Received: 27 September 2022 | Revised: 31 January 2023 | Accepted: 2 February 2023

DOI: 10.1111/dom.15007

ORIGINAL ARTICLE

WILEY

Comparative clinical efficacy and safety of insulin glargine 300 U/ml (Toujeo) versus insulin glargine 100 U/ml in type 2 diabetes and type 1 diabetes: A systematic literature review and meta-analysis

Shashank R. Joshi MD[1] | Gursharan Singh PhD[2] | Ashwani Marwah MSc[2] | Shivani Mittra PhD[2] | Viraj R. Suvarna MD[2] | Sandeep N. Athalye MD[2]

[1]Department of Diabetology and Endocrinology, Lilavati Hospital and Research Center, Mumbai, India

[2]Clinical Development and Medical Affairs, Biocon Biologics India Ltd., Bengaluru, India

Correspondence
Gursharan Singh, MBBS,Biocon Biologics Ltd., Biocon House, Tower 3, Semicon Park, Plot No 29-P1 & 31-P, KIADB Industrial Area, Electronic City Phase - 2, Bangalore - 560100, Karnataka, India.
Email: gursharan.singh@biocon.com

Funding information
Biocon Biologics Ltd.

Abstract

Aim: To compare the clinical efficacy and safety of glargine-U100 (Lantus/Gla-100) with glargine-U300 (Toujeo/Gla-300) in adult patients with type 2 diabetes (T2D) and type 1 diabetes (T1D).

Materials and Methods: A literature search on Gla-300/Gla-100 in diabetes management was conducted using the MEDLINE/Embase/Cochrane databases from inception to 10 January 2021. Eligible studies considered for inclusion were parallel-design, randomized controlled trials (RCTs). The Cochrane risk-of-bias tool was used to evaluate the quality of the included studies. The random-effects model was applied for interpretation of the results.

Results: Of 5348 records screened, 592 were assessed for eligibility and 15 RCTs were considered for data extraction and meta-analysis (T2D [$N = 10$; $n = 7082$]; T1D [$N = 5$; $n = 2222$]). In patients with T1D, all safety parameters were comparable between Gla-100 and Gla-300. In T2D, statistically significant differences were observed in favour of Gla-300 over Gla-100 for nocturnal and total hypoglycaemia. For efficacy parameters, a statistically and clinically significant difference favouring Gla-100 in basal insulin dose requirement was observed for both T2D and T1D. Change in HbA1c showed a statistically but not clinically significant reduction with Gla-100 compared with Gla-300 in T1D. Statistically significant but clinically less relevant differences favoured Gla-300 for control of body weight in T1D and T2D and Gla-100 for fasting blood glucose in T2D.

Conclusions: Gla-100 and Gla-300 had comparable efficacy and safety profiles in both T1D and T2D populations. Gla-300 showed a lower risk of nocturnal and total hypoglycaemia, significant in insulin-experienced/exposed patients with T2D. Patients on Gla-300 required significantly more units of insulin daily than the Gla-100 group to achieve equivalent efficacy.

KEYWORDS
antidiabetic drug, meta-analysis, systematic review, type 1 diabetes, type 2 diabetes

1 | INTRODUCTION

The global ubiquity of diabetes in 2021 was 10.8% (537 million people), and is expected to rise by 45% (783 million) in 2045.[1] The rising costs and subsequent inequitable access to life-saving insulins are forcing one in four patients with diabetes, even in developed countries like the United States, to ration their insulin.[2] As diabetes therapy imposes a huge financial burden on individuals, families and national health systems, reverting to first-generation insulin analogues and their biosimilars from the more expensive, newer, second-generation insulin analogues can positively impact patient access, patient compliance and the healthcare system. This underscores the importance of not only evaluating the clinical impact of switching patients back on to first-generation analogues based on available data in the literature, but also initiating new patients onto them. For individuals with type 1 diabetes (T1D) and about 10% with type 2 diabetes (T2D), non-availability or non-affordability of insulin may result in rapid progression towards morbidity and mortality because of diabetes complications. Cost and access remain key challenges for both sets of patients despite the varied insulin requirements of T1D and T2D patients, with the latter needing more insulin because of a higher level of insulin resistance.

Insulin glargine 100 U/ml (Lantus; Gla-100) is a first-generation, long-acting human insulin analogue,[3,4] whereas insulin glargine 300 U/ml (Toujeo; Gla-300), a three-fold more concentrated formulation of Gla-100, is a second-generation basal insulin analogue.[5,6] Scientific evidence from the available literature, comprehensive systematic reviews and meta-analyses of clinical and observational studies on the clinical benefits of Gla-300 versus Gla-100[7,8] are limited and lack clarity. This systematic review/meta-analysis aimed to analyse randomized controlled trials (RCTs) in T2D and T1D patients to compare the clinical efficacy and safety profiles of Gla-300 and Gla-100, providing evidence for a potential switch from Gla-300 to more affordable and, thus, more accessible Gla-100 or Gla-100 biosimilars.

2 | METHODS

2.1 | Literature search strategy

A systematic literature review and meta-analysis was performed to compare Gla-300 and Gla-100 for clinical efficacy and safety in T2D and T1D patients. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[9] were followed and the checklist (Appendix A and B in Data S1) implemented recommendations of the Cochrane Collaboration Handbook.[10] RCTs included were screened through a systematic search of PubMed/MEDLINE, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL) databases from their inception until 10 January 2021. A further search was performed from 10 January 2021 to 22 September 2022. The search strategy was designed using appropriate Boolean operators to describe records using the Medical Subject Headings (MeSH) terms/Emtree (for Embase)/keywords related to insulin Gla-300, insulin Gla-100, diabetes mellitus and their aliases. Filters were used to limit the literature search to clinical trials. References of original articles and relevant meta-analyses were screened manually and double-checked by the reviewers. Additionally, the references of identified articles were screened to retrieve potentially relevant data.

Study selection criteria, data extraction and quality (risk of bias) assessment are detailed in Appendix C and D in Data S1. In short, the Cochrane risk of bias 2 tool was used to evaluate the quality of all included studies. Using this tool, risk of bias was evaluated from five domains: selection, performance, detection, attrition and reporting bias for six individual elements (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting). Each domain was considered as high, unclear or low risk and was represented by colour codes as red (high risk), yellow (unclear) and green (low), respectively. Because the objective of this systematic literature review and meta-analysis was not aimed towards providing any formal clinical practice recommendations, we have not applied the GRADE methodology to the results and outcomes.

2.2 | Endpoints of meta-analysis

Meta-analysis was used to compare different groups in terms of efficacy outcomes, including changes from baseline in HbA1c, fasting plasma glucose (FPG), body weight, basal insulin dose and safety outcomes (incidence and severity of hypoglycaemic events, nocturnal hypoglycaemic events, total adverse events [AEs], treatment-emergent serious AEs [TESAEs], treatment-emergent AEs like hypersensitivity and injection-site reactions and withdrawal because of AEs). Definitions of different hypoglycaemic types are provided in Table S1 in Data S1.

2.3 | Data analysis

Outcomes between Gla-300 and Gla-100 cases were pooled using mean difference (MD) with a 95% confidence interval (CI). For dichotomous data (efficacy and safety analysis), the outcomes were expressed as risk ratio (RR) and 95% CI. Heterogeneity was assessed by calculating the I^2 statistic (0%-40%: not important/low; 30%-60%: moderate heterogeneity; 50%-90%: substantial heterogeneity; 75%-

TABLE 1 Baseline characteristics of included studies in this meta-analysis

Author, year, location, trial ID/study ID	Design	Study duration (wks)	eN	Gender (M/F)	HbA1c (SD; %)	Mean FPG (SD; mmol/L)	Mean age (SD; y)	Mean duration of diabetes (SD; y)	BW (SD; kg)	Patients	Treatment and basal insulin dose[a] (U/kg/d)	Outcomes measured
Ritzel et al. 2018, Germany[12] NCT02320721/SENIOR	Multinational, M, AC, R, OL, P, two-arm, phase IIIb trial	26	Gla-300 group, n = 508 Gla-100 group, n = 506	250/258 277/229	8.20 (0.91) 8.22 (0.92)	8.44 (0.11) 8.56 (0.10)	71.1 (4.9) 70.8 (4.8)	15.29 (8.9) 15.35 (7.70)	— —	T2D for ≥ 1 y on AHAs ≥ 8 wk, HbA1c 7.5%-11% in insulin-naive or 7%-10% in insulin-pretreated	Gla-300 or Gla-100 Basal insulin dose: 0.2	HbA1c FPG Hypoglycaemia TEAEs
Bolli et al. 2017, Italy[21] NCT01676220/ EDITION 3[c]	M, R, OL, P, two-arm, treat-to-target phase IIIa trial	52	Gla-300 group, n = 439 Gla-100 group, n = 439	253/186 254/185	8.51 (1.04) 8.57 (1.07)	10.07 (1.13) 10.11 (1.11)	58.2 (9.9) 57.2 (10.3)	10.1 (6.5) 9.6 (6.2)	95.1 (23.3) 95.6 (22.6)	T2D patients for > 1 y using non-insulin AHAs for at least > 6 mo and being insulin-naive	Once daily Gla-300 or Gla-100 Basal insulin dose: 0.2	Glycaemic response Insulin dose Hypoglycaemia HbA1c FPG Participant-reported outcomes BW TEAEs
Terauchi et al. 2017, Japan[22] NCT01689142/ EDITION JP2[c]	M, R, OL, P, two-arm, phase III trial	52	Gla-300 group, n = 121 Gla-100 group, n = 120	77/43 70/51	7.99 (0.72) 8.06 (0.77)	7.70 (2.1) 7.40 (1.90)	61.1 (10.8) 60.5 (12.0)	14.0 (8.0) 13.9 (8.7)	67.4 (13.6) 65.9 (12.8)	T2D patients and HbA1c ≥ 7% to ≤ 10% on basal insulin and OADs	Gla-300 or Gla-100 injected once daily at the same time each evening Basal insulin dose: 0.2	HbA1c FPG Basal insulin dose BW Hypoglycaemia TEAEs
Terauchi et al. 2016, Japan[13] NCT01689142/ EDITION JP2	M, R, OL, P, two-arm, phase III trial	26	Gla-300 group, n = 121 Gla-100 group, n = 120	77/43 70/51	7.99 (0.72) 8.06 (0.77)	7.70 (2.10) 7.40 (1.90)	61.1 (10.8) 60.5 (12.0)	14.0 (8.0) 13.9 (8.7)	67.4 (13.6) 65.9 (12.8)	T2D patients for ≥ 1 y and treated with basal insulin and OAD(s) for ≥ 6 mo, HbA1c ≥ 7% to ≤ 10%	Once-daily sc injections of Gla-300 or Gla-100 Basal insulin dose: 0.24	HbA1c FPG Basal insulin dose Hypoglycaemia BW TEAEs
Jarvinen et al. 2016, Finland[24] NCT01499095/ EDITION 2[c]	Multinational, M, R, OL, P, two-arm, phase IIIa trial	52	Gla-300 group, n = 404 Gla-100 group, n = 407	187/217 185/222	8.26 (0.86) 8.22 (0.77)	8.24 (2.97) 7.89 (2.67)	57.9 (9.1) 58.5 (9.2)	12.7 (7.1) 12.5 (7.0)	98.7 (22.3) 98.0 (20.8)	T2D patients treated with ≥ 42 U/d basal insulin (Gla-100 or NPH) and OADs	Gla-300 or Gla-100 self-administered once daily at the same time in the evening Basal insulin dose (SD): 0.67 (0.24)	HbA1c FPG SMPG Basal insulin dose Hypoglycaemia BW, treatment satisfaction TEAEs
Riddle et al. 2015, United States[25] NCT01499082/ EDITION 1[c]	M, R, OL, P, two-arm, phase IIIa trial	52	Gla-300 group, n = 404 Gla-100 group, n = 403	217/187 210/193	8.15 (0.78) 8.16 (0.77)	8.86 (2.90) 8.90 (2.90)	60.1 (8.5) 59.8 (8.7)	15.6 (7.2) 16.1 (7.8)	106.2 (21.5) 106.4 (20.0)	T2D patients using basal insulin plus meal-time insulin analogue	Once-daily injections of either Gla-300 or Gla-100 with meal-time insulin Basal insulin dose (SD): 0.67 (0.25)	HbA1c FPG, TEAEs SMPG Basal insulin dose Hypoglycaemia BW, treatment satisfaction
Bolli et al. 2015, Italy[15] NCT01676220/ EDITION 3	M, R, OL, P, two-arm, phase IIIa trial	26	Gla-300 group, n = 439 Gla-100 group, n = 439	253/186 254/185	8.51 (1.04) 8.57 (1.07)	9.93 (2.86) 10.21 (2.90)	58.2 (9.9) 57.2 (10.3)	10.1 (6.5) 9.6 (6.2)	95.1 (23.3) 95.6 (22.6)	T2D patients for > 1 y, having used OADs for > 6 mo and	Once-daily injections of either Gla-300 or Gla-100	HbA1c FPG SMPG Basal insulin dose

