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REVIEW

Twenty Years of Insulin Gla-100: A Systematic Evaluation of Its Efficacy and Safety in Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: This systematic review aims to present the current evidence base with respect to the initiation and intensification of insulin therapy with glargine 100 U/mL (Gla-100) compared to other insulins in people with type 2 diabetes mellitus (T2DM).

Methods: A systematic literature search of PubMed (MEDLINE), EMBASE, and the Cochrane Central Register of controlled clinical trials databases was performed to identify studies published up to September 30, 2020 that compared the effects of Gla-100 to that of other insulin regimens in people with T2DM. Relevant information pertaining to the predefined outcomes of interest was extracted. Glycated hemoglobin (HbA1c) change and response rates along with overall hypoglycemia incidence were the primary efficacy and safety outcomes of interest.

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Results: Seventy-nine studies (63 interventional and 16 non-interventional) in which Gla-100 was either initiated in previously insulin-naïve patients (n = 57) or used in an intensified regimen (n = 22) were identified and evaluated. In insulin-naïve patients, most studies demonstrated that Gla-100 was significantly better compared with premixed insulins and similar compared with neutral protamine Hagedorn (NPH) insulin, second-generation basal insulins, co-formulations, and other first-generation basal insulins in terms of the primary efficacy parameters. Overall hypoglycemia risk with Gla-100 was significantly lower compared with NPH, premixed, coformulation, and other first-generation basal insulins and significantly higher compared with second-generation basal insulins. In studies with intensified regimens, efficacy outcomes with Gla-100 were significantly better compared with insulin detemir (IDet); similar compared with NPH, second-generation basal insulins, co-formulations; and with premixed insulins. In these studies, overall hypoglycemia risk with Gla-100 was significantly lower compared with IDet and comparable to NPH, premixed insulins, co-formulations, and second-generation basal insulins. In addition, most intensification studies also revealed a significantly lower risk of nocturnal hypoglycemia with Gla-100–based regimens versus NPH and premixed insulins and a significantly greater risk compared to second-generation basal insulins.
Conclusions: The evidence presented in this review suggests that Gla-100 is an effective option for both insulin initiation and intensification strategies used in the management of T2DM.

Keywords: Gla-100; Glycemic outcomes; Premixed insulin; Second-generation basal insulin

Key Summary Points

This review highlights the efficacy and safety of Gla-100 in comparison to other insulin preparations in initiation and intensification strategies in type 2 diabetes mellitus (T2DM).

Initiation of Gla-100 in insulin-naïve patients with T2DM failing oral therapies resulted in better glucose-lowering outcomes than premixed insulins and showed comparable results to neutral protamine Hagedorn (NPH), second-generation basal insulins, co-formulations, as well as other first-generation basal insulins.

Most of the studies showed that Gla-100 initiation in insulin-naïve people with T2DM is associated with a lower risk of overall hypoglycemic events compared to other insulin molecules except for second-generation basal insulins.

Intensification of insulin therapy with Gla-100-based regimens in most of the studies showed significantly better glucose-lowering outcomes against insulin detemir (IDet), comparable results to NPH, second-generation basal insulins, co-formulations, and against premixed insulins.

Most of the Gla-100 intensification studies showed comparable overall hypoglycemia risk with all other insulin regimens, but a significantly lower risk of nocturnal hypoglycemia vs. NPH and premixed insulins and a significantly greater risk compared to second-generation basal insulins.

INTRODUCTION

The strategy of using insulin basal analogue as an add-on to oral anti-diabetic drugs (OADs)

was introduced with the intention of optimizing glycemic control and minimizing hypoglycemia and weight gain associated with other existing insulin molecules [1]. Insulin glargine 100 U/mL (Gla-100) was the first basal analog to be approved in 2000 [1]. Ever since its approval, Gla-100 has become one of the most widely studied basal insulin therapies globally, and has emerged as the reference basal insulin to which newer basal insulins are compared [1, 2]. Despite a strong evidence base accumulated from clinical trials as well as real-world studies over the course of two decades, there still exists certain ambiguity over the position of Gla-100 within the insulin landscape.

There is a dearth of systematic reviews that evaluate efficacy and safety of Gla-100 as an initiation therapy in insulin-naïve patients or in those who switched to Gla-100 after being on other insulin regimens. Furthermore, data on the current update with regard to the use of Gla-100 in treatment intensification strategies is scarce in people with T2DM. Therefore, with the purpose of evaluating efficacy and safety of Gla-100 in comparison to other insulin preparations in initiation and intensification strategies, this systematic review aims to shed a light on this voluminous evidence with Gla-100 and will present the evidence to address key questions on the use of Gla-100 from a clinician's perspective. This review will compare Gla-100 with different types of insulin analogs and summarize the glycemic outcomes (glycated hemoglobin [HbA1c] reduction, response rates, blood glucose [BG] profile, and glycemic variability) and safety outcomes (hypoglycemic events, weight change and insulin dose change, and treatment satisfaction).

METHODS

Search Strategy

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines and the methods for systematic reviews as specified by the National Institute for Health and Care Excellence (NICE) in Sect. 2.1 of the Single Technology Appraisal (STA) user guide [3] were followed to identify the clinical evidence through a systematic search of major bibliographic databases. PubMed (MEDLINE), EMBASE, and the Cochrane Central Register of controlled trials databases were separately searched for studies published up to September 30, 2020 in order to identify all publications that compared the effects of the administration of Gla-100 to that of other insulin regimens in patients with T2DM. The following search terms were used in combination with appropriate MeSH terms and Boolean operators (e.g., 'and', 'or', 'not'): insulin, basal insulin, glargine, U-100, long-acting insulin, insulin analog, type 2 diabetes, and T2DM. The search was not restricted by any time period; however, the language of publication was restricted to English (See Table S1 in the electronic supplementary material for detail). This article is based on previously conducted studies and does not contain any new studies with human participants or animals.

Inclusion and Exclusion Criteria

The inclusion criteria of the present systematic review were as follows: (i) adult people (age $\geq$ 18 years) with T2DM either initiating Gla-100 (insulin-naïve patients) or patients switching from other insulin regimens to Gla-100; (ii) studies that compared the effects of the administration of other insulins (premixed, co-formulations, and second-generation basal insulins) with that of Gla-100; (iii) studies that reported reduction in HbA1c, fasting blood glucose (FPG), postprandial blood glucose levels (PPG), weight gain or the proportion of patients achieving targets; hypoglycemic events or increase in insulin dose; (iv) studies conducted as randomized controlled trial (RCT), non-randomized controlled trial or comparative studies, observational studies (prospective or retrospective design), case–control studies and cross-sectional studies with $\geq$ 50 patients and (v) study duration of a minimum of 3 weeks. Furthermore, studies for treatment initiation were included and segregated into those with insulin-naïve patients and those with patients who were inadequately controlled on OADs and had

to be treated with insulin or combination of OADs with insulin. For insulin intensification studies, patients switching to a basal-bolus or any other regimen, including biphasic or premixed insulins with Gla-100 as a component, were considered eligible.

The exclusion criteria were as follows: (i) studies enrolling people with type 1 diabetes mellitus (T1DM) or other diseases or a mixed population of patients with both T1DM and T2DM were excluded unless separate subgroup data was presented for people with T2DM; (ii) single-arm studies or studies comparing the effects of Gla-100 with OADs or any injectable therapy other than insulin; (iii) case reports, letters to editors, abstracts, or proceedings of scientific meetings; and (iv) studies published in non-English language.

Screening of Eligible Studies

All references identified through literature searches were imported and duplicates were removed to evaluate the study for full-text eligibility. The study selection was instrict compliance with the pre-determined inclusion and exclusion criteria. Each of the retrieved documents was assessed for eligibility as per the selection process detailed in Fig. 1.

Outcomes

The outcomes of interest in this study varied on the basis of study type. For RCTs, the main outcomes were reduction in HbA1c, change in FPG, PPG, and response rates. Similarly, HbA1c reduction and response rates were the main outcomes of interest for observational studies. Other outcomes of interest irrespective of study type were rate of hypoglycemic events (nocturnal or overall), percentage weight gain, and change in insulin dose from baseline to the end of study. Among all the aforementioned outcomes, HbA1c change and response rates were the primary glycemic outcomes of interest and overall hypoglycemic events were the primary safety outcomes of interest.

Data Extraction

A predefined data extraction grid was developed in Microsoft Excel to extract data on study characteristics and outcomes. All relevant information from the eligible studies was extracted, which included study design, study duration, country, sample size, comorbid conditions, previous treatments, change in clinical parameters (including HbA1c, FPG, PPG, weight), changes in insulin regimen, as well as safety outcomes (hypoglycemic events); and their corresponding p values and 95% confidence interval (CI), whenever reported.

Quality Assessment

The quality of observational studies (cohort/cross-sectional studies) was assessed by using Newcastle–Ottawa Scale (NOS), whereas the quality of RCTs was assessed using the Cochrane Risk of Bias tool (CRBT) [4, 5].

RESULTS

Study Search

As shown in the study flow diagram (Fig. 1), the search yielded 13,942 hits; of which 79 studies were included in the final list for data extraction, including 63 interventional and 16 non-interventional studies. There were 57 studies (Table 1) wherein Gla-100 was initiated in either insulin-naïve or previously Gla-100 -naïve patients [6–62]and 22 studies (Table 2) wherein Gla-100 was used in an intensified regimen [63–85].

Study and Patient Characteristics

Initiation

In the 57 studies reporting the results of efficacy and safety of insulin initiation, the mean HbA1c level at baseline was > 8% with values ranging from 7.55 [6] to 10.3% [7]. The mean (SD) baseline FPG value ranged from 133.2 (34.2) mg/dL [8] to 194.4 mg/dL [9], whereas the baseline PPG value was reported in only five studies and ranged from 205.2 (61.2) mg/dL [10]

to 363.78 (110.34) mg/dL [11]. Similarly, the mean (SD) bodyweight of included patients ranged from 61.9 (9.29) kg [12] to 108 (25.7) kg [13] (Table 3) [6–62].

The most frequently used insulin analogs were Gla-100, NPH insulin, insulin degludec (IDeg), insulin lispro 75/25 mix and premixed insulins. The mean (SD) recorded baseline insulin dose varied from 0.11 (0.02) U/kg/day [53] to 77.6 (32.1) U/kg/day [34]. Several studies evaluated the efficacy and safety profile of Gla-100 given with one or more OAD therapy (such as acarbose, glimepiride, metformin [MET], sulphonylurea [SU]) to determine the best analog for initiation of insulin therapy among insulin-naïve patients.

Intensification

In the 22 studies reporting the results of efficacy and safety of insulin intensification with a basal or biphasic insulin regimen, the mean HbA1c level at baseline in majority of the studies was between 8 and 9% with values ranging from 8.0 (0.9) [63] to 9.5 (1.2) [67]. Out of the 22 studies, only nine reported mean (SD) baseline FPG values that ranged from 108 (28.8) mg/dL [65] to 207 (75.6) mg/dL [66], whereas the baseline PPG value was reported in three studies [67–69]. Similarly, the mean (SD) body weight of included patients ranged from 69.3 (15.1) kg [70] to 106.4 (20) kg [71] (Table 4).

