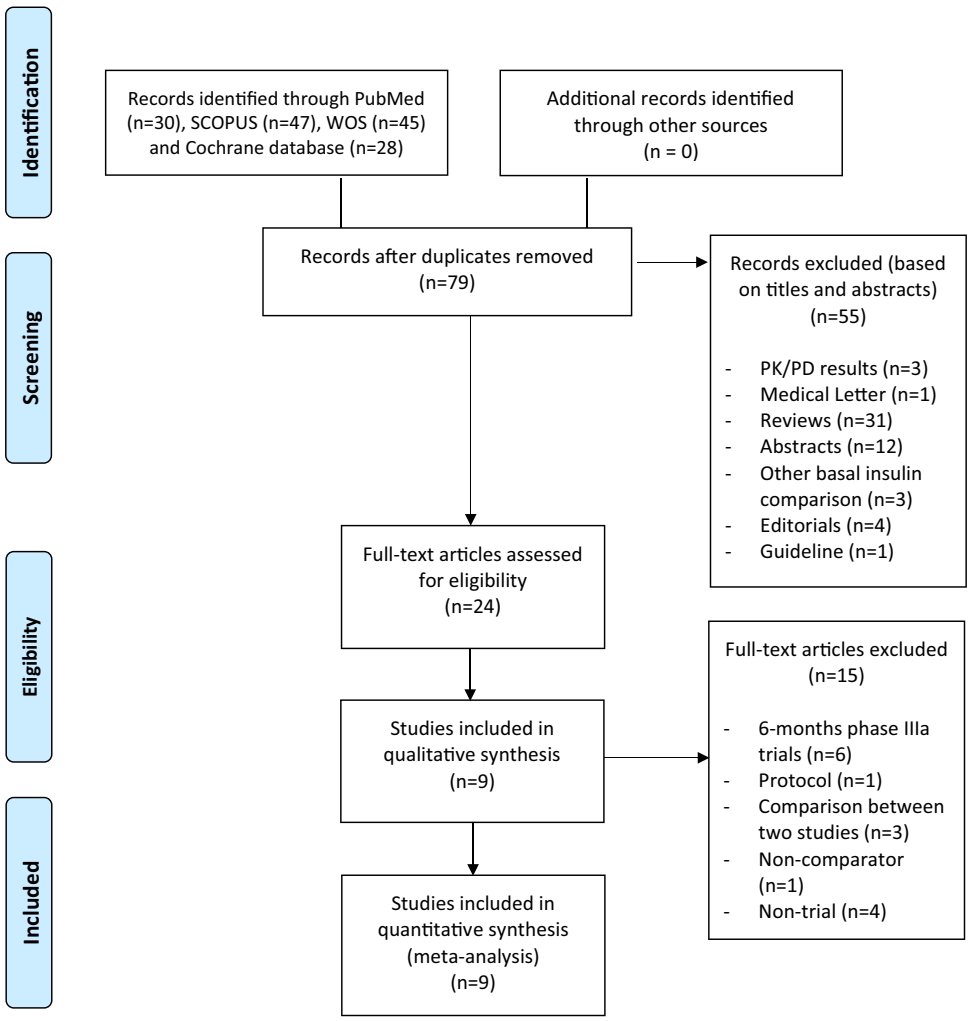

Fig. 1 Literature search PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) consort diagram

literature search was complemented by reviewing citations of the articles considered eligible for the systematic review and authors were contacted to obtain missing information when necessary.

Study selection

The criteria for including studies were as follows: (i) RCTs in any stage; (ii) studies that include type 1 and type 2 diabetes patients aged 18 years or older without any restriction of race, gender or year of diabetes status diagnosis; (iii) report of rate ratio or number of events of nocturnal hypoglycemia (from 00:00 to 05:59 h); (iv) studies reporting HbA_{1c} levels percentage or mmol/mol^{-1} at the baseline and the end-of-treatment period; (v) studies comparing only the following long-action insulins: Gla-300 and Gla-100; (vi) studies including hypoglycemia definitions by the American Diabetes Association (ADA) [13]; (vii) studies published in Portuguese, Spanish, German, or English.

The literature search was independently conducted by two reviewers (AD-F and IC-R), and disagreements were solved by consensus or involving a third researcher (VM-V).