(Continues)

TABLE 1 (Continued)

Author, year, location, trial ID/study ID	Design	Study duration (wks)	eN	Gender (M/F)	HbA1c (SD; %)	Mean FPG (SD; mmol/L)	Mean age (SD; y)	Mean duration of diabetes (SD; y)	BW (SD; kg)	Patients	Treatment and basal insulin dose[a] (U/kg/d)	Outcomes measured
										being insulin-naïve	Basal insulin dose: 0.24	Hypoglycaemia BW Treatment satisfaction TEAEs
Riddle et al. 2014, United States[16] NCT01499082/ EDITION 1	Multinational, M, OL, P	26	Gla-300 group, n = 404 Gla-100 group, n = 403	217/187 210/193	8.15 (0.78) 8.16 (0.77)	8.86 (2.9) 8.9 (2.9)	60.1 (8.5) 59.8 (8.7)	15.6 (7.2) 16.1 (7.8)	106.2 (21.5) 106.4 (20.0)	T2D using ≥ 42 U/d of Gla-100/NPH lispro/aspart/ glulisine with or without metformin for > 1 y HbA1c of 7%-10%	Once-daily injections of either Gla-300 or Gla-100 Basal insulin dose (SD): 0.67 (0.25)	HbA1c FPG SMPG Basal insulin dose Hypoglycaemia BW, TEAEs Treatment satisfaction
Jarvinen et al. 2014, Finland[17] NCT01499095/ EDITION 2	M, R, OL, P, two-arm, phase IIIa trial	26	Gla-300 group, n = 404 Gla-100 group, n = 407	187/217 185/222	8.26 (0.86) 8.22 (0.77)	8.24 (2.97) 7.89 (2.67)	57.9 (9.1) 58.5 (9.2)	12.7 (7.1) 12.5 (7.0)	98.7 (22.3) 98 (20.8)	T2D for > 1 y and > 6 mo on basal insulin ≥ 42 U/d of Gla-100/NPH with OAD	Once-daily sc injections of Gla-300 or Gla-100 administered in the evening Basal insulin dose: 0.64 (SD 0.22)	HbA1c FPG SMPG Basal insulin dose Hypoglycaemia BW, TEAEs Treatment satisfaction
Ji et al. 2019, China[18] NCT02855684/ EDITION AP	M, OL, R, AC, P, two-arm, treat-to-target, non-inferiority study	26	Gla-300 group, n = 401 G-100 group, n = 203	233/168 108/95	8.6 (0.9) 8.5 (1.0)	9.97 (2.30) 9.79 (2.17)	58.5 (9.6) 57.9 (10.2)	10.7 (6.4) 10.5 (5.8)	68.3 (11.7) 68.8 (11.5)	T2D insulin-naïve patients not adequately controlled with non-insulin AHAs	Once-daily Gla-300 or Gla-100 administered in the evening Basal insulin dose: 0.2	HbA1c FPG SMPG Basal insulin dose Hypoglycaemia BW, TEAEs Treatment compliance
Home et al. 2015, UK[11] NCT01683266/ EDITION 4	M, R, OL, P, four-arm, phase IIIa trial	26	Gla-300 group, n = 274 Gla-100 group, n = 275	149/125 164/111	8.11 (0.77) 8.14 (0.79)	185.9[b] (76.2) 199.3[b] (79.6)	46.4 (13.9) 48.2 (13.4)	20.5 (12.7) 21.4 (13.1)	81.9 (20.4) 81.8 (16.8)	T1D patients for > 1 y, using any mealtime insulin analogue for ≥ 3 mo with BMI of 27.6 kg/m^2	Once-daily morning or evening sc injection of Gla-300 or Gla-100 using a central treatment system Basal insulin dose (SD): 0.38 (0.17) for Gla-300 group and 0.37 (0.15) for Gla-100 group	HbA1c FPG Basal insulin dose Hypoglycaemia BW Participant-reported outcomes TEAEs and insulin antibodies
Home et al. 2018, UK[20] NCT01683266/ EDITION 4[c]	M, R, OL, P, four-arm, phase IIIa trial	52	Gla-300 group, n = 274 Gla-100 group, n = 275	149/125 164/111	8.11 (0.77) 8.14 (0.79)	10.26 (4.14) 10.04 (4.46)	46.4 (13.9) 48.2 (13.4)	20.5 (12.7) 21.4 (13.1)	81.9 (20.4) 81.8 (16.8)	T1D patients for > 1 y with HbA1c 7%-10%, spent > 1 y on basal insulin with a mealtime insulin analogue	Once-daily morning or evening sc injection of Gla-300 or Gla-100 while continuing mealtime insulin	HbA1c FPG Basal insulin dose Hypoglycaemia BW Participant-reported outcomes TEAEs and insulin antibodies

TABLE 1 (Continued)

Author, year, location, trial ID/study ID	Design	Study duration (wks)	eN	Gender (M/F)	HbA1c (SD; %)	Mean FPG (SD; mmol/L)	Mean age (SD; y)	Mean duration of diabetes (SD; y)	BW (SD; kg)	Patients	Treatment and basal insulin dose[a] (U/kg/d)	Outcomes measured
											Basal insulin dose (SD): 0.38 (0.17) for Gla-300 group and 0.37 (0.15) for Gla-100 group	
Pettus et al. 2019, United States[19] NCT02688933	M, R, AC, P, OL, phase IV trial	16	Gla-300 group, n = 320 Gla-100 group, n = 318	180/140 180/138	8.01 (0.82) 7.99 (0.82)	182.1[b] (81.3) 175.3[b] (81.9)	45.5 (14.0) 45.5 (13.9)	22.6 (13.1) 22.8 (13.4)	81.0 (17.2) 81.4 (17)	T1D patients with HbA1c 6.6%-9.9%, receiving basal bolus insulin therapy for > 1 y	Gla-300 or Gla-100 delivered using a pen device Basal insulin dose (SD): 0.38 (0.16) for Gla-300 group and 0.37 (0.15) for Gla-100 group	HbA1c Glucose target range FPG Basal insulin dose Hypoglycaemia Glycaemic variability Daily insulin dose Post hoc exploratory analyses TEAEs TESAEs Injection-site reactions Hypersensitivity reactions
Matsuhisa et al. 2016a, Japan[14] NCT01689129/ EDITION JP	M, R, OL, P, two-arm, phase III trial	26	Gla-300 group, n = 122 Gla-100 group, n = 121	56/66 56/65	8.06 (0.64) 8.07 (0.74)	10.32 (0.34) 10.04 (0.40)	44.1 (13.9) 46.3 (15.3)	12.2 (8.6) 13.9 (9.0)	63.9 (11.6) 61.0 (11.8)	T1D patients receiving basal and mealtime insulin for ≥ 1 y with HbA1c ≥ 7% to ≤ 10%	Once-daily sc injections of Gla-300 or Gla-100 Basal insulin dose (SD): 0.28 (0.12) for Gla-300 group and 0.30 (0.13) for Gla-100 group	HbA1c FPG Basal insulin dose Hypoglycaemia BW TEAEs
Matsuhisa et al. 2016b, Japan[23] NCT01689129/ EDITION JP 1[c]	M, R, OL, P, two-arm, treat-to-target, phase III trial	52	Gla-300 group, n = 122 Gla-100 group, n = 121	56/66 56/65	8.06 (0.64) 8.07 (0.74)	10.38 (0.38) 10.13 (0.46)	44.1 (13.9) 46.3 (15.3)	12.2 (8.6) 13.9 (9.0)	63.9 (11.6) 61.0 (11.8)	T1D patients HbA1c ≥ 7% to ≤ 10%, use of basal and mealtime insulin for > 1 y	Gla-300 or Gla-100 Basal insulin dose (SD): 0.26 (0.01) for Gla-300 group and 0.28 (0.01) for Gla-100 group	HbA1c FPG SMPG Basal insulin dose Hypoglycaemia BW TEAEs

Abbreviations: AC, active-controlled; AHAs, antihyperglycaemic agents; BMI, body mass index; BW, body weight; F, female; FPG, fasting plasma glucose; Gla-100, glargine-100 U/ml (Lantus); Gla-300, glargine-300 U/ml (Toujeo); M, male; M, multicentre; n, number of subjects in each group; N, total number of subjects in the trial; NPH, neutral protamine hagedorn insulin; OAD, oral antihyperglycaemic drug; OL, open-label; P, parallel-group; R, randomized; sc, subcutaneous; SD, standard deviation; SMPG, self-monitored plasma glucose; TEAEs, treatment-emergent adverse events; TESAEs, treatment-emergent serious adverse events; T1D, type 1 diabetes; T2D, type 2 diabetes.

[a]Basal insulin doses are adjusted every 3-4 days aiming for a fasting SMPG of 5.0-7.2 mmol/L.

[b]Values represented in mg/dl.

[c]Extension studies for previous trials.