Besides Gla-100 (either with other insulin or in combination with OADs), the other most

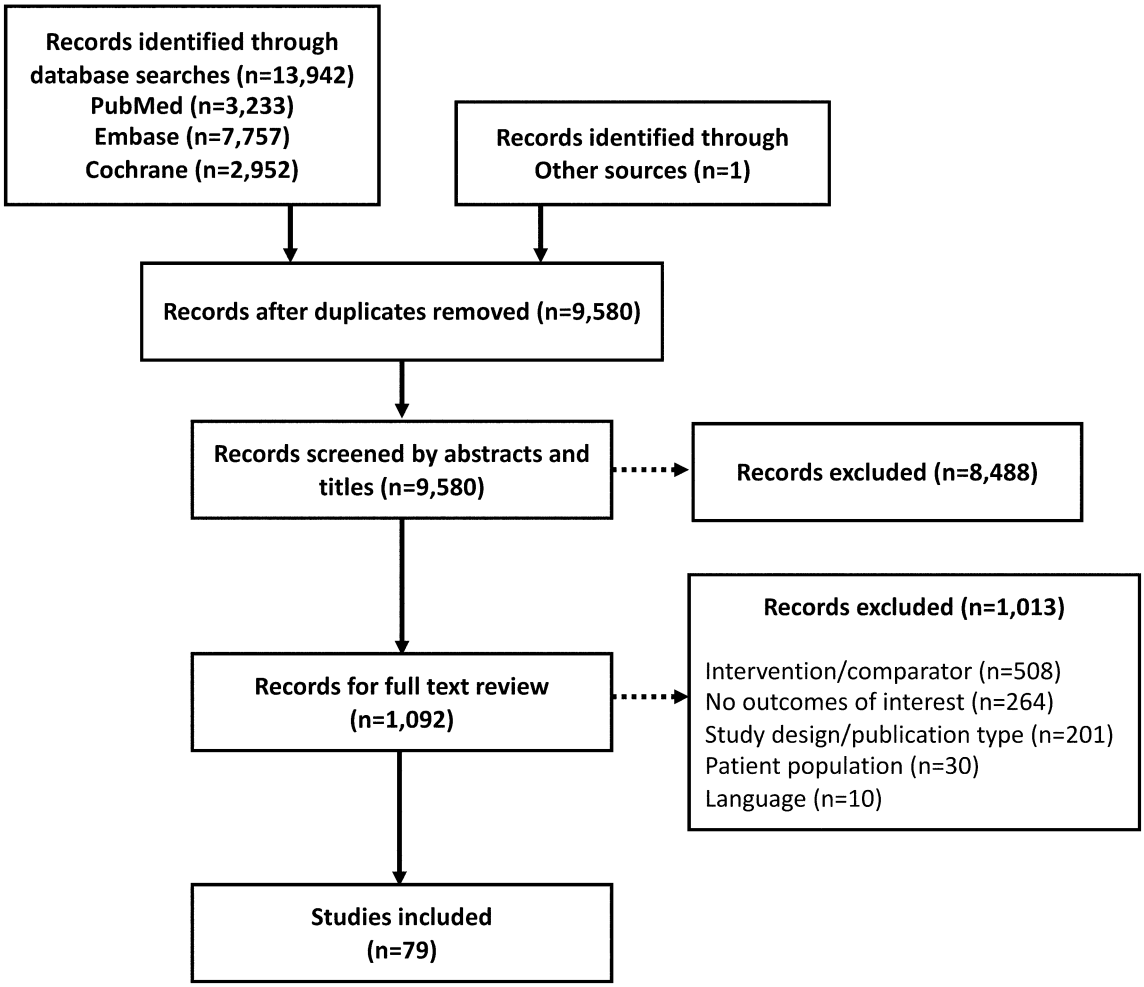

Fig. 1 PRISMA flow diagram

Table 1 Summary of included studies (initiation)

Author (year)	Study design; *n* (total)	Study duration in months[a] (weeks)	Intervention; *n* (each arm)	Age (years), mean (SD if available)	Sex (female), *n* (if available) (%)	Disease duration (years), mean (SD if available)
Gla-100 vs. NPH insulin						
Fiesselmann, 2016 [14]	Retrospective study; 1917	6–9 (24)	Gla-100 OD + OADs; 285 (PSM matched cohort)	63.7 (11.2)	133 (47.4)	5.5 (2.6)
			Insulin NPH OD / BD + OADs; 285 (PSM matched cohort)	64.4 (10.7)	131 (46.5)	5.3 (2.6)
Home PD, 2014 [15]	RCT; 701	9–12 (38)	Gla-100 + OADs; 352	57.3 (8.3)	198 (56.2)	9.1 (5.5)
			Insulin NPH + OADs; 349	57.2 (7.8)	195 (55.9)	9.4 (5.7)
Delgado E, 2012 [16]	Retrospective study; 1482	3–12 (17–39 [time of switch from NPH to Gla-100 to the study visit])	Gla-100 OD + OADs; 976	61.9 (11)	483 (49.5)	10.2
			Insulin NPH OD / BD + OADs; 506	64.3 (11.4)	276 (54.5)	12.4
Hsia SH, 2011 [17]	RCT; 85	6–9 (28)	Gla-100 HS + OADs; 30	50.3 (11.2)	15 (50.0)	9 (5.9)
			Gla-100 morning + OADs; 25	53 (8.6)	13 (52.0)	9.5 (5.2)
			Insulin NPH + OADs (previous); 30	53.2 (7.7)	21 (70.0)	7.8 (4.2)
Mu P, 2011 [18]	RCT; 250	3–6 (12)	Gla-100 OD + OADs; 124	40.3 (8.5)	69 (55.6)	4.9 (2.6)
			Insulin NPH + OADs; 126	40.6 (8.3)	74 (58.7)	4.7 (2.4)
Mattia, 2009 [19]	RCT; 20	3–6 (15)	Sequence A (Gla-100 followed by NPH insulin); 9	59.4 (8.2)	6 (30.0)	–
			Sequence B (NPH insulin followed by Gla-100); 11			
Pan, 2007 [20]	RCT; 443	6–9 (28)	Gla-100 + glimepiride 3 mg; 220	55.6 (8.4)	131 (59.6)	10.3 (6.3)
			Insulin NPH + glimepiride 3 mg; 223	56.6 (8.7)	124 (55.6)	10 (5.4)
Yki-Jarvinen, 2006 [21]	RCT; 110	9–12 (40)	Gla-100 + metformin; 61	56.0 (1.0)	23 (38)	9 (1)
			Insulin NPH + metformin; 49	57 (1)	17 (35)	9 (1)

Table 1 continued

Author (year)	Study design; *n* (total)	Study duration in months[a] (weeks)	Intervention; *n* (each arm)	Age (years), mean (SD if available)	Sex (female), *n* (if available) (%)	Disease duration (years), mean (SD if available)
Eliaschewitz, 2006 [22]	RCT; 481	6–9 (28)	Gla-100 + glimepiride 4 mg; 231	56.1 (9.9)	132 (57.1)	10.3 (6.4)
			Insulin NPH + glimepiride 4 mg; 250	57.1 (9.6)	155 (62.0)	10.8 (6.4)
Shi, 2004 [23]	RCT; 56	6–9 (24)	Gla-100 + glipizide GITS 5 mg; 42	60.13 (7.14)	20 (48)	7.13 (3.13)
			Insulin NPH + glipizide GITS 5 mg; 14	62.15 (5.16)	410 (72)	7.11 (4.11)
Benedetti, 2003 [24]	RCT; 570	> 12 (56)	Gla-100 OD + OADs; 289	59.6 (9.3)	135 (46.7)	10.2 (6.2)
			Insulin NPH OD / BD + OADs; 281	59.4 (9.1)	129 (45.1)	10.5 (6)
Riddle, 2003 [25]	RCT; 756	6–9 (28)	Gla-100 + OADs; 367	55 (9.5)	166(45)	8.4 (5.55)
			Insulin NPH + OADs; 389	56 (8.9)	171(44)	9 (5.57)
Yki-Jarvinen, 2000 [26]	RCT; 422	> 12 (56)	Gla-100 + OADs; 214	59 (1)	97 (45)	10 (1)
			Insulin NPH + OADs; 208	59 (1)	98 (47)	10 (1)
Gla-100 vs. premixed insulins						
Petrovski, 2018 [27]	Observational, prospective, switch study; 1041	6–9 (24)	Human/analog premixed alone switched to Gla-100 OD ± OADs	61.8 (9.31)	606 (58.2)	11.4 (6)
Zhang, 2017 [28]	Observational, prospective, switch study; 1847	3–6 (16)	Human/analog premixed ± OADs switched to Gla-100 OD + OADs	56.3 (11)	816 (44.2)	8.5 (6.2); duration of prior premixed use: 24.5 (27.4) months
Cao, 2017 [29]	RCT; 65	3–6 (16)	Gla-100 OD + 100 mg; 33	52.1 (9.6)	15 (46.6)	5.7 (3.6)
			Insulin aspart 30 BD; 32	49.8 (11.2)	16 (49.8)	6.4 (4.1)

Table 1 continued

Author (year)	Study design; *n* (total)	Study duration in months[a] (weeks)	Intervention; *n* (each arm)	Age (years), mean (SD if available)	Sex (female), *n* (if available) (%)	Disease duration (years), mean (SD if available)
Sehgal S, 2015 [7]	Retrospective study; 337	> 12 (52)	Human NPH + OADs (previous); 273	55.7 (13.9)	134 (49.1)	10.6 (6.7)
			Gla-100 OD + OADs (previous); 24	59.2 (16.5)	9 (37.5)	9.2 (6.6)
			Biphasic human premixed insulin + OADs (previous); 42	56.7 (11.4)	21 (50.0)	12 (9.8)
Zhang Y, 2014 [12]	Observational, prospective, switch study; *n* = 70	3–6 (20)	Human/analog premixed insulin alone switched to Gla-100 OD ± OADs	59.95 (10.21)	37 (52.8)	7.78 (2.95); Premixed therapy duration—3.21 (0.87)
Sun, 2014 [11]	RCT; 188	6–9 (32)	Gla-100 + acarbose TID; 94	68.2 (6.6)	48 (51.1)	7.5 (4)
			Novolin 30R (Human) BD; 94	70.3 (5.7)	51 (54.2)	6.8 (2.8)
Sakharova OV 2013 [30]	RCT; 14	3–6 (24)	Gla-100 + OADs	61 (12)	5 (35.7)	11 (6)
			Lispro mix 75/25 + OADs	-	-	-
Kalra, 2010 [31]	RCT; 155	6–9 (30)	Gla-100 + MET + SU (glimepiride); 79	51.58 (10.14)	48 (61)	8.6 (5.79)
			BI-Asp 30 + MET + SU (glimepiride); 76	51.95 (9.07)	46 (61)	8.62 (6.17)
Strojek, 2009 [32]	RCT; 469	6–9 (30)	Gla-100 + MET + SU (glimepiride); 231	56.1 (10)	140 (58.8)	9.5 (6.1)
			BI-Asp 30 + MET + SU (glimepiride); 238	55.9 (9.7)	123 (53.2)	9.1 (5.8)
Buse, 2009 [33]	RCT; 2091	6–9 (26)	Gla-100 + OADs (previous); 1046	57 (10)	493(47.2)	9.3 (5.9)
			Lispro mix 75/25 + OADs (previous); 1045	57 (10)	494(47.2)	9.7 (6.3)

Table 1 continued

Author (year)	Study design; *n* (total)	Study duration in months[a] (weeks)	Intervention; *n* (each arm)	Age (years), mean (SD if available)	Sex (female), *n* (if available) (%)	Disease duration (years), mean (SD if available)
Schiel, 2007 [34]	RCT; 52	3–6 (20)	Grp A: Gla-100 OD + glimepiride OD; 17	61.7 (10.7)	9 (53)	15.3 (8.4)
			Grp B: Gla-100 OD + glimepiride OD + MET BD; 18	65.4 (8.5)	8 (44)	14.2 (8)
			Grp C: Human premixed insulin 75/25 or 70/39; 17	69.8 (6.4)	8 (47)	16.3 (6.7)
Robbins, 2007 [35]	RCT; 315	6–9 (32)	Gla-100 OD + MET BD; 158	58.1 (8.9)	80 (50.6)	12.5 (6.8)
			Lispro mix 75/25 BD + MET BD; 157	57.4 (9.2)	78(49.7)	11.3 (5.8)
Raskin, 2007 [36]	RCT; 157	6–9 (28)	Gla-100 OD + MET; 78	51.7 (9.8)	36 (46.2)	-
			BiAsp 70/30 BD + MET; 79	52 (11)	38 (48.1)	-
Jacober, 2006 [37]	RCT; 60	6–9 (32)	Sequence A (16 weeks Gla-100 followed by 16 weeks premixed insulin 50/50 lispro mix pre-breakfast and 25/75 lispro mix pre-dinner); 29	54.9 (10)	26 (43.3)	8.4 (4.9)
			Sequence B (16 weeks premixed insulin 50/50 lispro mix pre-breakfast and 25/75 lispro mix pre-dinner followed by 16 weeks Gla-100); 31			
Kazda, 2006 [10]	RCT; 159	6–9 (26)	Lispro 50% TID; 52	60.4 (8.6)	20 (38.4)	5.3 (2.8)
			Lispro mid-mixture (50% lispro / 50% NPL); 54	58.7 (10.2)	22 (40.74)	5.9 (3)
			Gla-100 OD; 53	59.1 (9.6)	30 (56.60)	5.5 (2.8)
Roach, 2006 [13]	RCT; 20	6–9 (25)	Sequence A—Gla-100 OD + OADs followed by insulin lispro 25/75 BD + OADs; *n* = 10	53.5 (10.7)	10 (50)	-
			Sequence B—Insulin lispro 25/75 BD + OADs followed by Gla-100 OD + OADs; 10			