Data extraction and quality assessment

It was independently performed by two reviewers (AD-F and IC-R), and inconsistencies were solved by consensus or involving a third researcher (VM-V).

The methodological quality of RCTs was assessed using the Cochrane Collaboration's tool for assessing risk of bias [14]. This tool evaluates the risk of bias according to six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Each domain could be considered as strong, moderate, or weak, and studies could be classified as low risk of bias (with no weak ratings), moderate risk of bias (with one weak rating) or high risk of bias (with two or more weak ratings). Furthermore, design, analysis strategy, and outcome measures were checked from clinicaltrials.gov registration to avoid the bias of adherence to study protocol.

The following data were extracted from the original reports: (i) author information, (ii) name and design of study, (iii) duration, (iv) sample characteristics (sample size and age distribution), (v) type of DM, (vi) complementary therapy, and (vii) outcomes related with the meta-analyses and baseline % or mmol/mol^{-1} HbA_{1c} levels in each group.

Statistical analysis

Both the inverse-variance fixed-effects method [15] and the DerSimonian and Laird method were used to compute pooled estimates of rate ratio (RR) and their respective confidence intervals (95% CI) for the risk of nocturnal hypoglycemia. RR was extracted or calculated from the events per participant-year. For each RR estimate, the natural log HR (lnHR) was calculated by converting it to the natural log scale.

In addition, the inverse-variance fixed-effects method [15] and the DerSimonian and Laird method were used to compute the pooled estimates of effect size (ES) and respective 95% CI. A standardized mean difference score was calculated for HbA_{1c} levels using Cohen's d index as the ES statistic [16] in which negative ES values indicate a decrease in HbA_{1c} levels in favor of the intervention versus the control group. Cohen's d values around 0.2 were considered to be a weak effect, values around 0.5 were a moderate effect, values around 0.8 were a strong effect, and values larger than 1.0 were a very strong effect.

The heterogeneity of results across studies was assessed using the I^2 statistic. I^2 values are considered as: might not be important (0–40%), may represent moderate heterogeneity (30–60%), substantial heterogeneity (50–90%), or considerable heterogeneity (75–100%); the corresponding p values were also taken into account [12].

Subgroup analyses were conducted according to DM type (type 1 versus type 2 diabetes) and by type of complementary therapy (insulin or not). Besides, sensitivity analyses were conducted removing studies one by one to assess the robustness of the summary estimates. A univariate random-effect meta-regression was used to separately evaluate whether results differed according to the mean age of participants, the mean time of DM duration and with the events of hypoglycemia at any time of day (24 h). Publication bias was assessed by the Harbord modified test [17], and was considered statistically significant at p value < 0.10. Statistical analyses were performed using the Stata/SE software V.14.

Results

Search results

The literature search retrieved 150 studies and, after merging duplicates, screening and verifying all inclusion criteria, nine studies were included in the meta-analysis. Reasons for exclusion of articles are detailed in Fig. 1; the vast majority were literature reviews. In studies concerning any EDITION trial, we selected those that included the longest follow-up (12 months).

Study characteristics

A total of 3977 adult patients (age ranged from 44.2 to 71.1) were evaluated in the trials for the main outcomes (nocturnal hypoglycemia and HbA_{1c} levels), 1998 in the Gla-300

group and 1979 in the Gla-100 group (Table 1). Four studies included type 1 diabetes, where patients used a meal-time insulin analogue as a complementary therapy [18–21]; five studies included type 2 diabetes patients; in three of the latter studies, the patients included were in a complementary regimen with anti-hyperglycemic agents (AHAs) or oral anti-hyperglycemic drugs (OADs) [22–25]; in the remaining study, patients used meal-time insulin analogues [26].

All trials were sponsored by Sanofi and were published between 2015 and 2018. Seven trials had a parallel-group design (Gla-300 versus Gla-100) with two-arms [20, 23–26] or four-arms (switching from morning to evening injection) [19, 27], and two performed a two-period crossover study [19, 21]. All were open-label design due to injector pen characteristics and trial duration ranged from 8.4 weeks to 12 months. The titration protocol for either Gla-300 or Gla-100 was described in each included study.