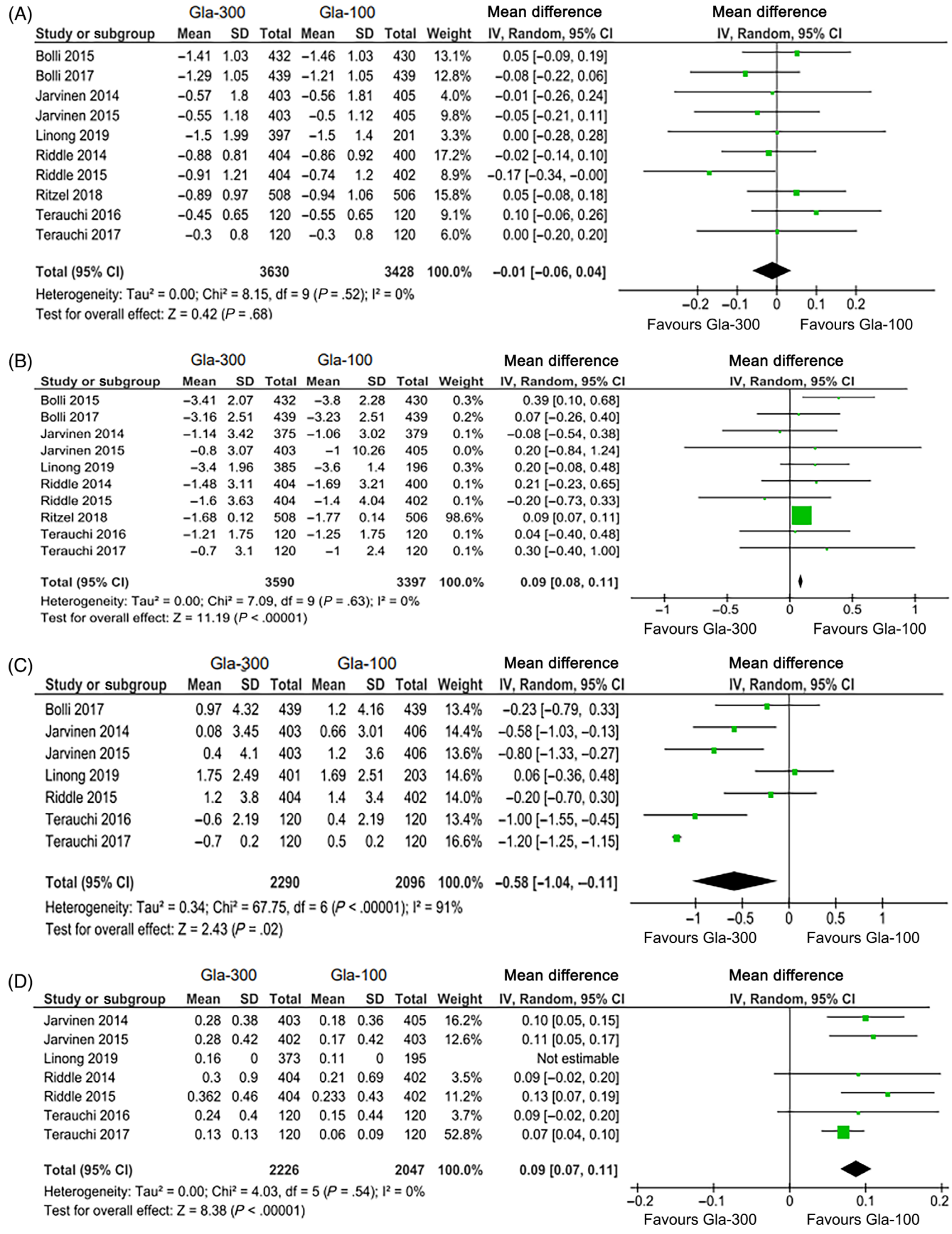


FIGURE 1 Legend on next page.

100%: considerable heterogeneity) and statistical significance was denoted with the corresponding *P*-value < .05 (two-tailed test). Clinical significance was measured and decided based on the standardized MD (SMD). The random-effects model was applied for statistical interpretation. Meta-analysis was performed using Review Manager (RevMan: computer program, version 5.4.1; The Cochrane Collaboration, 2020). Forest plots were generated to summarize study results graphically and WebPlotDigitizer was used for graph mining.

3 | RESULTS

3.1 | Study selection and characteristics of included studies

The electronic search retrieved 6294 records, of which 946 duplicates were excluded. Of the remaining 5348 unique records, 4756 were excluded and 592 full-text articles were assessed for eligibility, with 15 studies considered eligible for data extraction and meta-analysis. The search strategies for RCTs from Embase and MEDLINE/PubMed databases carried out from their inception until 10 January 2021 are provided in Tables S2 and S3 in Data S1, respectively. A further search yielded no relevant literature from 10 January 2021 to 22 September 2022. The PRISMA flowchart for identifying relevant studies and reasons for exclusion is depicted in Figure S1 in Data S1.

The characteristics of the 15 studies included in the meta-analysis are presented in Table 1. These studies were published from 2014 to 2019, with sample sizes ranging from 241 to 1014 patients. A total of 9304 adult patients were evaluated in the included studies, with nearly equal distribution in the Gla-300 and Gla-100 groups. Of the 15 included studies, 10 recruited T2D patients (N = 7082), while five recruited T1D patients (N = 2222). The most common study duration was 26 weeks,[11-18] with the shortest duration of 16 weeks in one study[19] and the longest duration of 52 weeks in six studies.[20-25] All included studies had a parallel-group, open-label design (Gla-300 vs. Gla-100) either with two[12-19,21-25] or four arms (switching from morning to evening injection).[11,20]

3.2 | Risk of bias (quality assessment)

The majority of the included studies did not have any bias concern except high risk in performance because of the open-label setting. Because there were differences in the pen injector devices, all the included studies were open-label trials. All 15 studies included were considered as having low risk in attrition bias. The study design included only RCTs, resulting in a low risk of selection bias for both T2D and T1D. RCTs were funded by industry, which is the normal practice for studies with such a large sample size. However, few studies had unclear risks in domains like selection, detection and reporting in T2D and T1D (Appendix-D in Data S1) as the publications did not describe the method for random sequence generation or blinding or the protocol was not available in the public domain to verify whether all data generated were reported. Based on the Cochrane Risk of Bias analysis, all studies were judged to be of moderate methodological quality. Risk of bias plots/summaries are presented as supporting information for both overall and separately for T2D (Figures S8 and S9 in Data S1) and T1D studies (Figures S10 and S11 in Data S1).

Results on various parameters are presented separately in the two indications as the comparative efficacy and safety profile of both drugs differs between indications.

3.3 | Gla-300 versus Gla-100 in T2D

3.3.1 | Efficacy

Hba1c Levels (%)

No statistically significant difference was noticed in HbA1c levels between the two treatment groups based on the meta-analysis of the 10 included studies (N = 7092; MD: −0.01; 95% CI: −0.06, 0.04; *P* = .68) (Figure 1A). Heterogeneity between the studies was low.

Fasting Plasma Glucose Levels (mmol/L)

Gla-100 showed a statistically significant reduction of FPG versus Gla-300 (MD: 0.09; 95% CI: 0.08, 0.11; *P* < .00001) based on the meta-analysis of the 10 included studies (N = 7092) (Figure 1B). Heterogeneity between the studies was low. However, the differences were not clinically significant, as evident from the SMD values (SMD: 0.12; 95% CI: −0.04, 0.27; *P* < .13; Figure S2 in Data S1).

Body Weight (kg)

Seven studies[13,17,18,21,22,24,25] (N = 4393) assessed the effect of interventions on body weight. Weight gain was controlled significantly with Gla-300 compared with Gla-100, with high heterogeneity between the studies (MD: −0.58; 95% CI: −1.04, −0.11; *P* = .02)

FIGURE 1 A, Mean treatment differences in HbA1c levels (%) between Gla-300 and Gla-100 in trials on T2D patients. B, Mean treatment differences in FPG levels (mmol/L) between Gla-300 and Gla-100 in trials on T2D patients. C, Mean treatment differences in body weight (kg) between Gla-300 and Gla-100 in trials on T2D patients. D, Mean treatment differences in basal insulin dose (U/kg/day) between Gla-300 and Gla-100 in trials on T2D patients. Chi^2, a statistical test for determining the difference between treatments; CI, confidence interval; FPG, fasting plasma glucose; Gla-300, Glargine-300; Gla-100, Glargine-100; I^2, measures the percentage variability in the treatment effect estimates that is attributed to between-study heterogeneity rather than chance; SD, standard deviation; Tau, estimated standard deviation in the random-effects model, underlying true effects (Tau^2 is the variance); T2D, type 2 diabetes; Z, the significant test for the weighted average effect size, conducted on a population that follows a normal distribution

(Figure 1C). The difference between the interventions was also clinically significant based on the SMD values (SMD: −0.87; 95% CI: −1.37, −0.37; $P < .0007$; Figure S3 in Data S1).

Basal Insulin Dose (U/kg/day)

Seven of the included studies[13,16-18,22,24,25] (N = 4322) reported changes in basal insulin dosages, with one study's data being inestimable.[18] There was a statistically significant difference in change in basal insulin dose with Gla-300 compared with Gla-100 (MD: 0.09; 95% CI: 0.07, 0.11; $P < .00001$) (Figure 1D), with low heterogeneity between the studies.

The basal insulin dose requirement increased significantly with Gla-300 compared with Gla-100. The Gla-300 group required significantly more units of insulin daily than the Gla-100 group to achieve equivalent efficacy (SMD: 0.27; 95% CI: 0.17, 0.38; $P < .000001$; Figure S4 in Data S1).

3.3.2 | Safety

Effect on Hypoglycaemic Events

Confirmed Or Severe Hypoglycaemia. Only three of the included studies[12,18,25] (N = 2425) reported confirmed or severe hypoglycaemia. In the meta-analysis of severe hypoglycaemic events, a lower incidence risk was observed with Gla-300 compared with Gla-100, with no statistical significance (RR: 0.87; 95% CI: 0.75, 1.01; $P = .06$) (Figure 2A). There was considerable heterogeneity between the studies.

Severe Hypoglycaemia. Severe hypoglycaemic episodes were assessed in patients from eight of the included studies[13,15-17,21,22,24,25] (N = 5474). The rate of severe hypoglycaemic events was similar with Gla-300 and Gla-100, with no statistically significant differences in the risk of hypoglycaemic events between the groups (RR: 0.90; 95% CI: 0.66, 1.23; $P = .51$) (Figure 2B). Heterogeneity between the studies was low.

Nocturnal Hypoglycaemia. Four included studies[13,16,17,24] (N = 2664) assessed nocturnal hypoglycaemic episodes. Statistically significant events were lower for Gla-300 compared with Gla-100 (RR: 0.77; 95% CI: 0.70, 0.85; $P < .00001$) (Figure 2C). Heterogeneity between the studies was low.

Nocturnal Severe Hypoglycaemia. Nocturnal severe hypoglycaemic episodes were assessed for six studies[13,17,21,22,24,25] (N = 3782). No statistically significant difference between the risk of severe nocturnal hypoglycaemia was observed in both interventions (RR: 0.63; 95% CI: 0.32, 1.22; $P = .17$) (Figure 2D). There was no heterogeneity between the studies.

Confirmed Or Severe Nocturnal Hypoglycaemia. Only four studies[12,15,18,25] (N = 3303) reported confirmed or severe nocturnal hypoglycaemia. A lower incidence of events was significantly in favour of Gla-300 compared with Gla-100 (RR: 0.84; 95% CI: 0.77, 0.91; $P < .0001$) (Figure 2E). There was low heterogeneity between the studies.

Total Hypoglycaemia. Only four studies[13,16-18] (N = 2463) assessed the occurrence of total hypoglycaemic events. A statistically significant difference in RR with a lower incidence of events was observed with Gla-300 compared with Gla-100 (RR: 0.86; 95% CI: 0.78, 0.96; $P = .009$) (Figure 2F). There was considerable heterogeneity between the studies.

Treatment-Emergent Serious Adverse Events. Six included studies[15-18,24,25] (N = 4718) assessed TESAEs. Similar rates of events with no significant difference in RR were observed between the two analogues (RR: 1.03; 95% CI: 0.80, 1.34; $P = .81$) (Figure 2G). Heterogeneity between the studies was low.

Withdrawal Because Of AEs. All 10 included studies[12,13,15-17,19,21,22,24,25] reported withdrawal because of AEs (N = 7092). A lesser risk of events was observed with Gla-100 compared with Gla-300, with no statistically significant difference in risks (RR: 1.18; 95% CI: 0.81, 1.72; $P = .39$) (Figure 2H). Heterogeneity between the studies was low.

Hypersensitivity Reactions. Six studies[13,17,21,22,24,25] (N = 3789) investigated hypersensitivity reactions because of the interventions. The number of hypersensitivity reactions observed was lower with Gla-100 compared with Gla-300; however, no statistically significant difference in risks was observed (RR: 1.08; 95% CI: 0.77, 1.52; $P = .66$) (Figure 2I). Heterogeneity between the studies was low.

Injection-Site Reactions. All 10 of the included studies[12,13,15-17,19,21,22,24,25] (N = 7092) reported injection-site reactions. Lower incidences of injection-site reactions were observed for Gla-300 compared with Gla-100, with no statistically significant difference in risks (RR: 0.77; 95% CI: 0.50, 1.20; $P = .25$) (Figure 2J). There was moderate heterogeneity between studies.