Table 1 continued

Author (year)	Study design; *n* (total)	Study duration in months[a] (weeks)	Intervention; *n* (each arm)	Age (years), mean (SD if available)	Sex (female), *n* (if available) (%)	Disease duration (years), mean (SD if available)
Bullano, 2006 [38]	Retrospective study; 2315	–	Gla-100 group; *n* = 1212	52 (14)	548 (46)	13.4 (7.8)
			Premixed insulin group (70 NPH or long-acting insulin: 30 units of short-acting or rapid-acting insulin); 1103	55 (13)	539 (48.9)	14 (8.5)
Janka, 2005 [39]	RCT; 364	6–9 (28)	Gla-100 + OADs (glimepiride + metformin); 177	60.9 (8.7)	69 (39)	9.9 (7.3)
			Human premixed insulin (30% regular, 70%	60.4 (9.1)	80 (43)	9.9 (6.4)
			NPH insulin; insulin actraphane HM 30/70); 187			
Raskin 2005 [40]	RCT; 209	6–9 (28)	BiAsp 70/30 BD + OADs; 117	52.6 (10.6)	47 (40.1)	9.5 (5.9)
			Gla-100 OD + OADs; 116	52.3 (9.8)	44 (37.9)	8.9 (4.8)
Malone, 2004 [41]	RCT; 105	9–12 (40)	Sequence A (Gla-100 HS + MET 1500–2550 mg/day followed by lispro mix 75/25 + MET 1500–2550 mg/day)	55.3 (9.5)	20 (37.7)	9.8 (7.4)
			Sequence B (lispro mix 75/25 + MET 1500–2550 mg/day followed by Gla-100 HS + MET 1500–2550 mg/day)	54.5 (11.4)	19 (36.5)	8.1 (5.8)
Gla-100 vs. Second-generation basal insulins						
Bailey, 2019 [42]	Retrospective cohort study; 3012	6–9 (26)	Gla-300 OD + OADs; 1004	60.2 (12.3)	481 (48)	-
			Gla-100 OD + OADs; 2008	60.5 (12.3)	928 (46)	-
Gupta, 2018 [43]	Retrospective cohort study; 553	6–9 (26)	Gla-100 OD + OADs; 92	54.4 (13.1)	36 (39.1)	11.1 (8.6)
			Gla-300 OD + OADs; 298	53.6 (11.9)	142 (47.7)	10.9 (9.5)
			Switched to Gla-300 OD + OADs; 163	56.3 (10.3)	67 (41.1)	13.3 (8.1)

Table 1 continued

Author (year)	Study design; *n* (total)	Study duration in months[a] (weeks)	Intervention; *n* (each arm)	Age (years), mean (SD if available)	Sex (female), *n* (if available) (%)	Disease duration (years), mean (SD if available)
Nakanishi, 2018 [6]	Retrospective observational switch study; 122	3–6 (12)	Switched to Gla-300 OD ± OADs; 62	62.1 (14.7)	26 (42)	–
			Gla-100 OD ± OADs; 60	70.3 (9.2)	27 (45)	–
Marso, 2017 [44]	RCT; 7637	> 12 (104 [30 days follow-up])	IDeg OD ± OADs; 3818	64.9 (7.3)	1422 (37.2)	16.6 (8.8)
			Gla-100 OD ± OADs; 3819	65 (7.5)	1437 (37.6)	16.2 (8.9)
Wysham, 2017 [45]	RCT; 721	> 12 (65)	Sequence B- IDeg OD ± OADs followed by Gla-100 ± OADs; 361	61.5 (10.7)	169 (47)	14.2 (8.3)
			Sequence A—Gla-100 OD ± OADs followed by IDeg OD ± OADs; 360	61.2 (10.3)	169 (47)	13.9 (8)
Pan, 2016 [46]	RCT; 833	6–9 (26)	IDeg 100 OD + MET; 555	55.9 (9.7)	256 (46.1)	7.55 (5.28)
			Gla-100 OD + MET; 278	56.6 (9.2)	146 (52.5)	8.26 (5.45)
Ghoshal, 2016 [47]	Retrospective cohort study; 64	6–9 (24)	IDeg 100 OD + OADs; 33	56.09 (13.59)	14 (42.4)	12.15 (7.19)
			Gla-100 OD + OADs; 31	58.97 (11.32)	13 (42)	9.93 (3.98)
Terauchi, 2016 [8]	RCT; 241	6–9 (26)	Gla-300 OD ± OADs; 121	61.1 (10.8)	44 (36.36)	14 (8)
			Gla-100 OD ± OADs; 120	60.5 (12)	50 (41.67)	13.9 (8.7)
Bolli, 2015 [48]	RCT; 878	6–9 (26)	Gla-300 OD + OADs—SUs / glinides; 439	58.2 (9.9)	186 (42)	10.1 (6.5)
			Gla-100 OD + OADs—SUs / glinides; 439	57.2 (10.3)	185 (42)	9.6 (6.2)

Table 1 continued

Author (year)	Study design; *n* (total)	Study duration in months[a] (weeks)	Intervention; *n* (each arm)	Age (years), mean (SD if available)	Sex (female), *n* (if available) (%)	Disease duration (years), mean (SD if available)
Yki-Jarvinen, 2014 [49]	RCT; 811	6–9 (26)	Gla-300 OD ± OADs; 404	57.9 (9.1)	217 (53.7)	12.7 (7.1)
			Gla-100 OD ± OADs; 407	58.5 (9.2)	222 (54.5)	12.5 (7.0)
Gough SC, 2013 [50]	RCT; 457	6–9 (26)	IDeg -200 + MET ± DPP-4; 228	57.8 (9)	109 (47.8)	8.4 (6.7)
			Gla-100 OD + MET ± DPP-4 inhibitors; 229	57.3 (9.4)	105 (45.9)	8 (5.6)
Onishi Y 2013 [51]	RCT; 435	6–9 (26)	IDeg OD + OADs—DPP-4 inhibitors; 289	58.8 (9.8)	131 (45.3)	11.8 (6.5)
			Gla-100 OD + OADs—DPP-4 inhibitors; 146	58.1 (10.1)	71 (48.6)	11.1 (6.5)
Meneghini L 2013 [52]	RCT; 687	6–9 (26)	IDeg OD Flex; 229	56.2 (10.3)	94 (41)	10.8 (6.9)
			IDeg OD in morning; 228	56.5 (9.6)	104 (46)	10.3 (6.7)
			Gla-100 OD; 230	56.7 (8.8)	119 (52.0)	10.8 (6.4)
Zinman B, 2012 [53]	RCT; 1030	> 12 (52)	IDeg -100 + MET ± DPP-4; 257	59.3 (9.7)	302 (39.1)	9.4 (6.3)
			Gla-100 OD + MET ± DPP-4 inhibitors; 773	58.7 (9.9)	90 (35.0)	8.6 (5.7)
Gla-100 vs. Co-formulations						
Kumar, 2017 [54]	RCT; 463	6–9 (26)	IDegAsp OD + metformin ± pioglitazone ± dipeptidyl peptidase-	57.8 (9.5)	41.3	11.6 (6.8)
			4 inhibitors; 233			
			Gla-100 OD + metformin ± pioglitazone ± dipeptidyl peptidase-	58.4 (10.1)	45.5	11.4 (7.3)
			4 inhibitors; 233			
Kumar, 2016 [55]	RCT; 529	> 12 (53)	IDegAsp OD + MET; 266	57.4 (9.0)	53	8.7 (6.1)
			Gla-100 OD + MET; 263	56.4 (9.2)	48.3	9.6 (6.1)

Table 1 continued

Author (year)	Study design; *n* (total)	Study duration in months[a] (weeks)	Intervention; *n* (each arm)	Age (years), mean (SD if available)	Sex (female), *n* (if available) (%)	Disease duration (years), mean (SD if available)
Onishi 2013 [56]	RCT; 296	6–9 (26)	IDegAsp + OADs minus DPP-4 inhibitors / SU / glinides; 147	60 (10.0)	57 (39.0)	10.9 (7.3)
			Gla-100 OD + OADs minus DPP-4 inhibitors / SU / Glinides; 149	61 (9.6)	51 (34.0)	12.4 (8.6)
Gla-100 vs. other basal insulins						
Cander S, 2014 [57]	RCT; 64	3–6 (12)	IDet OD + MET + SU; 22	57	15 (68)	6.5
			IDet BD + MET + SU; 22	54	7 (32)	7
			Gla-100 OD + MET + SU; 20	59	13 (65)	7
Odawara M, 2014 [58]	Prospective, observational study; 4219	6–9 (24)	Gla-100 OD + OADs (insulin-naïve); 3732	62.6 (12.1)	1495 (40)	–
			Gla-100 OD + OADs (insulin non-naïve); 487	64 (12.1)	239 (49)	–
Wei W, 2014 [59]	Retrospective, observational switch study; 5291	3–6 (12)	Cohort 2—Det-C Impact (Det OD continued); 780	60.8 (11.8)	388 (49.7)	–
			Cohort 1—Det-S Impact (Det OD switched); 536	53.8 (11.7)	262 (48.9)	–
			Cohort 1—Gla-C Impact (Gla-100 OD continued); 2668	53.5 (11.8)	1251 (46.9)	–
			Cohort 1—Det-S Humana (Det OD switched); 256	72.6 (5.4)	143 (55.9)	–
			Cohort 1—Gla-C Humana (Gla-100 OD continued); 1262	73 (5.6)	692 (54.8)	–
			Cohort 2—Gla-S Impact (Gla-100 OD switched); 419	60.9 (11.7)	222 (53.0)	–

Table 1 continued

Author (year)	Study design; *n* (total)	Study duration in months[a] (weeks)	Intervention; *n* (each arm)	Age (years), mean (SD if available)	Sex (female), *n* (if available) (%)	Disease duration (years), mean (SD if available)
Meneghini L, 2013 [60]	RCT; 453	6–9 (28)	Det OD + MET; 226	57.3 (10.2)	57	8 (5.6)
			Gla-100 OD + MET; 227	57.3 (10.3)	56	8.4 (6.6)
Esposito, 2008 [61]	RCT; 110	9–12 (40)	Gla-100 OD + OADs minus night time SU, replaced with MET	54.9 (6.9)	26 (47.3)	8.2 (5.3)
			Human NPL OD + OADs minus night time SU, replaced with MET	53.8 (7.1)	27 (49.1)	7.8 (5.4)
Rosenstock, 2008 [9]	RCT; 582	> 12 (52)	IDet OD + OADs; 291	58.4 (10.2)	125 (42.95)	9.1 (6.1)
			Gla-100 OD + OADs; 291	59.4 (9.6)	120 (41.23)	9.1 (6.4)
Malone, 2005 [62]	RCT; 97	9–12 (38)	Seq A—Gla-100 OD + MET followed by lispro mix 75/25 BD; 47	59.63 (8.03)	29 (62.0)	11.9 (6.27)
			Seq B—lispro mix 75/25 BD + MET followed by Gla-100 OD; 50	59.18 (8.58)	25 (50.0)	13.52 (8.18)

BD twice daily, *Gla-100* glargine-100, *IDeg* insulin degludec, *MET* metformin, *NPH* neutral protamine Hagedorn, *OADs* oral anti-diabetics, *OD* once daily, *RCT* randomized clinical trial, *SU* sulfonylurea, *TID* thrice a day

[a]Study duration in months categorization was done for the ease of interpretation; however, actual study duration is specified in the brackets

Table 2 Summary of included studies (intensification)