Nocturnal hypoglycemia (00:00–05:59 h) was categorized according to the ADA's definitions [13]. For the present analysis, the documented symptomatic (symptomatic events with self-monitoring plasma glucose (SMPG) ≤ 70 mg/dl (≤ 3·9 mmol/L)), asymptomatic (events confirmed by SMPG ≤ 70 mg/dl (≤ 3·9 mmol/L) but without symptoms), and severe (an event requiring the assistance of another person to actively administer a carbohydrate, glucagon or other resuscitative actions) hypoglycemia categories were combined in a category labelled "confirmed nocturnal hypoglycemia", and an additional category with a more stringent plasma glucose threshold of < 54 mg/dl (< 3.0 mmol/L) was analyzed separately and labelled "clinically significant nocturnal hypoglycemia".

Risk of bias

According to the Cochrane Collaboration's tool for assessing risk of bias, 37.5% studies were classified with unclear risk of bias in both random sequence generation and allocation concealment. All studies included in the meta-analysis were considered as having an unclear risk of bias regarding the performance of bias and detection bias (Table Suppl. 1).

Outcomes

The use of Gla-300 was significantly associated with a lower pooled RR for confirmed nocturnal hypoglycemia (RR = 0.81; 95% CI 0.69, 0.95), showing moderate heterogeneity ($I^2 = 39.3\%$, $p = 0.106$) (Fig. 2).

When the risk of clinically significant nocturnal hypoglycemia was assessed, the use of Gla-300 was significantly associated with a lower pooled RR (RR = 0.75; 95% CI 0.63, 0.91). There was no important heterogeneity in the RR estimates ($I^2 = 12.9\%$, $p = 0.327$). In the analysis of subgroups by type of diabetes for confirmed nocturnal hypoglycemia, the use of Gla-300 was associated with a lower pooled RR with this strictest threshold (RR = 0.64; 95% CI 0.42, 0.97) in type 1 diabetes patients (Fig. 3).

Furthermore, in the analysis of glycemic control (Fig. 4), there was a decrease in HbA_{1c} levels in favor of Gla-300 ES = − 0.08 (95% CI − 0.14, − 0.01). No heterogeneity was shown between studies ($I^2 = 0.0\%$, $p = 0.935$). In the subgroup analysis, only the pooled ES showed a decrease in HbA_{1c} levels in favor of Gla-300 for type 2 diabetes patients (ES = − 0.08; 95% CI − 0.15, − 0.01).

When performing the analyses using fixed factors, all results remain similar, except for the data of confirmed nocturnal hypoglycemia (Fig. 2), where the use of Gla-300 was associated with a lower protective effect (RR = 0.85; 95% CI 0.74, 0.98) in type 2 diabetes patients.

Another subgroup analysis by type of complementary therapy (insulin or non-insulin) was performed. The use of complementary insulin therapy or not regarding confirmed nocturnal hypoglycemia showed similar pooled estimates, though 95%IC included the null value (Figure Suppl. 1). The DerSimonian and Laird method was only significant for the group of non-insulin therapy in the clinically significant hypoglycemia analysis (RR = 0.78; 95% CI 0.63, 0.96) (Figure Suppl. 2) and for the insulin group with levels of HbA_{1c} (ES = − 0.10; 95% CI − 0.19, − 0.00) (Figure Suppl. 3).

The sensitivity analyses showed that the removal of each study did not reflect any change in the pooled RR for both confirmed and clinically significant nocturnal hypoglycemia. The pooled HbA_{1c} ES estimate was modified only when removing the Riddle MC and colleagues [34] study (Table Suppl. 2).

The random-effects meta-regression model showed that age and diabetes duration were not related to the heterogeneity across studies either for confirmed nocturnal hypoglycemia ($p = 0.360$ and $p = 0.440$, respectively), clinically significant nocturnal hypoglycemia ($p = 0.346$ for age and $p = 0.235$ for diabetes duration), or HbA_{1c} change ($p = 0$ 0.766 and $p = 0.880$, respectively) (data not shown). Moreover, the RR of events of hypoglycemia at any time of day was significant for confirmed nocturnal hypoglycemia ($p = 0.064$) and clinically significant nocturnal hypoglycemia ($p = 0.022$) (Figure Suppl. 4).