3.4 | Gla-300 versus Gla-100 in T1D

3.4.1 | Efficacy

HbA1c Levels (%)

HbA1c changes from baseline to endpoint were evaluated for all five of the included studies[11,14,19,20,23] (N = 2222). Change in HbA1c values relative to baseline showed a statistically significant reduction with Gla-100 compared with Gla-300 (MD: 0.02; 95% CI: 0.01, 0.03; $P < .0001$) (Figure 3A). Heterogeneity between the studies was low. A statistically significant but clinically small effect was observed based on the SMD values (SMD: 0.14; 95% CI: 0.01, 0.27; $P = .03$; Figure S5 in Data S1).

Fasting Plasma Glucose (mmol/L)

All five of the included studies were evaluated for FPG levels[11,14,19,20,23] (N = 1584). A reduction in FPG values was observed with Gla-100 compared with Gla-300, with no statistical significance (MD: 0.16; 95% CI: −0.80, 1.13; $P = .74$) (Figure 3B). Substantial heterogeneity was observed between the studies.

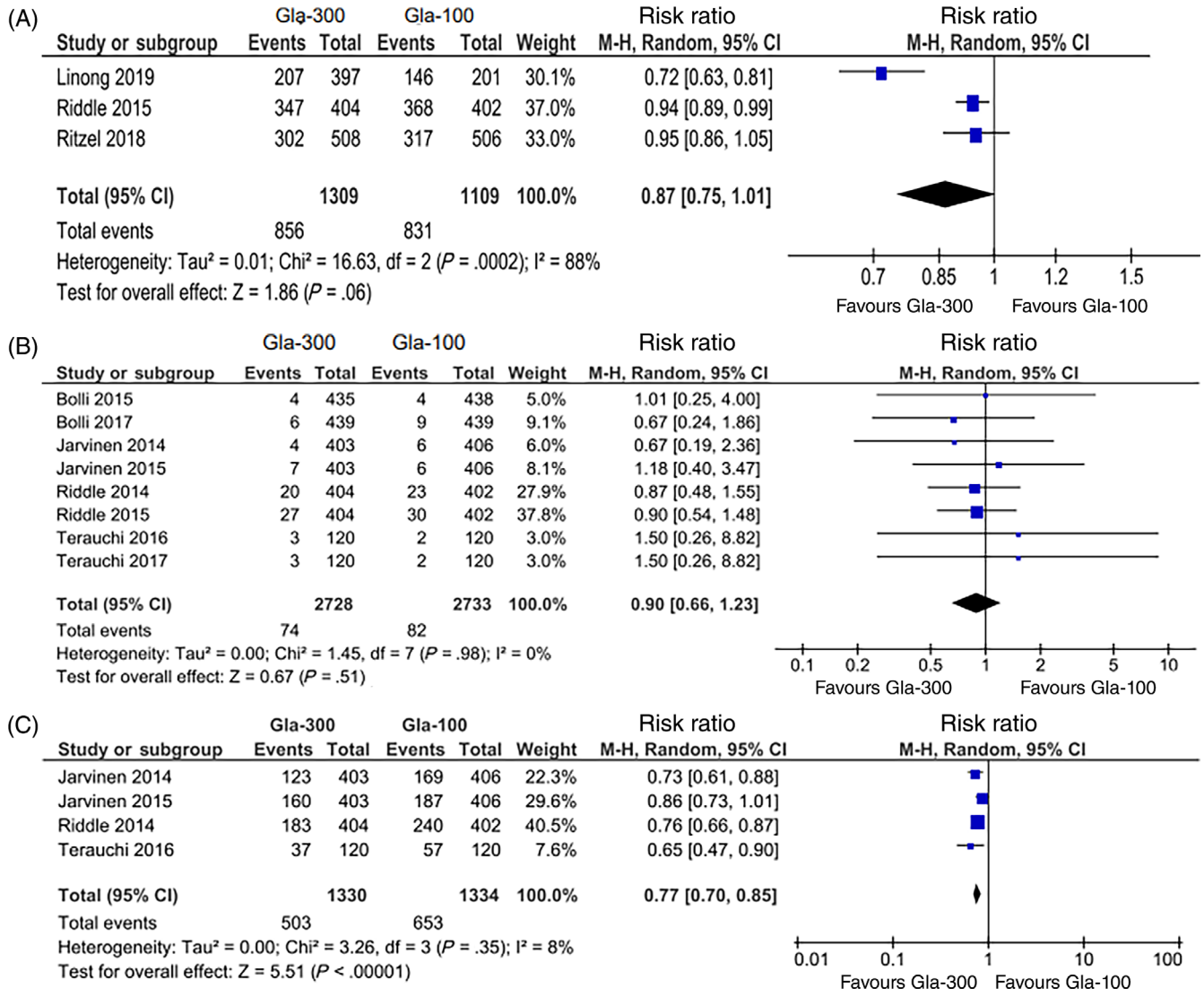
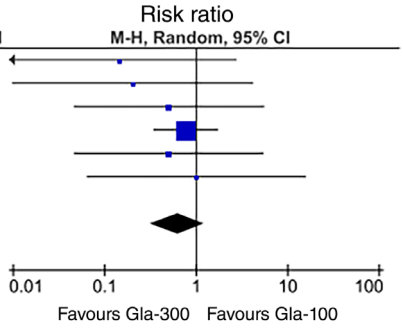


FIGURE 2 A, Confirmed or severe hypoglycaemic event rates with Gla-300 compared with Gla-100 in trials on T2D patients. A confirmed or severe hypoglycaemic event is defined as a hypoglycaemic event that is either severe, requires third-party assistance or is confirmed by blood glucose ≤ 3.9 mmol/L (≤ 70 mg/dl). B, Severe hypoglycaemic event rates with Gla-300 compared with Gla-100 in trials on T2D patients. Severe hypoglycaemic events are defined as episodes of an abnormally low plasma glucose concentration (≤ 70 mg/dl or lower), require third-part assistance and are ameliorated by normalization of plasma glucose. In severe hypoglycaemia, low blood glucose level (≤ 70 mg/dl, often much lower) may be associated with sufficient neuroglycopaenia to induce seizure or coma. C, Nocturnal hypoglycaemic event rates with Gla-300 compared with Gla-100 in trials on T2D patients. Statistical significance was denoted with the corresponding *P*-value < .05 (two-tailed test). D, Severe nocturnal hypoglycaemia event rates with Gla-300 compared with Gla-100 in trials on T2D patients. E, Confirmed or severe nocturnal hypoglycaemic event rates with Gla-300 compared with Gla-100 in trials on T2D patients.
Statistical significance was denoted with the corresponding *P*-value < .05 (two-tailed test). F, Total hypoglycaemic event rates with Gla-300 compared with Gla-100 in trials on T2D patients. G, TESAEs with Gla-300 compared with Gla-100 in trials on T2D patients. H, Withdrawal because of AEs with Gla-300 compared with Gla-100 in trials on T2D patients. I, Hypersensitivity reactions with Gla-300 compared with Gla-100 in trials on T2D patients. J, Injection-site reactions with Gla-300 compared with Gla-100 in trials on T2D patients. AEs, adverse events; Chi^2, a statistical test for determining the difference between treatments; CI, confidence interval; Gla-300, Glargine-300; Gla-100, Glargine-100; I^2, measures the percentage variability in the treatment effect estimates that is attributed to between-study heterogeneity rather than chance; SD, standard deviation; Tau, estimated standard deviation in the random-effects model, underlying true effects (Tau^2 is the variance); TESAEs, treatment-emergent serious adverse events; T2D, type 2 diabetes; Z, significant test for the weighted average effect size, conducted on a population that follows a normal distribution

(D)

Study or subgroup	Gla-300 Events	Gla-300 Total	Gla-100 Events	Gla-100 Total	Weight	Risk ratio M-H, Random, 95% CI
Bolli 2017	0	439	3	439	5.1%	0.14 [0.01, 2.76]
Jarvinen 2014	0	403	2	406	4.9%	0.20 [0.01, 4.18]
Jarvinen 2015	1	403	2	406	7.9%	0.50 [0.05, 5.53]
Riddle 2015	10	404	13	402	68.3%	0.77 [0.34, 1.73]
Terauchi 2016	1	120	2	120	7.9%	0.50 [0.05, 5.44]
Terauchi 2017	1	120	1	120	5.9%	1.00 [0.06, 15.80]
Total (95% CI)		**1889**		**1893**	**100.0%**	**0.63 [0.32, 1.22]**
Total events	13		23			

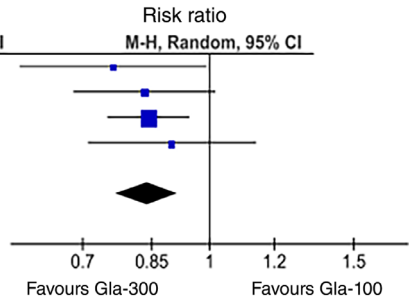
Heterogeneity: Tau² = 0.00; Chi² = 1.95, df = 5 (P = .86); I² = 0%
Test for overall effect: Z = 1.37 (P = .17)



(E)

Study or subgroup	Gla-300 Events	Gla-300 Total	Gla-100 Events	Gla-100 Total	Weight	Risk ratio M-H, Random, 95% CI
Bolli 2015	78	435	103	438	10.9%	0.76 [0.59, 0.99]
Linong 2019	148	397	90	201	18.8%	0.83 [0.68, 1.02]
Riddle 2015	220	404	260	402	56.9%	0.84 [0.75, 0.94]
Ritzel 2018	103	508	114	506	13.4%	0.90 [0.71, 1.14]
Total (95% CI)		**1744**		**1547**	**100.0%**	**0.84 [0.77, 0.91]**
Total events	549		567			

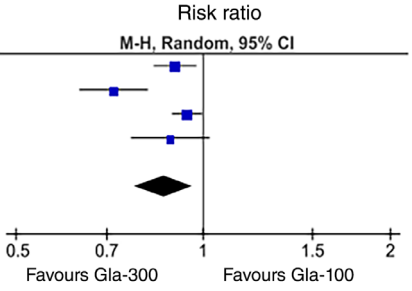
Heterogeneity: Tau² = 0.00; Chi² = 0.86, df = 3 (P = .84); I² = 0%
Test for overall effect: Z = 3.98 (P < .0001)



(F)

Study or subgroup	Gla-300 Events	Gla-300 Total	Gla-100 Events	Gla-100 Total	Weight	Risk ratio M-H, Random, 95% CI
Jarvinen 2014	288	403	322	406	27.5%	0.90 [0.83, 0.98]
Linong 2019	207	397	146	201	22.4%	0.72 [0.63, 0.81]
Riddle 2014	337	404	356	402	29.7%	0.94 [0.89, 1.00]
Terauchi 2016	85	120	96	120	20.4%	0.89 [0.77, 1.02]
Total (95% CI)		**1324**		**1129**	**100.0%**	**0.86 [0.78, 0.96]**
Total events	917		920			

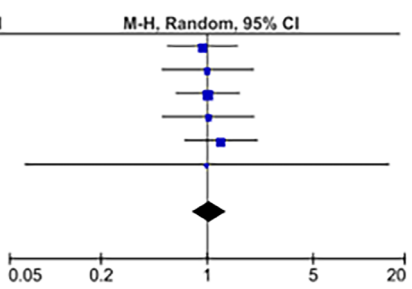
Heterogeneity: Tau² = 0.01; Chi² = 16.20, df = 3 (P = .001); I² = 81%
Test for overall effect: Z = 2.63 (P = .009)



(G)

Study or subgroup	Gla-300 Events	Gla-300 Total	Gla-100 Events	Gla-100 Total	Weight	Risk ratio M-H, Random, 95% CI
Bolli 2015	24	435	26	438	22.9%	0.93 [0.54, 1.59]
Jarvinen 2014	15	403	15	406	13.5%	1.01 [0.50, 2.03]
Jarvinen 2015	30	403	30	406	28.0%	1.01 [0.62, 1.64]
Linong 2019	22	397	11	201	13.4%	1.01 [0.50, 2.05]
Riddle 2014	26	404	21	402	21.3%	1.23 [0.70, 2.15]
Riddle 2015	1	404	1	402	0.9%	1.00 [0.06, 15.85]
Total (95% CI)		**2446**		**2255**	**100.0%**	**1.03 [0.80, 1.34]**
Total events	118		104			