Author (year)	Study design	Study duration in months (weeks)[a]	Intervention	Age (years), mean (SD)	Sex (female), *N* (if available) (%)	Disease duration (years), mean (SD)	Duration of prior insulin therapy (years), mean (SD)
Gla-100 vs. NPH							
Betonico, 2019 [72]	RCT; 34	9–12 (48)	Sequence A- Gla-100 OD + insulin lispro TID for 24 weeks followed by insulin NPH + lispro TID; 16	63 (7.0)	4 (25.0)	19 (11.6)	–
			Sequence B- Insulin NPH + insulin lispro TID for 24 weeks followed by Gla-100 OD + lispro TID; 18	60 (8.7)	7 (39.0)	19 (7.0)	–
Rosenstock, 2001 [73]	RCT; 518	6–9 (32)	Gla-100 OD ± premeal regular insulin; 259	59.5 (9.7)	109 (42.1)	13.4 (8.3)	8.4 (6.9)
			NPH insulin OD / BD ± premeal regular insulin; 259	59.2 (9.9)	98 (37.8)	14.1 (9)	8.3 (7.6)
Gla-100 vs. premixed							
Aschner, 2015 [74]	RCT; 923	6–9 (26)	Gla-100 OD + glulisine OD before main meal + MET ± SU; 462	56.7 (9.0)	231 (50.0)	9.1 (6.0)	–
			Premixed insulin BD MET ± SU; 461	55.8 (9.5)	221 (47.9)	8.8 (5.8)	–
Tinahones, 2014 [75]	RCT; 476	6–9 (26)	Insulin lispro mix BD + MET ± pioglitazone; 236	57.4 (9.9)	120 (51.8)	12.2 (7.7)	–
			Gla-100 OD + insulin lispro OD + MET ± pioglitazone; 240	57.7 (9.1)	142 (59.1)	11.3 (6.8)	–
Ito H, 2014 [71]	Prospective cohort study; 27	3–6 (16)	Human premixed insulin 50/50 switched to Gla-100 OD + glulisine BD	62 (16.0)	8 (29.6)	14 (8.0)	4 (3.8)

Table 2 continued

Author (year)	Study design	Study duration in months (weeks)[a]	Intervention	Age (years), mean (SD)	Sex (female), *N* (if available) (%)	Disease duration (years), mean (SD)	Duration of prior insulin therapy (years), mean (SD)
Jain, 2010 [67]	RCT; 383	6–9 (36)	Gla-100 OD + mealtime lispro TID; 195	59.9 (9.6)	94 (48.2)	12 (7.3)	–
			Insulin lispro mix 50/50 TID; 188	58.9 (8.8)	102 (54.3)	11.4 (5.6)	–
Rosenstock, 2008 [76]	RCT; 374	6–9 (24)	Premixed TID (lispro mix 50:50) + OADs (minus SU + glinides); 187	55.4 (9.8)	88 (47.0)	10.9 (6.3)	–
			Gla-100 OD + insulin lispro TID + OADs (minus SU + glinides); 187	54 (9.2)	89 (48.0)	11.2 (6.2)	–
Joshi, 2005 [70]	Prospective observational cohort study; 145	3–6 (12)	Premixed insulin analog (NovoMix 30) BD; 114	52.41 (10.04)	38 (33.3)	9.53 (5.08)	–
			Gla-100 OD + insulin aspart TID; 31	51.1 (14.04)	7 (22.5)	11.98 (9.01)	–
Fritsche 2010 [64]	RCT; 310	> 12 (52)	Gla-100 OD + insulin glulisine TID; 153	60.2 (7.5)	70 (45.8)	12.8 (5.8)	5 (3.7)
			Premixed BID; 157	60.9 (7.8)	82 (52.2)	12.5 (6.8)	4.7 (3.8)
Levin, 2011 [77]	Randomized pragmatic trial; 197	6–9 (36)	Gla-100 OD + insulin glulisine TID; 106	56.36 (12.44)	56 (52.8)	13.1 (8.78)	–
			Premixed BID; 91	55.92 (9.87)	51 (56)	12.9 (8.04)	–

Table 2 continued

Author (year)	Study design	Study duration in months (weeks)[a]	Intervention	Age (years), mean (SD)	Sex (female), *N* (if available) (%)	Disease duration (years), mean (SD)	Duration of prior insulin therapy (years), mean (SD)
Bowering, 2012 [78]	RCT; 433	9–12 (48)	Premixed TID stepwise (lispro mix 75:25) + metformin ± sulfonylurea)); 211	56.68 (8.03)	118 (55.9)	10.6 (6.18)	–
			Gla-100 OD + insulin lispro TID (stepwise fashion) + metformin; 212	56.29 (9.35)	107 (50.5)	10 (5.54)	–
Miser, 2010 [63]	RCT; 744	6–9 (24)	Intensification arm – A: Premixed TID (lispro mix 75:25) + OADs (minus sulfonylurea)); 200	55.9 (10.1)	92 (46)	8.9 (6)	–
			Intensification arm – A: Gla-100 OD + insulin lispro TID + OADs (minus sulfonylureas); 199	58.2 (9.7)	97 (49)	9.3 (5.8)	–
			Intensification arm – B: Premixed TID (lispro mix 50:50) + OADs (minus sulfonylurea)); 174	55.4 (10)	83 (48)	10 (6.7)	
			Intensification arm – B: Gla-100 OD + insulin lispro TID + OADs (minus sulfonylureas); 171	54.5 (9.1)	86 (50)	9.6 (6)	
Riddle, 2014 [66]	RCT; 588	> 12 (60)	Gla-100 OD + insulin glulisine OD + OADs; 194 (G + 1)	53.08 (9.08)	106 (56.4)	9.0 (5.72)	–
			Gla-100 OD + insulin glulisine TID + OADs; 194 (G + 3)	53.08 (9.08)	106 (56.4)	9.4 (6.8)	–
			Premixed BD (insulin aspart 70/30 BID) + OADs; 194 (PM 2 +)	53.7 (10.7)	109 (56.2)	9.5 (5.88)	–

Table 2 continued

Author (year)	Study design	Study duration in months (weeks)[a]	Intervention	Age (years), mean (SD)	Sex (female), *N* (if available) (%)	Disease duration (years), mean (SD)	Duration of prior insulin therapy (years), mean (SD)
Vora, 2015 [65]	RCT; 335	6–9 (24)	Gla-100 OD + insulin glulisine OD + metformin; 170	61.6 (8)	47 (27.6)	12.9 (6.2)	–
			Premixed BD (insulin aspart 70/30 BID) + metformin; 164	61.6 (8.9)	45 (27.4)	13 (6.6)	–
Jia. 2015 [79]	RCT; 402	6–9 (24)	Gla-100 OD + insulin lispro TID + OADs; 202	58.1 (9.07)	93 (46.04)	15.3 (6.6)	–
			Premixed TID (lispro 50/50 BID + lispro 75/25 OD + OADs; 197	59.1 (9.1)	95 (48.22)	15 (6.24)	–
Giugliano, 2014 [68]	RCT; 344	9–12 (48)	Gla-100 OD + insulin lispro TID (stepwise fashion) + OADs; 173	54.2 (8.6)	92 (53)	-	–
			Premixed TID (lispro 75/25 or lispro 50/50) stepwise + OADs; 171	54.3 (8.9)	84 (49)	-	–
Gla-100 vs. Second-generation basal insulin							
Hollander, 2015 [80]	RCT; 757	> 12 (78 [52 weeks main trial + 26 weeks extension period])	IDegOD OD + aspart ± MET ± pioglitazone; 566	58.9 (8.6)	249 (44.0)	13.4 (7.2)	–
			Gla-100 OD + aspart ± MET ± pioglitazone; 191	58.4 (9.9)	47.4	13.7 (6.8)	–
Riddle, 2014 [81]	RCT; 807	6–9 (26)	Gla-300 OD + meal-time insulin ± MET; 403	60.1 (8.5)	187 (46.29)	15.6 (7.2)	6.7 (4.7)
			Gla-100 OD + meal-time insulin ± MET; 403	59.8 (8.7)	193 (47.89)	16.1 (7.8)	6.5 (4.8)

Table 2 continued

Author (year)	Study design	Study duration in months (weeks)[a]	Intervention	Age (years), mean (SD)	Sex (female), *N* (if available) (%)	Disease duration (years), mean (SD)	Duration of prior insulin therapy (years), mean (SD)
Gla-100 vs. co-formulations (intensification)							
Philis-Tsimikas A, 2019 [82]	RCT; 532	9–12 (38)	IDegAsp OD / BD ± OADs minus SU and glinides; 267	58.2 (8.9)	53.2	12.9 (6.9)	-
			Gla-100 OD + aspart ± OADs minus SU and glinides; 265	59.2 (9.1)	48.3	13 (6.5)	-
Gla-100 vs. other basal insulins (intensification)							
Tentolouris N, 2013 [83]	Retrospective cohort switch study; 301	> 12 (Up to 52 weeks of treatment follow-up)	Premixed BD continued; 159	66.7 (9.6)	86 (54.1)	16 (8.6)	–
			Premixed BD switched to Gla-100 OD + rapid acting insulin; 142	63.2 (10.1)	82 (57.8)	13.5 (7.8)	–
Raskin, 2009 [84]	RCT; 385	6–9 (26)	IDet OD + aspart ± MET ± TZDs; 254	55.8 (10)	123 (48.4)	12.5 (6.8)	–
			Gla-100 OD + aspart ± MET ± TZDs; 131	55.9 (11)	52 (39.7)	11.9 (7.4)	-
Hollander, 2008 [85]	RCT; 319	> 12 (52)	IDet OD + aspart + OADs (minus secretagogues and α-glucosidase inhibitors); 214	59	84 (39.3)	13.6	–
			Gla-100 OD + aspart + OADs (minus secretagogues and α-glucosidase inhibitors); 105	58	50 (47.6)	13.4	–

BD twice daily, *IDeg* insulin degludec, *Gla-100* glargine-100, *MET* metformin, *NPH* neutral protamine Hagedorn, *OADs* oral anti-diabetics, *OD* once daily, *RCT* randomized clinical trial, *SU* sulfonylurea, *TID* thrice a day, *TZDs* thiazolidinediones

[a]Study duration in months categorization was done for the ease of interpretation; however, actual study duration is specified in the brackets

frequently used insulins were (NPH insulin, premixed insulin mix or lispro mix. The mean (SD) baseline insulin dose varied from 0.17 (0.03) U/kg/day [74] to 77.65 (48.5) U/kg/day [77]. Several studies reported the efficacy and safety profile of Gla-100 given with either one or more OAD therapy (MET, pioglitazone, SU) or insulin variants (insulin aspart, regular insulin, insulin lispro, insulin degludec-aspart [IDegAsp] or premixed) in order to determine the best treatment strategy using insulin intensification.

Clinical Outcomes

Insulin Initiation

Gla-100 vs. NPH Insulin Thirteen studies compared Gla-100 with NPH insulin which included use of the insulin doses in combination with OADs [14–26] (Table 3).

Glycemic Outcomes

Primary Outcomes

HbA1c

Out of 13 studies reporting mean HbA1c reduction, eight studies were of fair-to-good quality; of which two studies reported significantly higher HbA1c reduction in the Gla-100 group than NPH group, and the remaining six studies reported relatively similar HbA1c reduction with both the insulin types [14–17, 19, 21, 22, 25]. Of the remaining five studies that were of poor quality, three studies reported significant difference in HbA1c reduction favoring Gla-100 use over NPH insulin ($P < 0.001$–0.03) [18, 20, 26] (Table 3).

Response Rates

Out of eight studies, Gla-100 and NPH did not differ significantly with respect to the proportion of patients achieving target HbA1c ($n = 7$) and FPG ($n = 5$) in majority of the studies. However, three studies of fair to poor quality reported significant improvement in response rates of Gla-100 over NPH insulin [20, 22, 25]. Among these fair-to-poor quality studies, Eliaschewitz et al. showed that a higher proportion of patients receiving Gla-100 achieved HbA1c targets without confirmed hypoglycemia (26.8%), when compared to NPH (17.3%) [22]. Insulin Gla-100 appeared to be better than NPH in terms of proportion of patients achieving HbA1c targets with no nocturnal hypoglycemia (33.2 vs. 26.7%, $P = 0.05$ [25] and 22.9 vs. 14%, $P = 0.0174$ [20]) and also FPG targets with no nocturnal hypoglycemia (22.1 vs. 15.9%, $P < 0.03$ [25]) (see Table S2 in the electronic supplementary material for detail).