Finally, there was no evidence of publication bias for confirmed nocturnal hypoglycemia ($p = 0.219$), for clinically significant nocturnal hypoglycemia ($p = 0.246$), or for HbA1c change ($p = 0.643$) (Figure Suppl. 5).

Discussion

To the best of our knowledge, this is the first meta-analysis, since a patient-level metanalysis with type 2 diabetes patients was published by Ritzel et al. [28], that synthesizes

Table 1 Characteristics of the studies included

Source (study)	Study design/duration	n Gla-300/Gla-100	Type of diabetes, age (SD) Gla-300/Gla-100	Complementary therapy	Outcomes	Baseline HbA_{1c} % (mmol/mol) Gla-300/Gla-100
Ritzel et al. [25]	R, O, 4-arm, P/24 weeks	508/506	Type 2 diabetes, 71.1 (4.9)/70.8 (4.8)	OADs	Change in HbA_{1c} to month 12 Rate of confirmed and clinically significant nocturnal hypoglycemia	8.20/8.22 (66/66)
Home et al. (EDITION 4) [27]	R, O, 4-arm, P/12 months	219/225	Type 1 diabetes, 46.4 (13.9)/48.2 (13.4)	Meal-time insulin analogue	Change in HbA_{1c} to month 12 Rate of confirmed and clinically significant nocturnal hypoglycemia	8.13/8.12 (65/65)
Bolli et al. (EDITION 3) [22]	R, O, 2-arm, P/ 12 months	337/314	Type 2 diabetes (insulin-naïve), 58.2 (9.9)/57.2 (10.3)	Non-insulin AHAs	Change in HbA_{1c} to month 12 Rate of confirmed and clinically significant nocturnal hypoglycemia	8.49/8.58 (69/70)
Terauchi et al. (EDITION JP 2) [23]	R, O 2-arm, P/12 months	107/115	Type 2 diabetes, 61.1 (10.8)/60.5 (12.0)	OADs	Change in HbA_{1c} to month 12 Rate of confirmed and clinically significant nocturnal hypoglycemia	7.99/8.06 (64/65)
Bergenstal et al. [19]	Exploratory, R, O, P, two-period crossover/16 weeks	29/26	Type 1 diabetes, 44.9 (15.1)/43.5 (13.7)	Meal-time insulin analogue	Mean change in HbA_{1c} Rate of confirmed and clinically significant nocturnal hypoglycemia	7.51/7.41 (58/57)
Matsuhisa et al. (EDITION JP 1) [20]	R, O, 2-arm, P/12 months	114/114	Type 1 diabetes, 44.1 (13.9)/46.3 (15.3)	Meal-time insulin analogue	Change in HbA_{1c} to month 12 Rate of confirmed and clinically significant nocturnal hypoglycemia	8.1/8.1 (65/65)
Yki-Järvinen et al. (EDITION 2) [24]	R, O, 2-arm, P/12 months	315/314	Type 2 diabetes, 57.9 (9.1)/58.5 (9.2)	OADs	Change in HbA_{1c} to month 12 Rate of confirmed and clinically significant nocturnal hypoglycemia	8.26/8.22 (67/66)
Jinnouchi et al. [21]	R, O, 2-sequence, 2-arm, 2-period crossover /8.4 weeks	10/10	Type 1 diabetes, 52.1 (17.3)/52.1 (15.3)	Meal-time insulin analogue	Change in HbA_{1c} at day 25 Events of confirmed and clinically significant nocturnal hypoglycemia	8.49/7.93 (69/63)

Table 1 (continued)

Source (study)	Study design/duration	n Gla-300/Gla-100	Type of diabetes, age (SD) Gla-300/Gla-100	Complementary therapy	Outcomes	Baseline HbA_{1c} % (mmol/mol) Gla-300/Gla-100
Riddle et al. (EDITION 1) [26]	R, O, 2-arm, P/12 months	359/355	Type 2 diabetes, 60.1 (8.5)/59.8 (8.7)	Meal-time insulin analogue	Change in HbA_{1c} to month 12 Rate of confirmed and clinically significant nocturnal hypoglycemia	8.15/8.16 (66/66)