Heterogeneity: Tau² = 0.00; Chi² = 0.55, df = 5 (P = .99); I² = 0%
Test for overall effect: Z = 0.25 (P = .81)



(H)

Study or subgroup	Gla-300 Events	Gla-300 Total	Gla-100 Events	Gla-100 Total	Weight	Risk ratio M-H, Random, 95% CI
Bolli 2015	5	435	5	438	9.4%	1.01 [0.29, 3.45]
Bolli 2017	9	435	8	438	16.0%	1.13 [0.44, 2.91]
Jarvinen 2014	6	403	4	406	9.0%	1.51 [0.43, 5.31]
Jarvinen 2015	11	403	7	406	16.2%	1.58 [0.62, 4.04]
Linong 2019	5	397	2	201	5.3%	1.27 [0.25, 6.47]
Riddle 2014	9	404	8	402	16.0%	1.12 [0.44, 2.87]
Riddle 2015	3	374	8	371	8.2%	0.37 [0.10, 1.39]
Ritzel 2018	7	508	6	505	12.1%	1.16 [0.39, 3.43]
Terauchi 2016	3	120	1	120	2.8%	3.00 [0.32, 28.43]
Terauchi 2017	4	120	2	120	5.0%	2.00 [0.37, 10.71]
Total (95% CI)		**3599**		**3407**	**100.0%**	**1.18 [0.81, 1.72]**
Total events	62		51			

Heterogeneity: Tau² = 0.00; Chi² = 4.60, df = 9 (P = .87); I² = 0%
Test for overall effect: Z = 0.86 (P = .39)

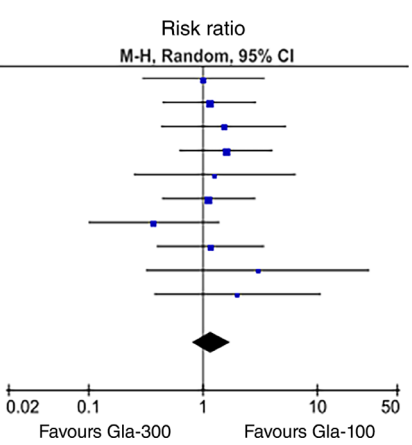


FIGURE 2 (Continued)

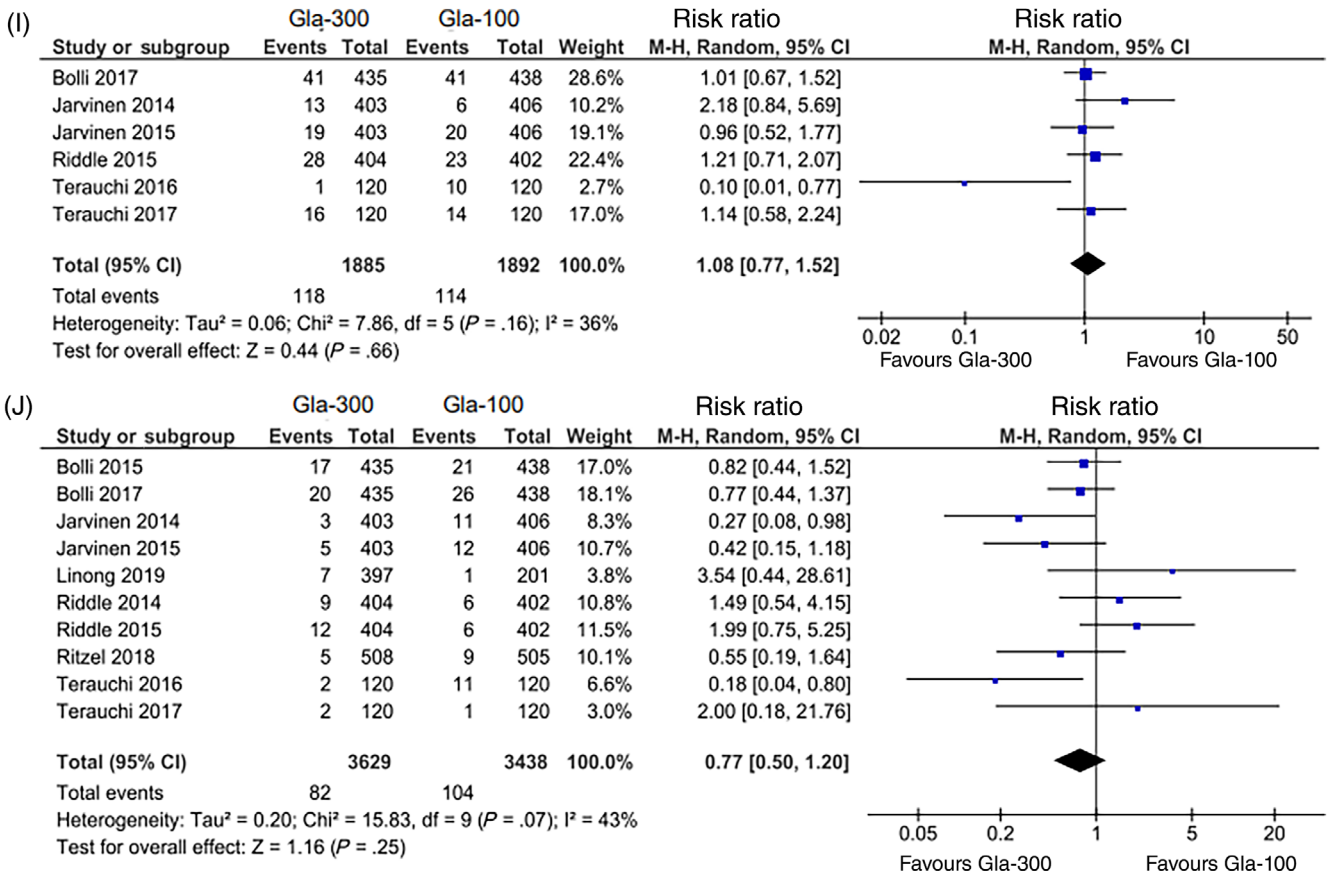


FIGURE 2 (Continued)

Body Weight (kg)

Three studies[11,14,23] (N = 1035) assessed the effect of interventions on body weight. Weight gain control was statistically significant with Gla-300 compared with Gla-100, with no heterogeneity (MD: −0.48; 95% CI: −0.85, −0.12; $P = .01$) (Figure 3C). However, the results were not clinically significant, as was evident from the SMD values (SMD: −0.13; 95% CI: −0.31, 0.04; $P = .13$; Figure S6 in Data S1).

Basal Insulin Dose (U/kg/day)

All five of the included studies reported a change in basal insulin dose[11,14,19,20,23] (N = 2222). Gla-100 reported a statistically significant effect on change in basal insulin dose compared with Gla-300 (MD: 0.05; 95% CI: 0.01, 0.09; $P = .02$) (Figure 3D). There was substantial heterogeneity between the studies. The analysis also highlighted a clinically significant difference favouring Gla-100 over Gla-300 based on the SMD values (SMD: 0.37; 95% CI: 0.04, 0.71; $P = .03$; Figure S7 in Data S1).

3.4.2 | Safety

Severe Hypoglycaemia

All five of the included studies reported severe hypoglycaemic episodes[11,14,19,20,23] (N = 2222). Fewer events were observed with Gla-300 compared with Gla-100, with no statistically significant differences in risks (RR: 0.82; 95% CI: 0.62, 1.10; $P = .18$) (Figure 4A). There was no heterogeneity between the studies.

Nocturnal Hypoglycaemia

Four of the included studies[11,14,19,23] (N = 1673) assessed the incidences of nocturnal hypoglycaemia. Similar rates of events were observed for Gla-300 and Gla-100, with no statistically significant difference in risks (RR: 0.98; 95% CI: 0.88, 1.08; $P = .63$) (Figure 4B). There was moderate heterogeneity between the studies.

Nocturnal Severe Hypoglycaemia

The effect of interventions on nocturnal severe hypoglycaemic episodes was evaluated in four of the included studies[14,19,20,23] (N = 1673). Similar rates of events were observed with Gla-300 and Gla-100, with no statistically significant difference in risks (RR: 0.94; 95% CI: 0.48, 1.81; $P = .84$) (Figure 4C). Heterogeneity between the studies was low.

Total Hypoglycaemia

Only two studies[14,19] (N = 881) included in the meta-analysis assessed the occurrence of total hypoglycaemic events. The number of events was lower with Gla-100 compared with Gla-300,