Safety Outcomes

Primary Outcomes

Hypoglycemic Events

A total of 13 studies reported overall hypoglycemia or nocturnal hypoglycemia. Of these, seven studies, in which Gla-100 was associated with lower incidence of overall hypoglycemic events ($P < 0.0001$ to < 0.04) [16, 20, 22, 23, 25, 26] and nocturnal hypoglycemia ($P < 0.001$ to < 0.03) [20, 22–26] compared to corresponding groups receiving NPH, were of fair-to-poor quality (Table 5).

Gla-100 vs. Premixed Insulins Twenty studies reported insulin initiation and compared the outcomes between Gla-100 and premixed insulins [7, 10–13, 27–41]. In a majority of studies ($n = 19$), the insulins were co-administered with OADs [7, 10–13, 27–37, 39–41] (Table 3).

Glycemic Outcomes

Primary Outcomes

HbA1c

Out of 20 studies reporting HbA1c reduction, 15 studies belonged to fair-to-good quality. The baseline and endpoint values for HbA1c were similar to the initiation studies reported above. When compared to premixed insulins, HbA1c reduction was reported in 15 of the 20 studies. The HbA1c reduction was significantly higher ($P < 0.05$) with Gla-100 compared to premixed insulins in 14 out of 20 studies [10, 12, 13, 27, 28, 30–33, 35–37, 39, 40] (Table 3).

Response Rates

In the studies reporting response rates ($n = 15$), six studies showed that the Gla-100 treatment regimen exhibited significant difference with respect to the proportion of patients achieving target HbA1c ($P < 0.001$–0.038) and FPG levels ($P = 0.0002$–0.019), when compared to patients on premixed insulin [7, 12, 33, 35, 36, 41]. All of these studies were

Table 3 Clinical outcomes in initiation studies

Author, year	Intervention	Study duration (months)	Mean HbA1c (SD if available)		Mean change (SD if available)	Intergroup *p* value
			Baseline	Post treatment		
Gla-100 vs. NPH insulin						
Fiesselmann, 2016 [14]	Gla-100 OD + OADs	6–9	–	–	− 1.2 (1.1)	< 0.0001
	Insulin NPH OD / BD + OADs		–	–	− 0.7 (0.9)	
Home PD, 2014 [15]	Gla-100 + OADs	9–12	8.2 (0.8)	7.1 (0.9)	− 1.07 (0.5)	–
	Insulin NPH + OADs		8.2 (0.9)	7.2 (1.0)	− 0.97 (0.5)	
Delgado E, 2012 [16]	Gla-100 OD + OADs	3–12	8.3 (1.2)	7.3 (0.9)	− 1 (1)	< 0.0001
	Insulin NPH OD / BD + OADs		7.9 (1.1)	7.8 (1.1)	− 0.2 (0.8)	
Mu P, 2011 [18]	Gla-100 OD + OADs	3–6	9.82 (1.56)	6.52 (1.34)	–	< 0.05
	Insulin NPH + OADs		9.68 (1.73)	7.63 (1.18)	–	
Hsia SH, 2011 [17]	Insulin NPH + OADs	6–9	9.3 (1.6)	7.9 (1.5)	− 1.4 (1.7)	–
	Gla-100 HS + OADs		9.2 (1.3)	7.9 (1.4)	− 1.3 (1.2)	
Mattia, 2009 [19]	Gla-100 followed by NPH	3–6	9.3 (1.4)	–	− 1.7 (1.6)	–
	NPH followed by Gla-100		9.3 (1.4)	–	- 1.6 (1.6)	
Pan, 2007 [20]	Gla-100 + glimepiride 3 mg	6–9	9 (0.86)	7.90 (1.16)	− 1.1	0.03
	Insulin NPH + glimepiride 3 mg		9.05 (0.86)	8.13 (1.19)	− 0.92	
Eliaschewitz, 2006 [22]	Gla-100 + glimepiride 4 mg	6–9	9.03 (1.09)	7.65 (1.30)	− 1.38 (1.32)	–
	Insulin NPH + glimepiride 4 mg		9.21 (0.99)	7.78 (1.29)	− 1.44 (1.33)	

Table 3 continued

Author, year	Intervention	Study duration (months)	Mean HbA1c (SD if available)		Mean change (SD if available)	Intergroup *p* value
			Baseline	Post treatment		
Jarvinen, 2006 [21]	Gla-100 + metformin	9–12	9.13 (0.15)	7.14 (0.12)	− 1.99	–
	Insulin NPH + metformin		9.26 (0.15)	7.16 (0.14)	− 2.1	
Shi, 2004 [23]	Gla-100 + glipizide GITS 5 mg	6–9 (24)	8.12 (2.19)	–	− 0.82	–
	Insulin NPH + glipizide GITS 5 mg		8.18 (3.1)	–	− 1.1	
Riddle, 2003 [25]	Gla-100 + OADs	6–9	8.61 (0.9)	6.96	− 1.65	–
	Insulin NPH + OADs		8.56 (0.9)	6.97	− 1.59	
Benedetti, 2003 [24]	Gla-100 OD + OADs	> 12	9 (1.2)	–	− 0.46	–
	Insulin NPH OD / BD + OADs		8.9 (1.1)	–	− 0.38	
Yki-Jarvinen, 2000 [26]	Gla-100 + OADs	> 12	9.1 (1)	8.34 (0.09)	− 0.76	$p < 0.001$
	Insulin NPH + OADs		8.9 (1)	8.24 (0.09)	− 0.66	
Gla-100 vs. premixed insulin						
Petrovski, 2018 [27]	Human/A-log premixed alone switched to Gla-100 OD ± OADs	6–9	9.5 (1.6)	7.5 (1.1)	–	< 0.05

Table 3 continued

Author, year	Intervention	Study duration (months)	Mean HbA1c (SD if available)		Mean change (SD if available)	Intergroup *p* value
			Baseline	Post treatment		
Cao Y, 2017 [29]	Gla-100 OD + sitagliptin 100 mg	3–6	8.07 (0.91)	–	− 1.14	–
	Insulin aspart 30 BD		8.23 (0.81)	–	− 0.94	
Zhang, 2017 [28]	Human / A-log premixed ± OADs switched to Gla-100 OD + OADs	3–6	7.8 (1.2)	7 (1)	− 0.8 (1.2)	< 0.0001
Sehgal S, 2015 [7]	Human NPH + OADs	> 12	10.3	8.8	− 1.5	–
	Gla-100 OD + OADs		10.9	8.5	− 2.4	–
	Biphasic human premixed insulin + OADs		10.7	8.6	− 2.1	–
Sun, 2014 [11]	Novolin 30R (Human) BD; *n* = 94	6–9	8.65 (0.43)	7.11 (0.50)	–	–
	Gla-100 + acarbose TID		8.62 (0.44)	7.23 (0.61)	–	
Zhang Y, 2014 [12]	Human / A-log premixed alone switched to Gla-100 OD ± OADs	3–6	8.28 (1.24)	6.83 (1.09)	–	0.01
Sakharova O V 2013 [30]	Lispro mix 75/25 + OADs	3–6	9.7 (2.4)	7.2 (0.7)	− 2.5 (2.4)	0.009
	Gla-100 + OADs		9.7 (2.4)	8 (1.1)	− 1.7 (2.07)	
Kalra, 2010 [31]	BI-Asp 30 + MET + SU (glimepiride)	6–9	8.47 (1.04)	7.25 (0.13)	− 1.22	0.015
	Gla-100 + MET + SU (glimepiride)		8.44 (1.1)	7.60 (0.13)	− 0.87	

Table 3 continued

Author, year	Intervention	Study duration (months)	Mean HbA1c (SD if available)		Mean change (SD if available)	Intergroup *p* value
			Baseline	Post treatment		
Buse, 2009 [33]	Lispro mix 75/25 + OADs	6–9	9.1 (1.3)	7.3 (1.1)	− 1.8 (1.3)	0.005
	Gla-100 + OADs		9 (1.2)	7.2 (1.1)	− 1.7 (1.3)	
Strojek, 2009 [32]	BI-Asp 30 + MET + SU (glimepiride)	6–9	8.5 (1)	7.1	–	0.029
	Gla-100 + MET + SU (glimepiride)		8.5 (1.1)	7.3	–	
	Grp A: Gla-100 OD + glimepiride OD	3–6	8.22 (0.69)	7.87 (0.66)	− 0.35 (0.52)	–
	Grp B: Gla-100 OD + glimepiride OD + MET BD		8.14 (0.9)	7.44 (0.92)	-0.69 (0.86)	-
	Grp C: Human premixed insulin 75/25 or 70/39		8.08 (0.84)	7.83 (1.13)	− 0.25 (1.02)	
Robbins, 2007 [35]	Lispro mix 75/25 BD + MET BD	6–9	7.8 (0.9)	7.1 (0.9)	− 0.7 (0.9)	< 0.001
	Gla-100 OD + MET BD		7.8 (1)	7.5 (1.0)	− 0.4 (0.9)	
Raskin, 2007 [36]	BiAsp 70/30 BD + MET	6–9	9.9 (1.5)	7.0 (1.3)	− 2.89 (1.6)	0.035
	Gla-100 OD + MET		9.9 (1.6)	7.4 (1.3)	− 2.46 (1.6)	
Jacober, 2006 [37]	16 weeks premixed insulin 50/50 lispro mix pre-breakfast and 25/75 lispro mix predinner followed by 16 weeks Gla-100	6–9	9.21 (1.33)	7.08 (0.11)	− 1.98 (0.1)	0.0083
	16 weeks Gla-100 followed by 16 weeks premixed insulin 50/50 lispro mix pre-breakfast and 25/75 lispro mix predinner		9.21 (1.33)	7.34 (0.11)	− 1.76 (0.1)	

Table 3 continued

Author, year	Intervention	Study duration (months)	Mean HbA1c (SD if available)		Mean change (SD if available)	Intergroup *p* value
			Baseline	Post treatment		
Kazda, 2006 [10]	Lispro 50% TID	6–9	8.2 (1.2)	–	− 1.1 (1.1)	< 0.001
	Lispro mid-mixture (50% lispro / 50% NPL)		8.1 (1.2)	–	− 1.2 (1.1)	
	Gla-100 OD		8.1 (1.3)	–	− 0.3 (1.1)	
Bullano, 2006 [38]	Gla-100	–	9.07 (2.1)	8.30 (1.7)	- 0.77 (1.8)	–
	Premixed insulin (70 units of NPH or long-acting insulin to 30 units of short-acting or rapid-acting insulin)		9.23 (2.3)	8.47 (2.2)	− 0.89 (1.9)	
Roach, 2006 [13]	Insulin lispro 25/75 BD + OADs followed by Gla-100 OD + OADs	6–9	8.4 (1.01)	6.9 (0.52)	–	0.035
	Gla-100 OD + OADs followed by insulin lispro 25/75 BD + OADs		8.4 (1.01)	7.3 (0.81)	–	
Janka, 2005 [39]	Gla-100 + OADs (glimepiride + metformin)	6–9	8.85 (0.98)	7.15 (0.90)	− 1.64	0.0003
	Human premixed insulin (30% regular, 70% NPH insulin; insulin actraphane HM 30/70)		8.83 (0.87)	7.49 (1.09)	− 1.31	
Raskin, 2005 [40]	BiAsp 70/30 BD + OADs	6–9	9.7 (1.5)	6.91 (1.17)	− 2.79 (0.11)	$P < 0.01$
	Gla-100 OD + OADs		9.8 (1.4)	7.41 (1.24)	− 2.36 (0.11)	
Malone, 2004 [41]	Lispro mix 75/25 + MET 1500–2550 mg/day followed by Gla-100 HS + MET 1500–2550 mg/day	9–12	8.7 (1.3)	7.4 (1.1)	− 1.32 (1.01)	0.003
	Gla-100 HS + MET 1500–2550 mg/day followed by lispro mix 75/25 + MET 1500–2550 mg/day		8.7 (1.3)	7.8 (1.1)	− 0.93 (0.89)	