R Randomized, *O* Open-label, *P* Parallel, *HbA_{1c}* Glycated hemoglobin, *AHAs* Anti-hyperglycemic agents, *OADs* oral anti-hyperglycaemic drugs

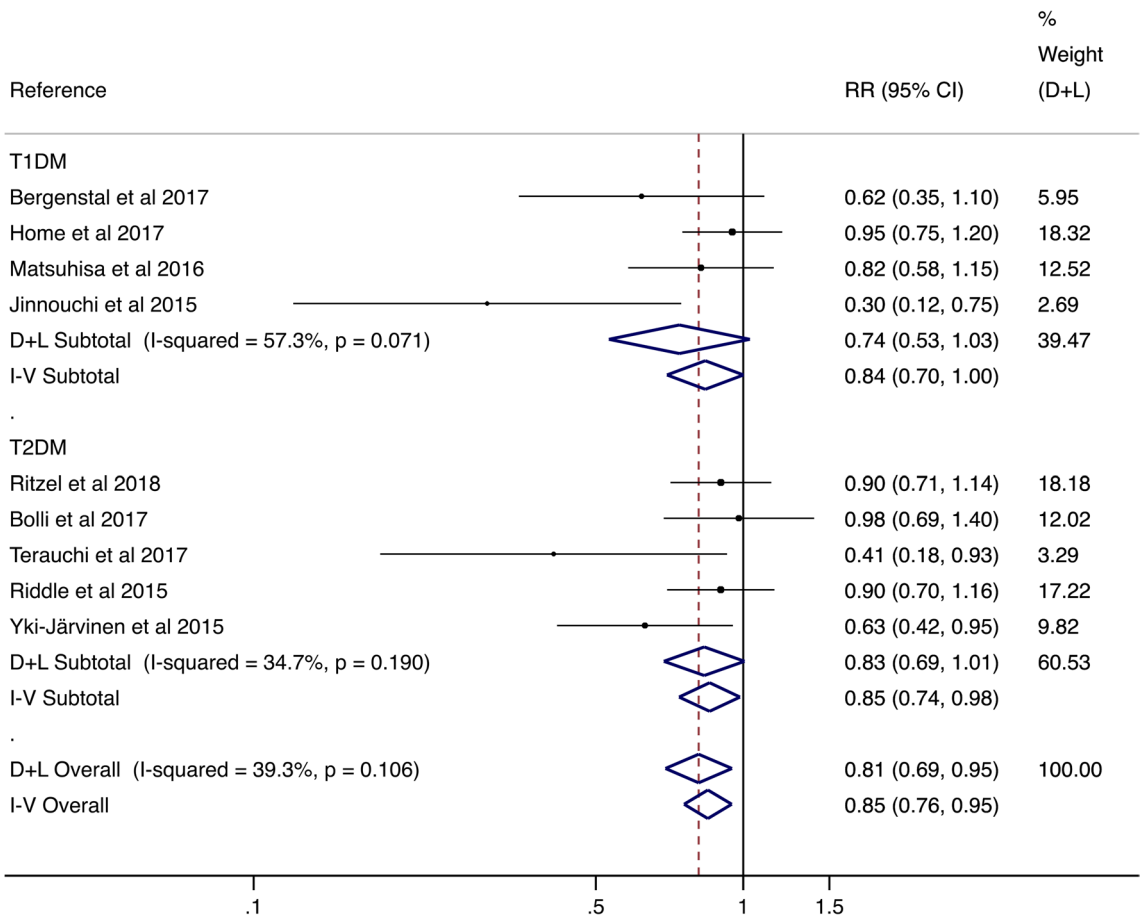

Fig. 2 Forest plot or the estimated rate ratio of confirmed nocturnal hypoglycemia ≤ 70 mg/dl (≤ 3.9 mmol/L), by type of diabetes and overall. *RR* rate ratio, *T1DM* type 1 diabetes, *T2DM* type 2 diabetes, *D + L* DerSirmonian and Laird method, *I–V* inverse-variance fixed effects method

the available evidence of the benefits of Gla-300, a new concentrated formulation of insulin glargine, in comparison with the standard concentration (Gla-100). Overall, our data show some reductions in the incidence of nocturnal hypoglycemia events and marginally clinical significant improvements in glycemic control in patients treated with Gla-300. Specifically, in patients treated with Gla-300, the incidence of confirmed nocturnal hypoglycemia was reduced by 19% and the incidence of clinically significant nocturnal hypoglycemia by 25% as compared with patients treated with Gla-100. For the second outcome, a slight reduction of 0.08% in HbA_{1c} levels was estimated.