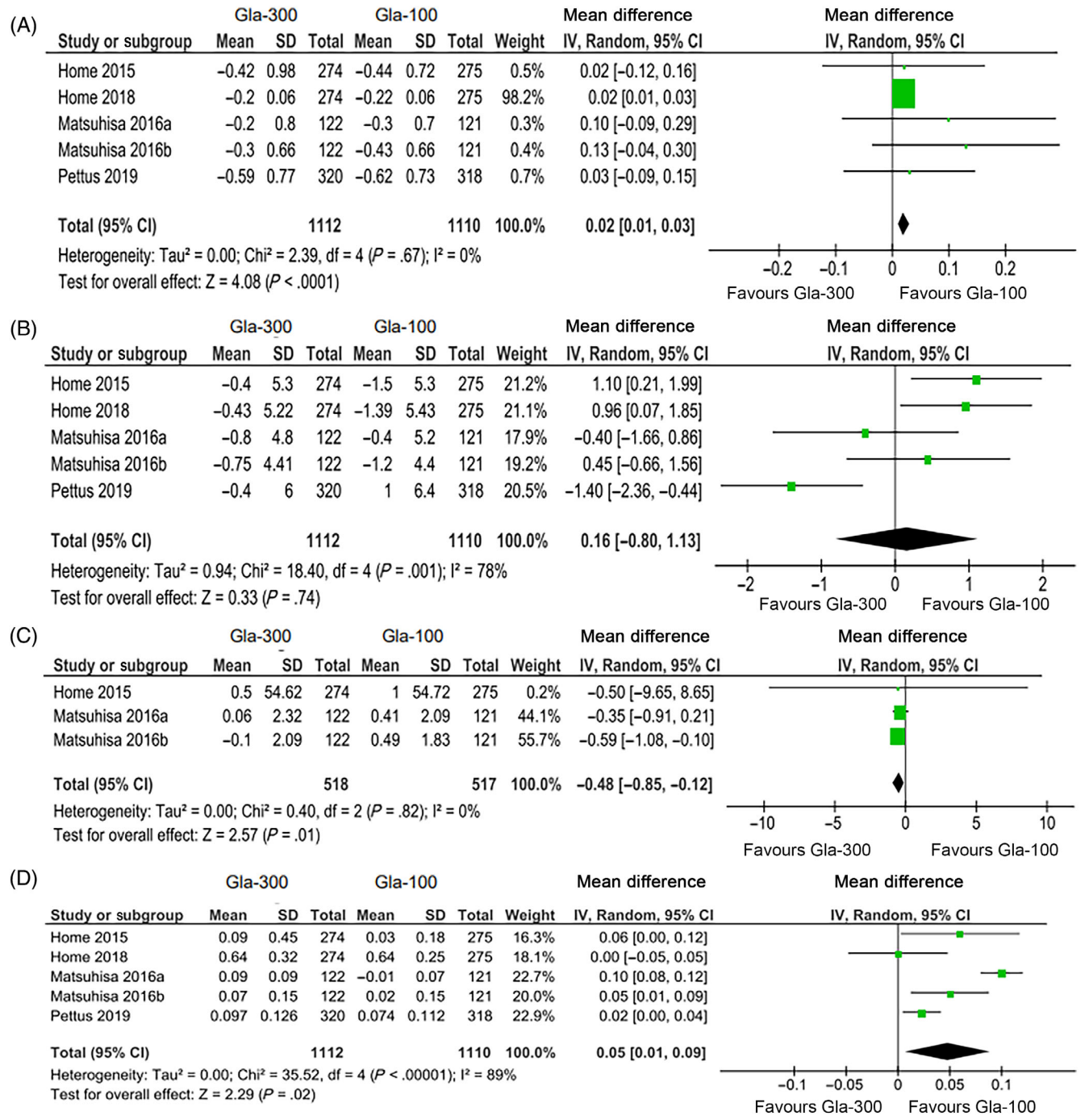


FIGURE 3 A, Mean treatment differences in HbA1c levels (%) between Gla-300 and Gla-100 in trials on T1D patients. Statistical significance was denoted with the corresponding *P*-value < .05 (two-tailed test). B, Mean treatment differences in FPG levels (mmol/L) between Gla-300 and Gla-100 in trials on T1D patients. C, Mean treatment differences in body weight (kg) between Gla-300 and Gla-100 in trials on T1D patients. Statistical significance was denoted with the corresponding *P*-value < .05 (two-tailed test). D, Mean treatment differences in basal insulin (U/kg/day) between Gla-300 and Gla-100 in trials on T1D patients. Statistical significance was denoted with the corresponding *P*-value < .05 (two-tailed test). Chi^2, a statistical test for determining the difference between treatments; CI, confidence interval; FPG, fasting plasma glucose; Gla-300, Glargine-300; Gla-100, Glargine-100; I^2, measures the percentage variability in the treatment effect estimates that is attributed to between-study heterogeneity rather than chance; SD, standard deviation; Tau, estimated standard deviation in the random-effects model, underlying true effects (Tau^2 is the variance); T1D, type 1 diabetes; Z, significant test for the weighted average effect size, conducted on a population that follows a normal distribution

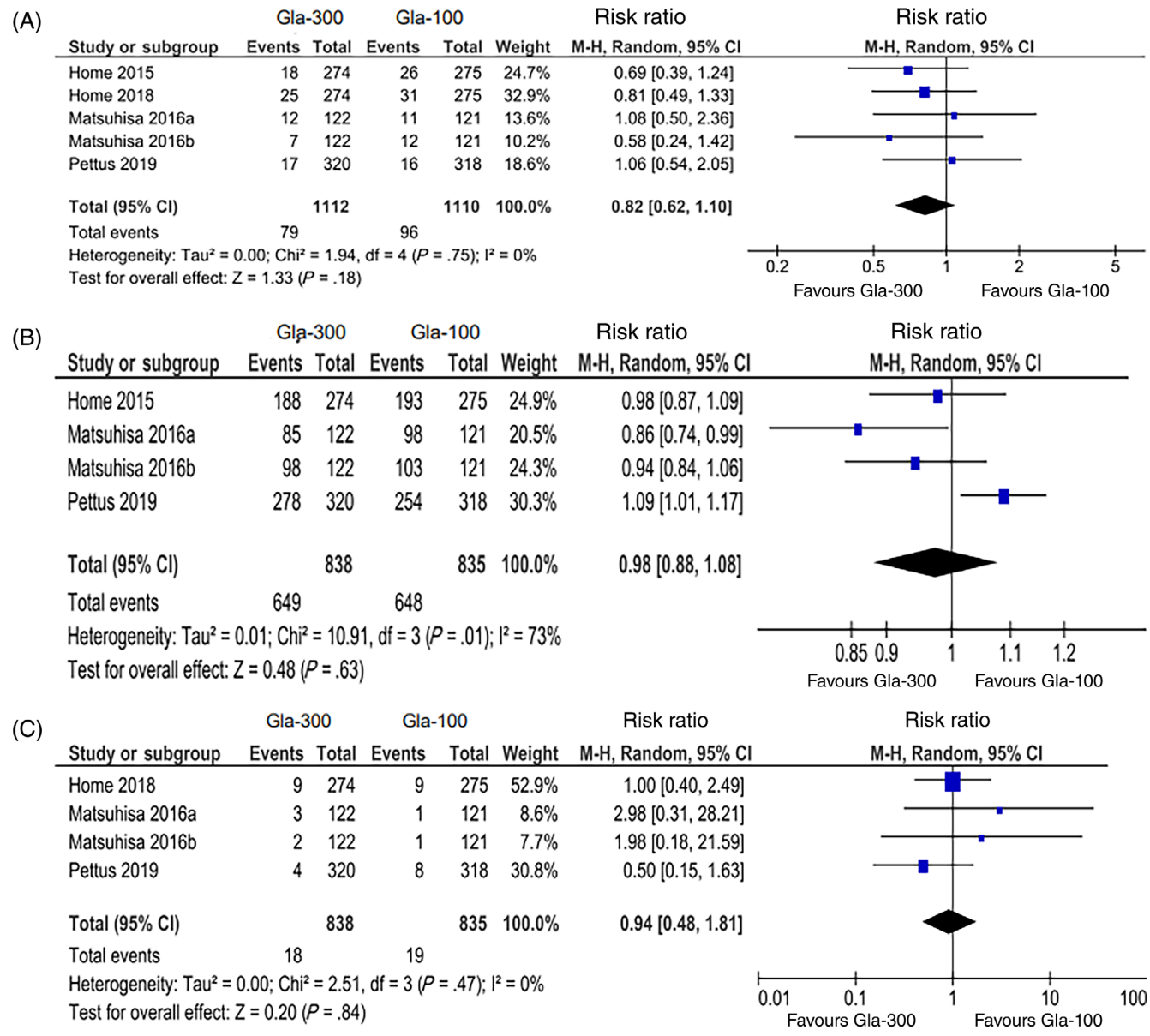
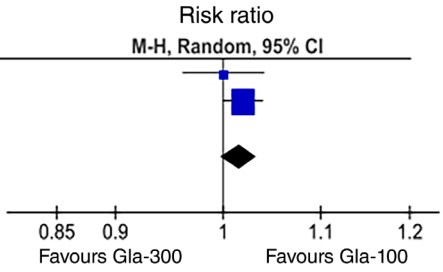


FIGURE 4 A, Severe hypoglycaemic event rates with Gla-300 compared with Gla-100 in trials on T1D patients. Severe hypoglycaemic events are defined as episodes of an abnormally low plasma glucose concentration (≤ 70 mg/dl or lower), require third-part assistance and are ameliorated by normalization of plasma glucose. In severe hypoglycaemia, low blood glucose level (≤ 70 mg/dl, often much lower) may be associated with sufficient neuroglycopaenia to induce seizure or coma. B, Nocturnal hypoglycaemic event rates with Gla-300 compared with Gla-100 in trials on T1D patients. Nocturnal hypoglycaemia is defined as hypoglycaemia (plasma glucose concentration ≤ 70 mg/dl) that occurs during sleep at night (00:00–05:59 hrs). Episodes of nocturnal hypoglycaemia range from asymptomatic to severe and are potentially fatal if untreated. C, Nocturnal severe hypoglycaemic event rates with Gla-300 compared with Gla-100 in trials on T1D patients. D, Total hypoglycaemic event rates with Gla-300 compared with Gla-100 in trials on T1D patients. Total hypoglycaemia events are defined as the sum total of all hypoglycaemic episodes at any time of day (within a 24-hour time frame). Statistical significance was denoted with the corresponding *P*-value < .05 (two-tailed test). E, TESAEs with Gla-300 compared with Gla-100 in trials on T1D patients. F, Withdrawal attributed to AEs with Gla-300 compared with Gla-100 in trials on T1D patients. G, Hypersensitivity reactions with Gla-300 compared with Gla-100 in trials on T1D patients. H, Injection-site reactions with Gla-300 compared with Gla-100 in trials on T1D patients. AEs, adverse events; Chi^2, a statistical test for determining the difference between treatments; CI, confidence interval; Gla-300, Glargine-300; Gla-100, Glargine-100; I^2, measures the percentage variability in the treatment effect estimates that is attributed to between-study heterogeneity rather than chance; SD, standard deviation; Tau, estimated standard deviation in the random-effects model, underlying true effects (Tau^2 is the variance); TESAEs, treatment-emergent serious adverse events; T1D, type 1 diabetes; Z, the significant test for the weighted average effect size, conducted on a population that follows a normal distribution

(D)

Study or subgroup	Gla-300 Events	Total	Gla-100 Events	Total	Weight	Risk ratio M-H, Random, 95% CI
Matsuhisa 2016a	119	122	118	121	19.5%	1.00 [0.96, 1.04]
Pettus 2019	318	320	310	318	80.5%	1.02 [1.00, 1.04]
Total (95% CI)		**442**		**439**	**100.0%**	**1.02 [1.00, 1.03]**
Total events	437		428			

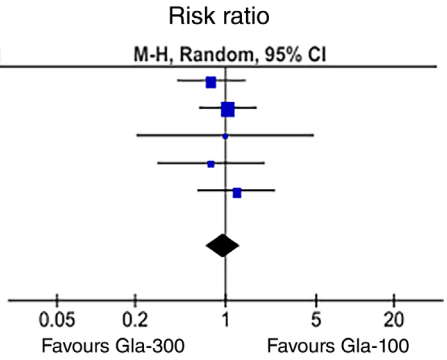
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 1 (*P* = .39); I² = 0%
Test for overall effect: Z = 1.72 (*P* = .09)



(E)

Study or Subgroup	Gla-300 Events	Total	Gla-100 Events	Total	Weight	Risk ratio M-H, Random, 95% CI
Home 2015	17	274	22	275	26.6%	0.78 [0.42, 1.43]
Home 2018	27	274	26	275	37.8%	1.04 [0.62, 1.74]
Matsuhisa 2016a	3	122	3	121	4.0%	0.99 [0.20, 4.82]
Matsuhisa 2016b	7	122	9	121	10.9%	0.77 [0.30, 2.00]
Pettus 2019	17	320	14	318	20.8%	1.21 [0.61, 2.41]
Total (95% CI)		**1112**		**1110**	**100.0%**	**0.96 [0.70, 1.31]**
Total events	71		74			

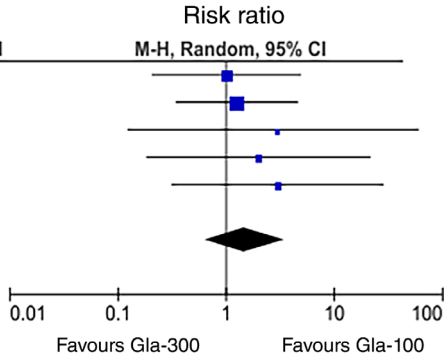
Heterogeneity: Tau² = 0.00; Chi² = 1.19, df = 4 (*P* = .88); I² = 0%
Test for overall effect: Z = 0.26 (*P* = .80)



(F)

Study or Subgroup	Gla-300 Events	Total	Gla-100 Events	Total	Weight	Risk ratio M-H, Random, 95% CI
Home 2015	3	274	3	275	27.2%	1.00 [0.20, 4.93]
Home 2018	5	274	4	275	40.5%	1.25 [0.34, 4.62]
Matsuhisa 2016a	1	122	0	121	6.8%	2.98 [0.12, 72.33]
Matsuhisa 2016b	2	122	1	121	12.1%	1.98 [0.18, 21.59]
Pettus 2019	3	320	1	318	13.5%	2.98 [0.31, 28.51]
Total (95% CI)		**1112**		**1110**	**100.0%**	**1.49 [0.65, 3.41]**
Total events	14		9			