Table 3 continued

Author, year	Intervention	Study duration (months)	Mean HbA1c (SD if available)		Mean change (SD if available)	Intergroup *p* value
			Baseline	Post treatment		
Gla-100 vs. second-generation basal insulin						
Bailey, 2019 [42]	Gla-300 OD + OADs	6–9	9.59 (1.96)	8.07	− 1.52 (2.08)	0.003
	Gla-100 OD + OADs		9.56 (1.94)	8.26	− 1.3 (2.12)	
Gupta, 2018 [43]	Insulin–ive patients: Started Gla-100 OD + OADs	6–9	8.45	7.33	− 1.12	–
	Insulin–ive patients: Started Gla-300 OD + OADs		8.63	7.42	− 1.21	
	Insulin-experienced patients: Switched to Gla-300 OD + OADs		8.5	7.55	− 0.95	
Nakanishi, 2018 [6]	Switched to Gla-300 ± OADs	3–6	8.07 (0.97)	7.79 (1.20)	–	–
	Gla-100 OD ± OADs		7.55 (0.82)	7.5 (0.73)	–	–
Wysham, 2017 [45]	Sequence A—Gla-100 OD ± OADs followed by IDeg OD ± OAD	> 12	7.6 (1.1)	7.08 (1.23)	–	-
	Sequence B—IDeg OD ± OADs followed by Gla-100 ± OADs		7.6 (1.1)	7.11 (1.23)	–	
Marso, 2017 [44]	IDeg OD ± OADs	> 12	8.44 (1.63)	7.5	–	–
	Gla-100 OD ± OADs		8.41 (1.67)	7.5	–	
Pan, 2016 [46]	IDeg 100 OD + MET	6–9	8.3 (0.9)	7.0 (0.9)	− 1.3 (1.1)	–
	Gla-100 OD + MET		8.3 (0.8)	7.0 (0.9)	− 1.2 (1)	

Table 3 continued

Author, year	Intervention	Study duration (months)	Mean HbA1c (SD if available)		Mean change (SD if available)	Intergroup *p* value
			Baseline	Post treatment		
Ghosal, 2016 [47]	IDeg 100 OD + OADs	6–9	8.58 (1.35)	7.12 (0.64)	− 1.45 (1.17)	–
	Gla− 100 OD + OADs		8.42 (0.89)	7.32 (0.72)	− 1.09 (0.55)	
Terauchi, 2016 [8]	Gla-300 OD ± OADs	6–9	7.99 (0.72)	-	− 0.45 (0.06)	–
	Gla-100 OD ± OADs		8.06 (0.77)	-	− 0.55 (0.06)	
Bolli, 2015 [48]	Gla-300 OD + OADs (previous)—SUs / Glinides	6–9	8.49 (1.04)	7.08 (0.96)	− 1.42 (0.05)	–
	Gla-100 OD + OADs (previous)—SUs / Glinides		8.58 (1.07)	7.05 (0.95)	− 1.46 (0.05)	
Yki-J̈arvinen, 2014 [49]	Gla-300 OD ± OADs	6–9	8.26 (0.86)	7.57	-	–
	Gla-100 OD ± OADs		8.22 (0.77)	7.56	-	
Gough SC, 2013 [50]	IDeg -200 + MET ± DPP-4 inhibitors	6–9	8.3 (1)	-	− 1.3 (1.01)	–
	Gla-100 OD + MET ± DPP-4 inhibitors		8.2 (0.9)	-	− 1.3 (1.01)	
Onishi Y 2013 [51]	IDeg OD + OADs minus DPP-4 inhibitors	6–9	8.4 (0.8)	7.2	− 1.24	–
	Gla-100 OD + OADs minus DPP-4 inhibitors		8.5 (0.8)	7.1	− 1.35	
Meneghini L 2013 [52]	IDeg OD Flex	6–9	8.5 (1)	-	− 1.28	–
	IDeg OD in morning		8.4 (0.9)	-	− 1.07	
	Gla-100 OD		8.4 (0.9)	-	− 1.26	

Table 3 continued

Author, year	Intervention	Study duration (months)	Mean HbA1c (SD if available)		Mean change (SD if available)	Intergroup *p* value
			Baseline	Post treatment		
Zinman B, 2012 [53]	IDeg -100 + MET ± DPP-4 inhibitors	> 12	8.2 (0.8)	7.1	− 1.06 (1.01)	–
	Gla-100 OD + MET ± DPP-4 inhibitors		8.2 (0.8)	7	− 1.19 (0.97)	
Gla-100 vs. Co-formulations						
Kumar, 2017 [54]	IDegAsp OD + metformin ± pioglitazone ± dipeptidyl peptidase-4 inhibitors	6–9	8.3 (0.8)	7.3	− 0.97	–
	Gla-100 OD + metformin ± pioglitazone ± dipeptidyl peptidase-4 inhibitors		8.4 (1)	7.4	-1	–
Kumar, 2016 [55]	Gla-100 OD + MET	> 12	8.9 (1)	7.6	− 1.34	–
	IDegAsp OD + MET		8.9 (0.9)	7.5	− 1.39	
Onishi Y 2013 [56]	IDegAsp + OADs (previous) minus DPP-4 Inhibitors / SU / Glinides	6–9	8.3 (0.8)	7 (0.8)	− 1.4 (0.9)	–
	Gla-100 OD + OADs (previous) minus DPP-4 Inhibitors / SU / Glinides		8.5 (0.8)	7.3 (0.9)	− 1.2 (1)	
Gla-100 vs. other basal insulins						
Cander S, 2014 [57]	IDet OD + MET + SU	3–6	9.9	-	− 1.9	–
	IDet BD + MET + SU		9.3	-	− 1.2	
	Gla-100 OD + MET + SU		9.6	-	− 1.35	
Odawara M, 2014 [58]	Gla-100 OD + OADs (insulin-naïve)	6–9	9.53 (1.19)	8.07 (1.2!)	-	–
	Gla-100 OD + OADs (insulin non-naïve)		9.08 (1.11)	8.46 (1.39)	-	

Table 3 continued

Author, year	Intervention	Study duration (months)	Mean HbA1c (SD if available)		Mean change (SD if available)	Intergroup *p* value
			Baseline	Post treatment		
Wei W, 2014 [59]	Cohort 1—Gla-C impact Gla-100 OD continued	3–6	8.6 (1.7)	8.35	− 0.13	< 0.05 for Gla-100 and Det comparison in favor of Gla-100
	Cohort 1—Det-S impact (Det OD switched)		8.7 (1.7)	8.64	− 0.06	
	Cohort 1—Gla-C Huma- (Gla-100 OD continued)		8.2 (1.5)	8.04	− 0.14	
	Cohort 1—Det-S Huma- (Det OD switched)		8.3 (1.5)	8.31	0	
	Cohort 2—Det-C impact (Det OD continued)		8.9 (1.8)	8.54	-− 0.68	
	Cohort 2—Gla-S Impact (Gla-100 OD switched)		9.1 (1.9)	8.34	− 0.36	
Meneghini L, 2013 [60]	IDet OD + MET	6–9	7.96 (0.62)	7.48 (0.91)	− 0.48 (0.94)	–
	Gla-100 OD + MET		7.86 (0.58)	7.13 (0.72)	− 0.74 (0.76)	
Esposito, 2008 [61]	Human NPL OD + OADs minus night-time SU, replaced with MET	9–12	8.8 (0.7)	-	− 1.83	–
	Gla-100 OD + OADs minus night-time SU, replaced with MET		8.7 (0.7)	-	− 1.89	
Rosenstock, 2008 [9]	IDet OD + OADs	> 12	8.64 (0.78)	7.16 (0.08)	–	–
	Gla-100 OD + OADs		8.62 (0.77)	7.12 (0.08)	–	
Malone, 2005 [62]	Lispro mix 75/25 BD + MET followed by Gla-100 OD	9–12	8.5 (0.95)	7.54 (0.87	− 1 (0.85)	< 0.001
	Gla-100 OD + MET followed by lispro mix 75/25 BD		8.48 (0.8)	8.14 (1.03	− 0.42 (0.92)	

Table 3 continued

Author, year	Mean FPG (SD if available)		Mean change (SD if available)	Intergroup *p* value	PPG (SD if available)		Mean change (SD if available)	Intergroup *p* value
	Baseline	Post treatment			Baseline	Baseline		
Gla-100 vs. NPH insulin								
Fiesselmann, 2016 [14]	–	–	43.6 (57.4)	< 0.01	–	–	–	–
	–	–	30.3 (46.9)		–	–	–	
Home PD, 2014 [15]	165.6 (37.8)	111.6 (21.6)	51.3 (1.08)	0.009	–	–	–	–
	160.2 (34.2)	115.2 (21.6)	48.24 (1.08)		–	–	–	
Delgado E, 2012 [16]	179.2	137.8	–	< 0.0001	–	–	–	–
	161.6	157.3	–		–	–	–	
Mu P, 2011 [18]	183.78 (50.76)	99 (3.96)	–	–	291.6 (77.94)	138.78 (9.36)	–	< 0.05
	189.36 (11.34)	97.56 (4.68)	–		284.4 (71.46)	148.78 (11.34)	–	
Hsia SH, 2011 [17]	147 (40)	113 (19)	− 33 (39)	–	–	–	–	–
	171 (48)	125 (27)	− 46 (45)		–	–	–	
Mattia, 2009 [19]	203.6 (58.3)	103.7	99.9	–	–	–	–	–
	203.6 (58.3)	103.2	100.4		–	–	–	
Pan, 2007 [20]	226 (51)	117 (25)	− 106	–	–	–	–	–
	223 (53)	119 (26)	− 104		–	–	–	

Table 3 continued

Author, year	Mean FPG (SD if available)		Mean change (SD if available)	Intergroup *p* value	PPG (SD if available)		Mean change (SD if available)	Intergroup *p* value
	Baseline	Post treatment			Baseline	Baseline		
Eliaschewitz, 2006 [22]	201.8 (58.7)	115.6 (36)	− 86.2 (67.2)	–	–	–	–	–
	194.1 (56.6)	19.5 (44.1)	− 74.6 (66.2)		–	–	–	
Jarvinen, 2006 [21]	203.4 (1.8)	102.6 (0.36)	–	–	–	–	–	–
	198 (1.8)	108 (0.54)	–	–	–	–	–	–
Shi, 2004 [23]	146.5 (38.2)	122.4 (39.6)	–	–	–	–	–	–
	163.9 (39.1)	160.2 (63)	–		–	–	–	
Riddle, 2003 [25]	198 (11)	117	− 81	–	–	–	–	–
	194 (10.8)	120	− 74		–	–	–	
Benedetti, 2003 [24]	178.2 (3.6)	–	− 48.6 (1.8)	< 0.05	–	–	–	–
	180 (3.6)	–	46.8 (1.8)		–	–	–	
Yki-Jarvinen, 2000 [26]	–	–	–	–	–	–	–	–
	–	–	–		–	–	–	
Gla-100 vs. premixed insulin								
Petrovski, 2018 [27]	217.8 (66.6)	138.6 (37.8)	–	< 0.05	–	–	–	–
Cao Y, 2017 [29]	163.98 (43.74)	–	–	–	–	–	–	–
	182.16 (38.34)	–	–		–	–	–	

Table 3 continued

Author, year	Mean FPG (SD if available)		Mean change (SD if available)	Intergroup *p* value	PPG (SD if available)		Mean change (SD if available)	Intergroup *p* value
	Baseline	Post treatment			Baseline	Baseline		
Zhang, 2017 [28]	145.8 (37.8)	120.6 (32.4)	25.2 (43.2)	< 0.0001	207 (61.2)	171 (45)	37.8 (70.2)	< 0.0001
Sehgal S, 2015 [7]	–	–	–	–	–	–	–	–
	–	–	–	–	–	–	–	
	–	–	–	–	–	–	–	
Sun, 2014 [11]	200.16 (28.08)	165.24 (16.56)	–	–	353.26 (94.14)	162.18 (38.52)	–	–
	201.6 (25.02)	170.10 (17.1)	–		363.78 (110.34)	181.8 (30.78)	–	
Zhang Y, 2014 [12]	137.52 (24.48)	100.26 (21.78)	–	< 0.01	217.26 (21.06)	160.96 (28.08)	–	< 0.01
Sakharova O V 2013 [30]	188 (64)	108 (36)	–	–	294 (97)	153 (36)	–	0.001
	188 (64)	110 (22)	–		294 (97)	199 (49)	–	
Kalra, 2010 [31]	–	–	–	–	–	–	–	–
	–	–	–		–	–	–	
Buse, 2009 [33]	193 (53.2)	134 (35)	–	< 0.0001	–	–	–	–
	196 (55.1)	122 (33)	–		–	–	–	
Strojek, 2009 [32]	–	–	–	–	–	–	–	–
	–	–	–		-	-	-	
	158 (35)	122 ± 34	–	–	–	–	–	–
	171 (61)	128 ± 31	-	-	-	-	-	-
	153 (49)	133 (43.0)	–		–	–	–	