Differences in PK/PD characteristics are among the possible explanations for the reduction of nocturnal hypoglycemia of Gla-300 compared with Gla-100 [29]. The subcutaneous depot of Gla-300 is more compact, increasing the residence

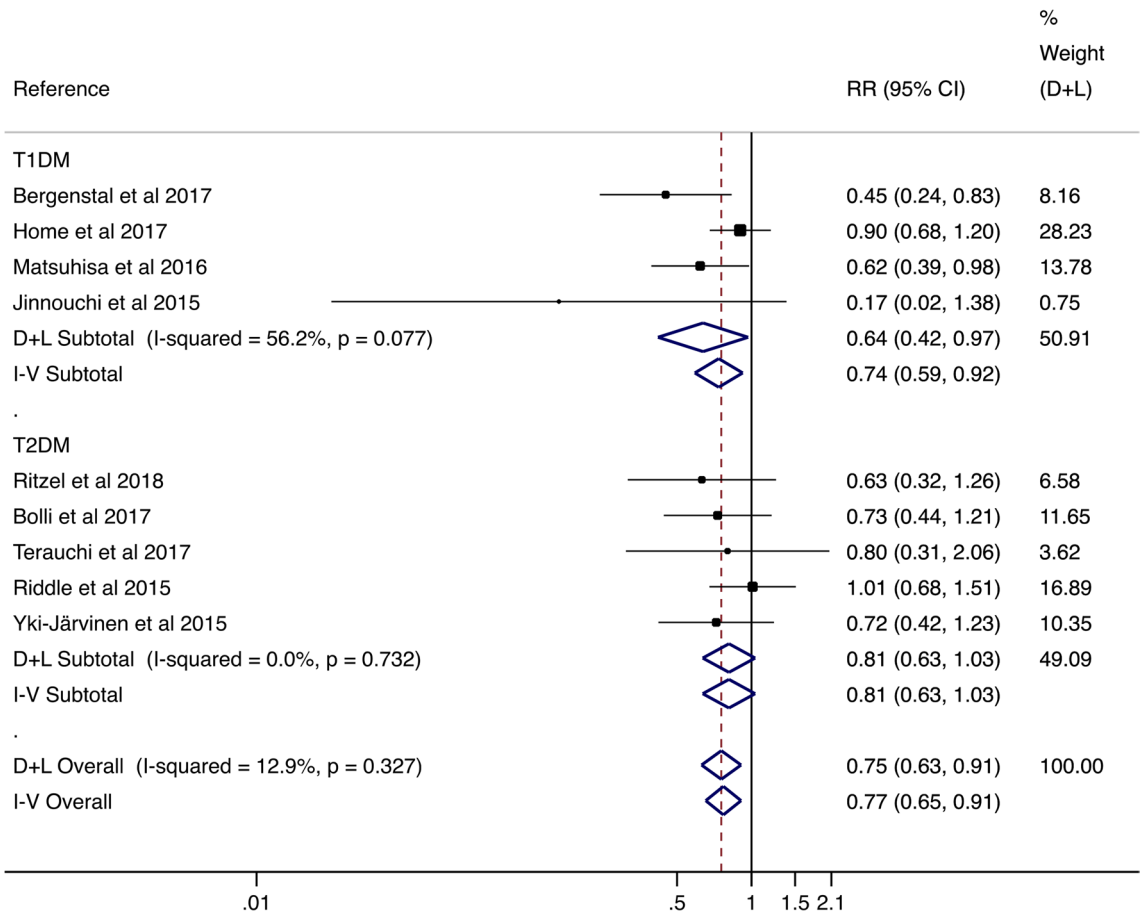

Fig. 3 Forest plot or the estimated rate ratio of clinically significant nocturnal hypoglycemia < 54 mg/dl (< 3.0 mmol/L), by type of diabetes and overall. *RR* rate ratio, *T1DM* type 1 diabetes, *T2DM* type 2 diabetes, *D + L* DerSirmonian and Laird method, *I–V* inverse-variance fixed-effects method

time of Gla-300 in subcutaneous tissue, which could be translated into less variability and a predictable 24-h duration of insulin [7].