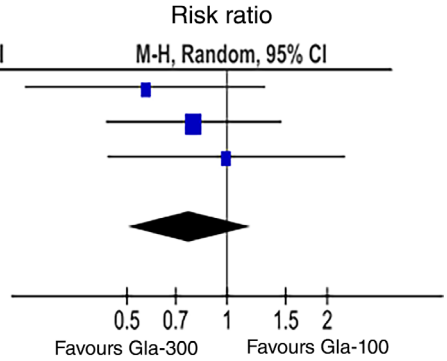
Heterogeneity: Tau² = 0.00; Chi² = 0.91, df = 4 (*P* = .92); I² = 0%
Test for overall effect: Z = 0.94 (*P* = .35)



(G)

Study or Subgroup	Gla-300 Events	Total	Gla-100 Events	Total	Weight	Risk ratio M-H, Random, 95% CI
Matsuhisa 2016a	8	122	14	121	25.6%	0.57 [0.25, 1.30]
Matsuhisa 2016b	16	122	20	121	48.1%	0.79 [0.43, 1.46]
Pettus 2019	11	320	11	318	26.3%	0.99 [0.44, 2.26]
Total (95% CI)		**564**		**560**	**100.0%**	**0.77 [0.51, 1.18]**
Total events	35		45			

Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 2 (*P* = .64); I² = 0%
Test for overall effect: Z = 1.20 (*P* = .23)



(H)

Study or Subgroup	Gla-300 Events	Total	Gla-100 Events	Total	Weight	Risk ratio M-H, Random, 95% CI
Home 2015	6	274	4	275	44.1%	1.51 [0.43, 5.28]
Home 2018	8	274	4	275	49.1%	2.01 [0.61, 6.59]
Matsuhisa 2016b	0	122	0	121		Not estimable
Pettus 2019	1	320	0	318	6.8%	2.98 [0.12, 72.91]
Total (95% CI)		**990**		**989**	**100.0%**	**1.82 [0.79, 4.18]**
Total events	15		8			

Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 2 (*P* = .90); I² = 0%
Test for overall effect: Z = 1.40 (*P* = .16)

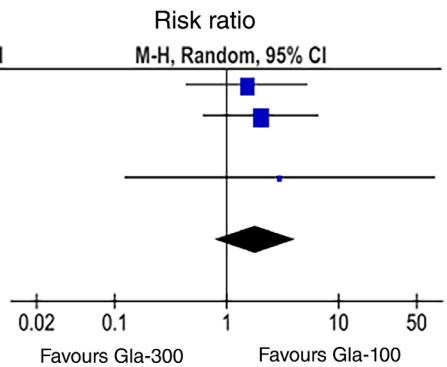


FIGURE 4 (Continued)

with no statistically significant differences in risks (RR: 1.02; 95% CI: 1.00, 1.03; $P = .09$) (Figure 4D). Heterogeneity between the studies was low.

Treatment-Emergent Serious Adverse Events

Five of the included studies assessed TESAEs (N = 2222). Similar rates of events without any statistically significant difference in RR were observed between the two analogues (RR: 0.96; 95% CI: 0.70, 1.31; $P = .80$) (Figure 4E). There was no heterogeneity between the studies.

Withdrawal Because Of AEs

All five of the included studies reported withdrawal because of AEs (N = 2222). A higher number of withdrawals because of AEs was observed with Gla-100 (0.8%) compared with Gla-300 (1.3%), with no statistically significant difference in risks (RR: 1.49; 95% CI: 0.65, 3.41; $P = .35$) (Figure 4F). Heterogeneity between the studies was low.

Hypersensitivity Reactions

Three studies[14,19,23] (N = 1124) investigated the hypersensitivity reactions caused by the interventions. Lower rates of events were observed with Gla-300 compared with Gla-100, with no statistically significant difference in risks (RR: 0.77; 95% CI: 0.51, 1.18; $P = .23$) (Figure 4G). Heterogeneity between the studies was low.

Injection-Site Reactions

Four of the included studies[11,19,20,23] (N = 197) reported injection-site reactions as the most common AEs. Lower incidences of injection-site reactions were observed with Gla-100 compared with Gla-300, with no statistically significant difference in risks (RR: 1.82; 95% CI: 0.79, 4.18; $P = .16$) (Figure 4H). Heterogeneity between the studies was low.

4 | DISCUSSION

In this systematic review with meta-analysis of 15 RCTs, we aimed to assess the comparative efficacy and safety of Gla-100 and Gla-300 for the treatment of 9304 patients in 10 T2D (n = 7082) and five T1D trials (n = 2222). The strengths and limitations of this meta-analysis are listed in Appendix E in Data S1.

No statistically significant differences were observed between Gla-300 and Gla-100 for the efficacy parameters of FPG for the T1D population and of HbA1c for the T2D population. Statistically, but not clinically significant differences, were observed, favouring Gla-100 for HbA1c in T1D and for FPG control in T2D. The EDITION trials reported a weight gain by both treatments that was not of any clinical concern, although with Gla-300 it was statistically significantly less than with Gla-100.[6,17,24] Similarly, in our meta-analysis, weight gain was observed with both Gla-300 and Gla-100. However, it was less with Gla-300 in both T2D and T1D. A pertinent observation was of a difference in dose requirement of basal insulin that was both statistically and clinically significant and in favour of Gla-100 over Gla-300, for both the T1D and T2D populations. Both RCTs and real-world evidence (RWE) studies have shown that the basal insulin doses for Gla-300 needed to achieve equivalent glycaemic control were 10%-20% higher than for Gla-100 in T1D and T2D patients.[8,12,18,21,26-29] This difference is more pronounced in insulin-naïve populations treated with Gla-300 or Gla-100. The reason for the higher dose requirement of Gla-300 may be attributed to its longer duration in the subcutaneous depot than Gla-100, thereby allowing greater enzymatic inactivation of the glargine molecule. Also interesting is the observation that while the mean daily dose of Gla-100 remains unchanged between 6 and 18 months of treatment, the dose requirement of Gla-300 does not plateau even after 18 months of treatment initiation. This is supported by the results of the EDITION clinical trial programme,[8] Spanish RWE study DosInGlar[27] and two open-label, parallel-group, pragmatic studies: REACH and REGAIN.[29] Collectively, this can translate into 13%-15% higher treatment costs on a unit/kg basis, even if the price per unit is equal for both Gla-300 and Gla-100.[27]

In patients with T1D, all safety parameters, including hypoglycaemia, were comparable between Gla-100 and Gla-300. In T2D, no statistically significant differences were observed between Gla-300 and Gla-100 for severe hypoglycaemia, nocturnal severe hypoglycaemia, TESAEs, hypersensitivity reactions and injection-site reactions. Fewer patients withdrew from Gla-100 treatment because of AEs, although this difference was not statistically significant. However, statistically significant differences were observed in favour of Gla-300 for nocturnal hypoglycaemia, confirmed or severe nocturnal hypoglycaemia and total hypoglycaemia. This has been established in three of the four EDITION RCTs and several reviews have captured the EDITION 1, 2, 3, 4 and JP2 data and subgroup analyses in detail.[8,26]

In prior insulin-experienced patients, Gla-300 shows superiority over Gla-100 in reducing the risk of nocturnal hypoglycaemia by 21%-23%,[16,17] with no difference[16] or just a small 10%-14% risk reduction[13,17] in hypoglycaemia at any time of day (24 hours). However, in insulin-naive patients, there is no difference between groups in risk to nocturnal hypoglycaemia.[15] Similar observations were made when real-world outcomes were compared between Gla-300 versus standard-of-care (SoC) basal insulins, including Gla-100, in the REACH (insulin-naïve) and REGAIN (basal insulin-treated) studies in the T2D population. In both REACH (n = 703) and REGAIN (n = 609), no differences in hypoglycaemia outcomes or glycaemic control with Gla-300 versus SoC basal insulins were seen over 12 months.[29] Hence, based on the real-world outcomes, the efficacy and safety outcomes seen in the RCTs may or may not completely reflect in clinical practice and a real-world scenario. Appendix-F and Table-S4 in Data S1 provide real-world outcomes of treating T2D patients with Gla-300 or Gla-100 from the REALITY,[28] REACH CONTROL,[29] REGAIN CONTROL,[29] DosInGlar,[27] DELIVER Naïve[30] and ACHIEVE CONTROL studies.[31,32]

Therapeutic inertia[33,34] observed in clinical practice is a global unmet medical need for diabetes management, one that the American

Diabetes Association and European Association for the Study of Diabetes seek to address through their 2018 consensus report.[35] US Food and Drug Administration-approved, device-supported self-titration is helping to achieve the HbA1c targets sooner with fewer hypoglycaemic events.[36] By alleviating some of the challenges with insulin initiation and dose adjustment, these products facilitate improved glycaemic management and patient outcomes, including fewer incidents of hypoglycaemia.[36,37] In addition, fewer visits to super specialty set-ups lowers the cost incurred by patients and frees up specialists to reach out to more patients through telemedicine.

The importance of appropriate patient population selection and customized treatment also needs to be understood for optimal diabetes care. Patients with higher body weight and patients with insulin resistance not related to higher body mass index, requiring larger insulin doses, can benefit from taking Gla-300 as smaller volumes suffice.[38] Others may still benefit from the first-generation basal insulins and need not be initiated directly on Gla-300 for fear of nocturnal hypoglycaemia. In the EDITION RCTs, in addition to the requirement of lesser insulin dose in the subset of insulin-naïve patients, it was also observed in the subgroup analyses that patients with diabetes duration <10 years and age <65 years had no differences in the rates of nocturnal hypoglycaemia between Gla-300 and Gla-100.[8] Collectively, this creates a population of patients with T2D who are younger than 65 years, with a diabetes duration of less than 10 years and exposed to insulin for the first time (insulin-naïve). This population of patients can be initiated on Gla-100, remain on Gla-100, or be switched back to Gla-100 if initiated on Gla-300, based on the ample data that have been generated through RCTs and RWE studies.[28-32]

One hundred years since its discovery, it is important to ensure that every patient who requires insulin has access to it. Accessibility to high-quality, affordable insulins is a joint responsibility of regulators, payors, healthcare professionals and manufacturers. Review and approval authorities should spur the conduct of comparative effectiveness research and head-to-head meta-analyses to substantiate whether the incremental improvements in newer insulins also lead to improved patient outcomes in the real world. First-generation basal insulins and their biosimilars, especially 'interchangeable' biosimilars, are likely to be the mainstay of diabetes care going ahead.

5 | CONCLUSIONS

In conclusion, in both T1D and T2D populations, Gla-100 and Gla-300 have comparable efficacy and safety profiles. A lower risk of nocturnal and total hypoglycaemia was observed with Gla-300, significant in insulin-experienced/exposed patients with T2D. Patients on Gla-300 required significantly more units of insulin daily than the Gla-100 group to achieve equivalent efficacy, indicating a cost implication. The use of Gla-100 biosimilars may further offset the cost differential, leading to increased accessibility, affordability and adherence and reduced healthcare costs without compromising patient outcomes.

AUTHOR CONTRIBUTIONS

GS, AM, SM, SNA and SRJ designed and conceptualized the study. GS, AM and SM conducted the study and were involved in data collection. SRJ, GS, AM, SM, VRS and SNA were involved in analysis of the data. All the authors were involved in writing, review and approval of the manuscript. SNA, as the guarantor of this work, takes full responsibility for the work, including the systematic literature review and meta-analysis design, data analysis and the decision to submit and publish the manuscript.

ACKNOWLEDGEMENTS

The authors acknowledge Molecular Connections Pvt. Ltd, Bengaluru, India, for running the systematic literature search, supporting the meta-analysis and preparing the preliminary draft of this article, as well as providing editorial support towards its development. This paper was funded by Biocon Biologics Ltd., India.