Table 3 continued

Author, year	Mean FPG (SD if available)		Mean change (SD if available)	Intergroup *p* value	PPG (SD if available)		Mean change (SD if available)	Intergroup *p* value
	Baseline	Post treatment			Baseline	Baseline		
Robbins, 2007 [35]	–	–	–	–	–	–	–	–
	–	–	–		–	–	–	
Raskin, 2007 [36]	255.6 (70.02)	128.88 (75.06)	–	–	–	–	–	–
	239.4 (74.16)	126 (61.2)	–	–	–	–	–	
Jacober, 2006 [37]	–	–	–	–	–	–	–	–
	–	–	–		–	–	–	
Kazda, 2006 [10]	176.4 (50.4)	–	16.2 (39.6)	< 0.001	205.2 (61.2)	151.2	− 54 (63)	–
	167.4(37.8)	–	16.2 (32.4)		214.2 (50.4)	163.8	− 50.4 (52.2)	
	172.8 (43.2)	–	46.08 (43.2)		219.6 (55.8)	172.8	− 46.8 (59.4)	
Bullano, 2006 [38]	–	–	–	–	–	–	–	–
	–	–	–		–	–	–	
Roach, 2006 [13]	–	–	–	–	–	–	–	–
	–	–	–		–	–	–	
Janka, 2005 [39]	171 (35)	115	–	< 0.0001	–	–	–	–
	172 (38)	133	–		–	–	–	
Raskin, 2005 [40]	252 (67.4)	127 (40.6)	125 (72.9)	–	–	–	–	–
	243 (68.8)	117 (44.3)	125 (74.)		–	–	–	

Table 3 continued

Author, year	Mean FPG (SD if available)		Mean change (SD if available)	Intergroup *p* value	PPG (SD if available)		Mean change (SD if available)	Intergroup *p* value
	Baseline	Post treatment			Baseline	Baseline		
Malone, 2004 [41]	150.2 (44.7)	139.3 (36.6)	11.3 (44.5)	0.001	–	–	–	-
	155.3 (50.1)	123.9 (34.9)	29 (47.4)		–	–	–	
Gla-100 vs. second-generation basal insulin								
Bailey, 2019 [42]	–	–	–	–	–	–	–	–
	–	–	–		–	–	–	
Gupta, 2018 [43]	–	–	–	–	–	–	–	–
	–	–	–		–	–	–	
	–	–	–		-	-	-	
Nakanishi, 2018 [6]	–	–	–	–	–	–	–	–
	–	–	–	–	–	–	–	
Wysham, 2017 [45]	134.9 (51.6)	107.6 (51.3)	–	–	–	–	–	–
	139.2 (53.5)	114.1 (51.9)	–		–	–	–	
Marso, 2017 [44]	169.8 (70.3)	128 (56)	39.9	< 0.0001	–	–	–	–
	173.5 (70.7)	136 (57)	34.9		–	–	–	

Table 3 continued

Author, year	Mean FPG (SD if available)		Mean change (SD if available)	Intergroup *p* value	PPG (SD if available)		Mean change (SD if available)	Intergroup *p* value
	Baseline	Post treatment			Baseline	Baseline		
Pan, 2016 [46]	169.2 (43.2)	108 (36)	60.30 (52.38)	–	–	–	–	–
	169.2 (45)	113.4 (34.2)	56.52 (48.78)		–	–	–	
Ghosal, 2016 [47]	182.88 (37.25)	107 (19.25)	75.88 (40.15)	–	–	–	–	–
	182.35 (34.85)	109.55 (24.20)	72.81 (37.71)		–	–	–	
Terauchi, 2016 [8]	138.6 (37.8)	-	21.8 (2.9)	–	–	–	–	–
	133.2 (34.2)	-	22.5 (2.9)		–	–	–	
Bolli, 2015 [48]	178.74 (51.48)	120 (38.88)	61.2 (1.8)	–	–	–	–	–
	183.6 (52.2)	113.4 (32.76)	68.4 (1.98)		–	–	–	
Yki-J̈arvinen, 2014 [49]	8.24 (2.97)	7.09 (2.47)	1.14 (3.42)	–	–	–	–	–
	7.89 (2.67)	6.83 (2.37)	1.06 (3.02)		–	–	–	
Gough SC, 2013 [50]	172.4 (51.7)	105.7	66.7	–	–	–	–	–
	174.1 (46.8)	113.1	60.9		–	–	–	

Table 3 continued

Author, year	Mean FPG (SD if available)		Mean change (SD if available)	Intergroup *p* value	PPG (SD if available)		Mean change (SD if available)	Intergroup *p* value
	Baseline	Post treatment			Baseline	Baseline		
Onishi Y 2013 [51]	151.2 (37.8)	99	51.84	–	–	–	–	–
	154.8 (34.2)	102.6	53.46		–	–	–	
Meneghini L 2013 [52]	162 (46.8)	104.4	-	0.04	–	–	–	–
	158.4 (50.4)	104.4	-		–	–	–	
	162 (50.4)	111.6	-		–	–	–	
Zinman B, 2012 [53]	172.8 (46.8)	106.2	68.4 (54.72)	–	–	–	–	–
	174.6 (46.8)	115.2	59.4 (51.66)		–	–	–	
Gla-100 vs. Co-formulations								
Kumar, 2017 [54]	144 (45)	113.4	–	–	–	–	–	–
	140 (50)	108	–	–	–	–	–	
Kumar, 2016 [55]	187.4 (50.5)	-	67.86	–	–	–	–	–
	182 (52.3)	-	63		–	–	–	
Onishi Y 2013 [56]	162 (28.8)	102.6 (37.8)	59.4 (43.2)	–	–	–	–	–
	163.8 (34.2)	100.8 (34.2)	63 (43.2)		–	–	–	

Table 3 continued

Author, year	Mean FPG (SD if available)		Mean change (SD if available)	Intergroup *p* value	PPG (SD if available)		Mean change (SD if available)	Intergroup *p* value
	Baseline	Post treatment			Baseline	Baseline		
Gla-100 vs. other basal insulins								
Cander S, 2014 [57]	–	–	–	–	–	–	–	–
	–	–	–		–	–	–	
	–	–	–		–	–	–	
Odawara M, 2014 [58]	–	–	–	–	–	–	–	–
	–	–	–		–	–	–	
Wei W, 2014 [59]	–	–	–	–	–	–	–	–
	–	–	–		–	–	–	
	–	–	–		–	–	–	
	–	–	–		–	–	–	
	–	–	–		–	–	–	
	–	–	–		–	–	–	
Meneghini L, 2013 [60]	156 (40.7)	112 (33.8)	− 44.8 (46.3)	–	–	–	–	–
	152.4 (39.8)	109.6 (42.8)	− 43.4 (52.7)		–	–	–	
Esposito, 2008 [61]	192 (41)	107 (11)	–	–	–	–	–	–
	193 (40)	105 (12)	–		–	–	–	
Rosenstock, 2008 [9]	194.4	128.52 (3.78)	–	–	–	–	–	–
	194.4	125.64 (3.78)	–		–	–	–	

Table 3 continued

Author, year	Mean FPG (SD if available)		Mean change (SD if available)	Intergroup *p* value	PPG (SD if available)		Mean change (SD if available)	Intergroup *p* value
	Baseline	Post treatment			Baseline	Baseline		
Malone, 2005 [62]	155.34 (52.74)	142.2 (34.56)	–	< 0.007	–	–	–	–
	147.78 (37.62)	133.02 (35.28)	–		–	–	–	

BD bi-daily, *DPP-4* dipeptidyl peptidase-4, *IDeg* insulin degludec, *Gla-100* glargine-100, *Gla-300* glargine-300, *MET* metformin, *NPH* neutral protamine Hagedorn, *OADs* oral anti-diabetics, *OD* once daily, *RCT* randomized clinical trial, *SU* sulfonylurea, *TID* thrice a day, *TZDs* thiazolidinediones

of fair-to-good quality. However, no statistically significant difference was observed between Gla-100 and premixed insulin regimens pertaining to the proportion of patients achieving HbA1c either with no confirmed hypoglycemia or with no nocturnal hypoglycemia and proportion of patients achieving FPG target with no confirmed nocturnal hypoglycemia or with no nocturnal hypoglycemia (see Table S2 in the electronic supplementary material for details).

Safety Outcomes

Primary Outcomes

Hypoglycemia Events

In the Gla-100 vs. premixed insulin initiation studies ($n = 18$) reporting hypoglycemia events, six studies with Gla-100 insulin initiation regimen were associated with significantly lower incidence of overall hypoglycemia ($P < 0.0001$–0.04) and nocturnal hypoglycemia ($P = 0.009$–0.021) vs. premixed insulin [29, 32, 33, 36, 37, 39]. All of these studies, except one study [37], were of fair-to-good quality (see Table S4 in the electronic supplementary material for details).

Gla-100 vs. Second-Generation Basal Insulins Overall, 14 insulin initiation studies comparing Gla-100 with second-generation basal insulin treatment regimens in insulin-naïve patients with T2DM were of fair-to-good quality [6, 8, 42–53] (Table 3).

Glycemic Outcomes

Primary Outcomes

HbA1c

In eight studies, Gla-100 did not differ significantly with respect to HbA1c reduction when compared to IDeg-100 or 200 administered once a day [44–47, 50–53]. However, one study exhibited significant reduction in HbA1c levels with Gla-300 when compared with Gla-100 ($P = 0.003$) [42] (Table 3).

Response rates

In nine studies, Gla-100 treatment did not offer any significant improvements over second-generation basal insulins in any of the response-rate parameters being assessed. Only one study, which was a good-quality study, reported significantly higher proportion of patients achieving target HbA1c in Gla-300 group when compared with Gla-100 group

Table 4 Clinical outcomes in intensification studies

Author, year	Intervention	Study duration (months)	Mean HbA1c (SD if available)		Mean change (SD if available)	Intergroup *p* value	Mean FPG (SD if available)		Mean change (SD if available)	Intergroup *p* value
			Baseline	Post-treatment			Baseline	Post-treatment		
Gla-100 vs. NPH insulin										
Betonico, 2019 [72]	Gla-100 OD + insulin lispro TID for 24 weeks followed by insulin NPH + lispro TID	9–12	8.9 (1.3)	7.95 (1.1)	–	0.028	–	–	–	–
	Insulin NPH + insulin lispro TID for 24 weeks followed by Gla-100 OD + lispro TID		8.6 (1.1)	8.44 (1.3)	–		–	–	–	
Rosenstock, 2001 [73]	Gla-100 OD ± premeal regular insulin	6–9	8.6 (1.2)	–	–	–	–	–	–	–
	NPH insulin OD / BD ± premeal regular insulin		8.5 (1.2)	–	–		–	–	–	
Gla-100 vs. premixed insulins										
Aschner, 2015 [74]	Gla-100 OD + glulisine OD before main meal + MET ± SU	6–9	8.7 (0.9)	7.2 (0.9)	− 1.48 (0.04)	0.0008	160.2 (37.8)	108 (21.6)	-54 (1.08)	< 0.001
	Premixed insulin BD MET ± SU		8.7 (0.9)	7 (0.9)	− 1.64 (0.04)		162 (41.4)	113.4 (25.2)	- 46.8 (1.08)	
Tentolouris N, 2013 [83]	Premixed BD continued	> 12	8.18 (1.33)	7.58 (1.06)	− 0.6	< 0.001	168.9 (47.2)	148.5 (42.7)	- 19.73	< 0.001
	Premixed BD switched to Gla-100 OD + rapid-acting insulin		8.53 (1.29)	7.39 (0.81)	− 1.14		182.6 (57.1)	135.6 (34.5)	- 47.02	
Ito H, 2014 [71]	Human premixed insulin 50/50 switched to Gla-100 OD + glulisine BD	3–6	8.3 (1.8)	8.2 (1.1)	− 0.1 (1.4)	NS	–	–	–	–
Tinahones, 2014 [75]	Insulin lispro Mix BD + MET ± pioglitazone	6–9	8.7 (0.8)	Not mentioned	− 1.3	0.010	–	–	–	–
	Gla-100 OD + insulin lispro OD + MET ± pioglitazone		8.6 (0.7)	Not mentioned	− 1.08		–	–	–	–