Iatrogenic episodes of hypoglycemia in type 1 diabetes and advanced type 2 diabetes patients lead to hypoglycemia unawareness and deficient hypoglycemia counterregulation mechanisms. These main components of hypoglycemia-associated autonomic failure [30] can be behind the differences found in this meta-analysis when performing subgroup analyses with type 1 and type 2 diabetes patients. It is stated that, in type 1 diabetes patients, after a few years of the course of the disease, glucagon and epinephrine counterregulation mechanisms are absent, which substantially increase the risk of clinically significant or severe hypoglycemia [3, 31]. Therefore, the PK properties of Gla-300, independent of the minimal effect of meal-time insulin at night, could explain the observed reduction of clinically significant nocturnal hypoglycemia.

Conversely, the lower incidence of confirmed hypoglycemia in type 2 diabetes patients could be related to the fact that in those patients, the epinephrine-related response to hypoglycemia generally remains undamaged, and this counter regulatory mechanism appears at higher blood glucose levels [32]. Furthermore, the different complementary therapies among type 2 diabetes patients highlight the importance of reducing confirmed nocturnal hypoglycemia when initiating insulin-treatment with Gla-300, probably driven, as in type 1 diabetes, by the PK/PD characteristics in most insulin-treated type 2 diabetes patients.

The potential of Gla-300 compared with other basal insulins in type 2 diabetes patients has been observed in a network meta-analysis [33], where lower rate of nocturnal hypoglycemia and similar glycemic control was observed. Furthermore, two recent real-world observational studies reported significant decreases in the number of hypoglycemic events and HbA_{1c} levels in type 2 diabetes patients switching from Gla-100 to Gla-300 and in insulin-naïve patients [34] and between Gla-300 and other basal insulins [35], which supports the results of the present meta-analysis.