CONFLICT OF INTEREST STATEMENT

SRJ has received Speaker/Advisory/Research Grants from Abbott, Astra, Biocon, Boeringher Ingelheim, Eli Lilly, Franco Indian, Glenmark, Lupin, Marico, MSD, Novartis, Novo Nordisk, Roche, Sanofi, Serdia and Zydus. GS, AM, SM and SNA are employees of Biocon Biologics Ltd. and hold stocks in Biocon. VRS was employed with Biocon Biologics Ltd. at the time of project conduct and preparation of this manuscript but is no longer employed by Biocon Biologics Ltd. He reports no conflict of interest. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.15007.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Gursharan Singh https://orcid.org/0000-0003-2416-1266

REFERENCES

1. Home, Resources, diabetes L. IDF Diabetes Atlas|Tenth Edition. https://diabetesatlas.org/. Accessed March 3, 2022.
2. Insulin — the new battleground for drug pricing [Editorial]. *Nat Biotechnol*. 2022;40(1):1. doi:10.1038/s41587-021-01203-z
3. Lantus [prescribing information]. Sanofi-Aventis U.S. LLC, NJ, USA. 2018. 021081s072lbl.pdf. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021081s072lbl.pdf. Accessed March 3, 2022.
4. US Food and Drug Administration. Information for Lantus (insulin glargine). Silver Spring, MD, USA: 2015. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/information-lantus-insulin-glargine. Accessed on March 3, 2022.

5. Scheen AJ. INSULIN GLARGINE 300 U/mL (TOUJEO®). *Rev Med Liege*. 2016;71(2):101-107.
6. Bolli GB, Landgraf W, Bosnyak Z, Melas-Melt L, Home PD. Hypoglycaemia risk with insulin glargine 300 U/mL compared with glargine 100 U/mL across different baseline fasting C-peptide levels in insulin-naïve people with type 2 diabetes: a post hoc analysis of the EDITION 3 trial. *Diabetes Obes Metab*. 2020;22(9):1664-1669. doi:10.1111/dom.14065
7. Díez-Fernández A, Cavero-Redondo I, Moreno-Fernández J, Pozuelo-Carrascosa DP, Garrido-Miguel M, Martínez-Vizcaíno V. 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. *Acta Diabetol*. 2019;56(3):355-364. doi:10.1007/s00592-018-1258-0
8. Vargas-Uricoechea H. Efficacy and safety of insulin glargine 300 U/mL versus 100 U/mL in diabetes mellitus: a comprehensive review of the literature. *J Diabetes Res*. 2018;2018:2052101. doi:10.1155/2018/2052101
9. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62(10):1006-1012. doi:10.1016/j.jclinepi.2009.06.005
10. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022)*. Cochrane, 2022. www.training.cochrane.org/handbook. Assessed on March 3, 2022.
11. Home PD, Bergenstal RM, Bolli GB, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 1 diabetes: a randomized, phase 3a, open-label clinical trial (EDITION 4). *Diabetes Care*. 2015;38(12):2217-2225. doi:10.2337/dc15-0249
12. Ritzel R, Harris SB, Baron H, et al. A randomized controlled trial comparing efficacy and safety of insulin glargine 300 units/mL versus 100 units/mL in older people with type 2 diabetes: results from the SENIOR study. *Diabetes Care*. 2018;41(8):1672-1680. doi:10.2337/dc18-0168
13. Terauchi Y, Koyama M, Cheng X, et al. New insulin glargine 300 U/ml versus glargine 100 U/ml in Japanese people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: glucose control and hypoglycaemia in a randomized controlled trial (EDITION JP 2). *Diabetes Obes Metab*. 2016;18(4):366-374. doi:10.1111/dom.12618
14. Matsuhisa M, Koyama M, Cheng X, et al. New insulin glargine 300 U/ml versus glargine 100 U/ml in Japanese adults with type 1 diabetes using basal and mealtime insulin: glucose control and hypoglycaemia in a randomized controlled trial (EDITION JP 1). *Diabetes Obes Metab*. 2016;18(4):375-383. doi:10.1111/dom.12619
15. Bolli GB, Riddle MC, Bergenstal RM, et al. New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naïve people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). *Diabetes Obes Metab*. 2015;17(4):386-394. doi:10.1111/dom.12438
16. Riddle MC, Bolli GB, Ziemen M, Muehlen-Bartmer I, Bizet F, Home PD. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using basal and mealtime insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 1). *Diabetes Care*. 2014;37(10):2755-2762. doi:10.2337/dc14-0991
17. Yki-Järvinen H, Bergenstal R, Ziemen M, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). *Diabetes Care*. 2014;37(12):3235-3243. doi:10.2337/dc14-0990
18. Ji L, Kang ES, Dong X, et al. Efficacy and safety of insulin glargine 300 U/mL versus insulin glargine 100 U/mL in Asia Pacific insulin-naïve people with type 2 diabetes: the EDITION AP randomized controlled trial. *Diabetes Obes Metab*. 2020;22(4):612-621. doi:10.1111/dom.13936
19. Pettus J, Gill J, Paranjape S, et al. Efficacy and safety of a morning injection of insulin glargine 300 units/mL versus insulin glargine 100 units/mL in adult patients with type 1 diabetes: a multicentre, randomized controlled trial using continuous glucose monitoring. *Diabetes Obes Metab*. 2019;21(8):1906-1913. doi:10.1111/dom.13751
20. Home PD, Bergenstal RM, Bolli GB, et al. Glycaemic control and hypoglycaemia during 12 months of randomized treatment with insulin glargine 300 U/mL versus glargine 100 U/mL in people with type 1 diabetes (EDITION 4). *Diabetes Obes Metab*. 2018;20(1):121-128. doi:10.1111/dom.13048
21. Bolli GB, Riddle MC, Bergenstal RM, Wardecki M, Goyeau H, Home PD. Glycaemic control and hypoglycaemia with insulin glargine 300U/mL versus insulin glargine 100U/mL in insulin-naïve people with type 2 diabetes: 12-month results from the EDITION 3 trial. *Diabetes Metab*. 2017;43(4):351-358. doi:10.1016/j.diabet.2017.04.007
22. Terauchi Y, Koyama M, Cheng X, et al. Glycaemic control and hypoglycaemia with insulin glargine 300 U/mL compared with glargine 100 U/mL in Japanese adults with type 2 diabetes using basal insulin plus oral anti-hyperglycaemic drugs (EDITION JP 2 randomised 12-month trial including 6-month extension). *Diabetes Metab*. 2017;43(5):446-452. doi:10.1016/j.diabet.2017.03.001
23. Matsuhisa M, Koyama M, Cheng X, et al. Sustained glycaemic control and less nocturnal hypoglycaemia with insulin glargine 300U/mL compared with glargine 100U/mL in Japanese adults with type 1 diabetes (EDITION JP 1 randomised 12-month trial including 6-month extension). *Diabetes Res Clin Pract*. 2016;122:133-140. doi:10.1016/j.diabres.2016.10.002
24. Yki-Järvinen H, Bergenstal RM, Bolli GB, et al. Glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus insulin glargine 100 U/ml in people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: the EDITION 2 randomized 12-month trial including 6-month extension. *Diabetes Obes Metab*. 2015;17(12):1142-1149. doi:10.1111/dom.12532
25. Riddle MC, Yki-Järvinen H, Bolli GB, et al. One-year sustained glycaemic control and less hypoglycaemia with new insulin glargine 300 U/ml compared with 100 U/ml in people with type 2 diabetes using basal plus meal-time insulin: the EDITION 1 12-month randomized trial, including 6-month extension. *Diabetes Obes Metab*. 2015;17(9):835-842. doi:10.1111/dom.12472
26. Wang F, Zassman S, Goldberg PA. rDNA insulin glargine U300 - a critical appraisal. *Diabetes Metab Syndr Obes Targets Ther*. 2016;9:425-441. doi:10.2147/DMSO.S87873
27. Duque N, Artime E, Romera I, et al. Real-world use of insulin glargine U100 and U300 in insulin-Naïve patients with type 2 diabetes mellitus: DosInGlar study. *Adv Ther*. 2021;38(7):3857-3871. doi:10.1007/s12325-021-01773-z
28. Abitbol A, Brown RE, Jiandani D, Sauriol L, Aronson R. Real-world health outcomes of insulin glargine 300 U/mL vs insulin glargine 100 U/mL in adults with type 1 and type 2 diabetes in the Canadian LMC diabetes patient registry: the REALITY study. *Can J Diabetes*. 2019;43(7):504-509.e1. doi:10.1016/j.jcjd.2019.04.012
29. Freemantle N, Mauricio D, Giaccari A, et al. Real-world outcomes of treatment with insulin glargine 300 U/mL versus standard-of-care in people with uncontrolled type 2 diabetes mellitus. *Curr Med Res Opin*. 2020;36(4):571-581. doi:10.1080/03007995.2019.1708287
30. Bailey TS, Zhou FL, Gupta RA, et al. Glycaemic goal attainment and hypoglycaemia outcomes in type 2 diabetes patients initiating insulin glargine 300 units/mL or 100 units/mL: real-world results from the DELIVER Naïve cohort study. *Diabetes Obes Metab*. 2019;21(7):1596-1605. doi:10.1111/dom.13693
31. Meneghini LF, Sullivan SD, Oster G, et al. A pragmatic randomized clinical trial of insulin glargine 300 U/mL vs first-generation basal insulin analogues in insulin-naïve adults with type 2 diabetes:

6-month outcomes of the ACHIEVE control study. *Diabetes Obes Metab*. 2020;22(11):2004-2012. doi:10.1111/dom.14152
32. Meneghini L, Blonde L, Gill J, et al. Insulin glargine 300 U/mL versus first-generation basal insulin analogues in insulin-naïve adults with type 2 diabetes: 12-month outcomes of ACHIEVE control, a prospective, randomized, pragmatic real-life clinical trial. *Diabetes Obes Metab*. 2020;22(11):1995-2003. doi:10.1111/dom.14116
33. Chan JCN, Gagliardino JJ, Ilkova H, et al. One in seven insulin-treated patients in developing countries reported poor persistence with insulin therapy: real world evidence from the cross-sectional international diabetes management practices study (IDMPS). *Adv Ther*. 2021;38(6):3281-3298. doi:10.1007/s12325-021-01736-4
34. Meneghini LF, Mauricio D, Orsi E, et al. The diabetes unmet need with basal insulin evaluation (DUNE) study in type 2 diabetes: achieving HbA1c targets with basal insulin in a real-world setting. *Diabetes Obes Metab*. 2019;21(6):1429-1436. doi:10.1111/dom.13673
35. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of diabetes (EASD). *Diabetes Care*. 2018;41(12):2669-2701. doi:10.2337/dci18-0033
36. Rossi MC, Nicolucci A, Lucisano G, et al. Impact of the "diabetes interactive diary" telemedicine system on metabolic control, risk of hypoglycemia, and quality of life: a randomized clinical trial in type 1 diabetes. *Diabetes Technol Ther*. 2013;15(8):670-679. doi:10.1089/dia.2013.0021
37. Franc S, Joubert M, Daoudi A, et al. Efficacy of two telemonitoring systems to improve glycaemic control during basal insulin initiation in patients with type 2 diabetes: the TeleDiab-2 randomized controlled trial. *Diabetes Obes Metab*. 2019;21(10):2327-2332. doi:10.1111/dom.13806
38. Cheng AYY, Wong J, Freemantle N, Acharya SH, Ekinci E. The safety and efficacy of second-generation basal insulin analogues in adults with type 2 diabetes at risk of hypoglycemia and use in other special populations: a narrative review. *Diabetes Ther*. 2020;11(11):2555-2593. doi:10.1007/s13300-020-00925-8

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Joshi SR, Singh G, Marwah A, Mittra S, Suvarna VR, Athalye SN. Comparative clinical efficacy and safety of insulin glargine 300 U/ml (Toujeo) versus insulin glargine 100 U/ml in type 2 diabetes and type 1 diabetes: A systematic literature review and meta-analysis. *Diabetes Obes Metab*. 2023;25(6):1589-1606. doi:10.1111/dom.15007