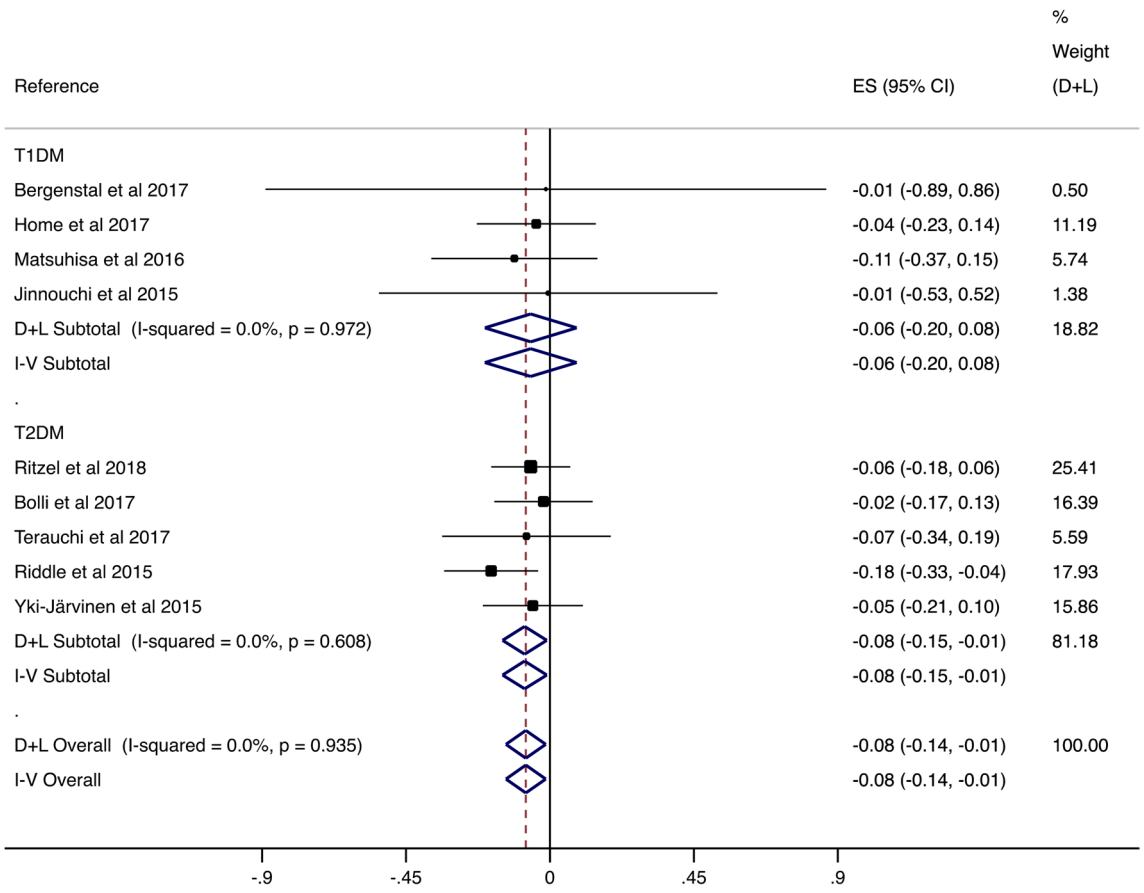

Fig. 4 Forest plot of the estimated effect size for change in HbA_{1c} mean, by type of diabetes and overall. *ES* effect size, *T1DM* type 1 diabetes, *T2DM* type 2 diabetes, *D + L* DerSirmonian and Laird method, *I–V* inverse-variance fixed-effects method

All ESs of the studies included in this meta-analysis favored Gla-300 in terms of glycemic control (ES for HbA1c levels ranged from −0.18 to −0.01) as compared with Gla-100 treatment regimens, though, from the clinical point of view, this difference seems negligible. Further real-world studies in type 1 and type 2 diabetes patients, with larger sample sizes, longer follow-up, the evaluation of complementary therapies, and independently financed are needed to assess the efficacy of Gla-300 in the clinical setting.

The strengths of this meta-analysis include the comprehensive systematic search of all considered RCTs published until July 2018, with the same definitions of hypoglycemia and different clinical factors (type of diabetes and complementary therapy). Furthermore, the pre-specified subgroup analyses allowed us to examine differences between type 1 and type 2 diabetes patients in the effect of Gla-300 versus Gla-100. Finally, the methodological rigor of the included trials may prevent from overestimating effectiveness of Gla-300.

Some limitations that should be acknowledged for this systematic review and meta-analysis are: (i) the relative short duration of the RCTs (especially three of them); (ii) differences in the injector devices used in the studies; (iii) some diabetes related-outcomes such as weight gain, increased insulin dose, or adverse event outcomes related to Gla-300 have not been included in the analyses; (iv) there was a certain degree of between-study heterogeneity in type 1 diabetes studies regarding confirmed and clinically significant nocturnal hypoglycemia. Possible reasons for the substantial heterogeneity may include the difference in trial duration (six studies were 12 months long, one was 24 weeks long, other 16 weeks, and the last was 8.4 weeks long) and the smaller sample size, which could have altered the pooled results; although those studies with a shorter duration were the ones with the lowest weight in the analysis, especially the Jinnouchi and colleagues study [21].

Conclusions

In conclusion, this systematic review and meta-analysis confirms that, in the light of the best current evidence, the use of Gla-300 compared with Gla-100 is associated with lower confirmed and less clinically significant nocturnal

hypoglycemia events in people with DM, with minimal differences, although favorable, in glycemic control. Future studies are needed to consistently confirm this decrease of nocturnal hypoglycemic events. Meanwhile, these new studies with stronger designs, higher sample sizes and follow-up periods are being published, our data provide to the clinician evidence supporting the preferential use of Gla-300 as a basal insulin regimen use in type 1 and type 2 diabetes patients, especially in insulin-treated patients with important nocturnal hypoglycemia rates.

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Compliance with ethical standards

Conflict of interest AD-F declares that she has no conflict of interest. IC-R declares that he has no conflict of interest. JM-F declares that he has no conflict of interest. DP-C declares that she has no conflict of interest. MG-M declares that she has no conflict of interest. VM-V declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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