Table 4 continued

Author, year	Intervention	Study duration (months)	Mean HbA1c(SD if available)		Mean change (SD if available)	Intergroup *p* value	Mean FPG (SD if available)		Mean change (SD if available)	Intergroup *p* value
			Baseline	Post-treatment			Baseline	Post-treatment		
Jain, 2010 [67]	Gla-100 OD + mealtime lispro TID	6–9	9.3 (1.2)	7.50 (0.20)	− 1.8	NS	–	–	–	–
	Insulin lispro mix 50/50 TID		9.5 (1.2)	7.58 (0.20)	− 1.92		-	-	-	
Rosenstock, 2008 [76]	Prandial premixed (insulin lispro protamine suspension/lispro)	6–9	8.83 (1.04)	6.95	− 1.87	0.021	–	–	–	–
	Gla-100 OD + insulin lispro TID + OADs (minus SU + glinides)		8.89 (1.09)	6.78	− 2.09		–	–	–	
Joshi, 2005 [70]	Premixed insulin analog (NovoMix 30) BD	3–6	8.79 (1.13)	7.2 (0.83)	− 1.59	< 0.05	186.59 (47.35)	114.83 (18.68)	Not mentioned	**NS**
	Gla-100 OD + insulin aspart TID		8.53 (1.22)	7.37 (0.83)	− 1.16		190.23 (55.63)	110.61 (16.79)	Not mentioned	
Fritsche, 2010 [64]	Once-daily insulin glargine bedtime every day and insulin glulisine 0–15 min before mealtime	> 12	8.6 (0.8)	7.3 (1.2)	− 1.3 (1.2)	0.0001	177 (54)	134 (57)	- 43 (70)	0.0684
	Twice-daily premixed insulin (pre-breakfast and evening meal)		8.5 (0.9)	7.7 (1.1)	− 0.8 (1.0)		174 (59)	144 (52)	- 29 (59)	
Levin, 2011 [77]	Insulin glargine/glulisine therapy	6–9	9.33 (1.8)	6.93	− 2.3	< 0.01	–	–	–	–
	Premixed analogue therapy		9.35 (1.8)	7.52	− 1.7		–	–	–	
Bowering, 2012 [78]	Premixed TID stepwise (lispro mix 75:25) + metformin ± sulfonylurea))	9–12	8.98 (1.04)	7.1 (1.04)	− 1.84	**NS**	–	–	–	–
	Gla-100 OD + insulin lispro TID (stepwise fashion) + metformin		9.03 (1.05)	7.3 (1.03)	− 1.8		=	-	-	

Table 4 continued

Author, year	Intervention	Study duration (months)	Mean HbA1c(SD if available)		Mean change (SD if available)	Intergroup *p* value	Mean FPG (SD if available)		Mean change (SD if available)	Intergroup *p* value
			Baseline	Post-treatment			Baseline	Post-treatment		
Miser, 2010 [63]	Intensification arm – A: Premixed TID (lispro mix 75:25) + OADs (minus sulfonylurea))	6–9	8.0 (1)	8.0 (1.2)	–	**NS**	–	–	–	–
	Intensification arm – A: Gla-100 OD + insulin lispro TID + OADs (minus sulfonylureas)		8.0 (1)	8.1 (1.5)	–		–	–	–	
	Intensification arm – B: Premixed TID (lispro mix 50:50) + OADs (minus sulfonylurea))		8.0 (0.9)	8.2 (1.3)	–		–	–	–	
	Intensification arm – B: Gla-100 OD + insulin lispro TID + OADs (minus sulfonylureas)		8.0 (0.9)	8.2 (1.4)	–		–	–	–	
Riddle, 2014 [66]	G + 1	> 12	9.4 (1.7)	7.1 (1.68)	− 2.3 (0.12)	**0.05 vs. premix**	198 (70.2)	117 (57.6)	- 79.2 (73.2)	0.0005 vs. premix
	G + 3		9.4 (1.7)	7.0 (1.21)	− 2.4 (0.12)	**0.005 vs. premix**	207 (75.6)	115.2 (48.6)	- 86.4 (90)	0.0002 vs. premix
	PM (2 +)		9.3 (1.6)	7.2 (1.37)	− 2.0 (0.12)		203.4 (64.8)	133.2 (55.8)	- 61.2 (72)	
Vora, 2015 [65]	Gla-100 OD + insulin glulisine OD + metformin	6–9	8.6 (0.9)	-	− 1.0	**NS**	109.8 (28.8)	–	–	–
	Premixed BD (insulin aspart 70/30 BID) + metformin		8.6 (0.9)	-	− 1.22		108 (28.8)	–	–	–

Table 4 continued

Author, year	Intervention	Study duration (months)	Mean HbA1c(SD if available)		Mean change (SD if available)	Intergroup *p* value	Mean FPG (SD if available)		Mean change (SD if available)	Intergroup *p* value
			Baseline	Post-treatment			Baseline	Post-treatment		
Jia, 2015 [79]	Gla-100 OD + insulin lispro TID + OADs	6–9	8.7 (1.1)	–	− 1.1	**NS**	–	–	–	–
	Premixed TID (lispro 50/50 BID + lispro 75/25 OD + OADs		8.6 (1)	–	− 1.1		–	–	–	–
Giugliano, 2014 [68]	Gla-100 OD + insulin lispro TID (stepwise fashion) + OADs	9–12	9.07 (0.99)	7.58	− 1.57 (0.10)	**NS**	–	–	–	–
	Premixed TID (lispro 75/25 or lispro 50/50) stepwise + OADs		8.98 (0.95)	7.40	− 1.65 (0.10)		–	–	–	–
Gla-100 vs. second-generation basal insulins										
Riddle, 2014 [81]	Gla-300 OD + meal-time insulin ± MET	6–9	8.15 (0.78)	7.25 (0.85)	− 0.83 (0.06)	–	158.3 (51.8)	130.32 (46.26)	–	–
	Gla-100 OD + meal-time insulin ± MET		8.16 (0.77)	7.28 (0.92)	− 0.83 (0.06)		160.7 (52.8)	129.78 (43.2)	–	
Hollander, 2015 [80]	IDeg OD	> 12	8.2 (0.8)	7.2	− 1	–	165.6 (54)	–	− 43.2	–
	Gla-100 OD		8.3 (0.9)	7.1	− 1.2		165.6 (57.6)	–	− 39.6	
Gla-100 vs. co-formulations										
Philis-Tsimikas A, 2019 [82]	IDegAsp OD / BD ± OADs minus SU & glinide	9–12	8.2 (0.8)	–	− 1.3 (0.8)	–	162 (48)	–	− 48.6 (54)	–
	Gla-100 OD + aspart ± OADs minus SU & glinides		8.1 (0.7)	–	− 1.2 (0.8)		158 (48)	–	− 41.4 (55.8)	
Gla-100 vs. other basal insulins										

Table 4 continued

Author, year	Intervention	Study duration (months)	Mean HbA1c(SD if available)		Mean change (SD if available)	Intergroup *p* value	Mean FPG (SD if available)		Mean change (SD if available)	Intergroup *p* value
			Baseline	Post-treatment			Baseline	Post-treatment		
Raskin, 2009 [84]	IDet OD + aspart ± MET ± TZDs	6–9	8.4 (1)	7.13 (0.013)	− 1.08 (1.077)	0.035	174 (3.73)	129.7 (3.16)	− 43.2 (3.16)	–
	Gla-100 OD + aspart ± MET ± TZDs		8.4 (1)	6.92 (0.091)	− 1.28 (1.117)		172.2 (5.11)	134.3 (4.32)	− 38.7 (4.32)	
Hollander, 2008 [85]	IDet OD + aspart + OADs (minus secretagogues and α-glucosidase inhibitors)	> 12	8.6 (1)	7.19	− 1.52	**NS**	171 (54)	127	− 46.08	NS
	Gla-100 OD + aspart + OADs (minus secretagogues and α-glucosidase inhibitors)		8.8 (1.1)	7.03	− 1.68		176.4 (52.2)	120.2	− 52.56	

PPG values were not reported for any of the studies included

BD bi-daily, *DPP-4* dipeptidyl peptidase-4, *IDeg* insulin degludec, *Gla-100* glargine-100, *Gla-300* glargine-300, *MET* metformin, *NPH* neutral protamine Hagedorn, *OADs* oral anti-diabetics, *OD* once daily, *RCT* randomized clinical trial, *SU* sulfonylurea, *TID* thrice a day

Table 5 Safety outcomes (Initiation studies)

Author, year	Study duration (months)	Overall hypoglycemia[a]	Intergroup *p* value	Nocturnal hypoglycemia[a]	Intergroup *p* value	Severe hypoglycemia[a]	Intergroup *p* value
Gla-100 vs. NPH insulin							
Fiesselmann, 2016 [14]	6–9	7.4 vs. 19.3	–	1.4 vs. 10.5	–	0.4 vs. 2.1	–
Home PD, 2014 [15]	9–12	64.7 vs. 61.1	–	34.7 vs. 38	–	–	–
Delgado E, 2012 [16]	3–12	21.8 vs. 47.6	< 0.0001	1.3 vs. 8.3	–	0.2 vs. 1.85	–
Mu P, 2011 [18]	3–6	4.84 vs. 7.14	–	–	–	0 vs. 0	–
Hsia SH, 2011[a] [17]	6–9	96 vs. 77 vs. 77	–	20 vs. 13 vs. 10			
Mattia, 2009 [19]	3–6	1.04 vs. 2.12 episodes/patient/month	–	0 vs. 0	–	–	–
Pan, 2007 [20]	6–9	682 vs. 1019	< 0.004	5 vs. 28	< 0.03	221 vs. 620	< 0.001
Jarvinen, 2006 [21]	9–12	5.4 vs. 8	–	98% vs. 93% of the confirmed symptomatic hypoglycemia	NS	–	–
Eliaschewitz, 2006 [22]	6–9	52.8 vs. 62.8	< 0.042	20.4 vs. 34.8	< 0.001	2.6 vs. 4.4	0.303
Shi, 2004 [23]	6–9 (24)	7.1 vs. 35.7	0.008	–	–	-	–
Riddle, 2003 [25]	6–9	13.9 vs. 17.7	< 0.02	4 vs. 6.9	< 0.001	2.5 vs. 1.9	–
Benedetti, 2003 [24]	> 12	35 vs. 41	–	12 vs. 24	0.0002	–	–

Table 5 continued

Author, year	Study duration (months)	Overall hypoglycemia[a]	Intergroup *p* value	Nocturnal hypoglycemia[a]	Intergroup *p* value	Severe hypoglycemia[a]	Intergroup *p* value
Yki-Jarvinen, 2000 [26]	> 12	33 vs. 42	< 0.04	9.9 vs. 24	< 0.001	–	–
Gla-100 vs. premixed insulin							
Petrovski, 2018 [27]	6–9	5.2%	–	0.8%	–	0	–
Cao Y, 2017 [29]	3–6	2.85 vs. 13.3	< 0.01	–	–	–	–
Zhang, 2017 [28]	3–6	15.5	–	1.1%	-	0.3%	–
Sehgal S, 2015 [7]	> 12	–	–	–	–	4.0 vs. 0.0 vs. 11.9	–
Sun, 2014 [11]	6–9	10.6 vs. 13.8%	NS	–	–	–	–
Zhang Y, 2014 [12]	3–6	0.3 episodes /patient/month	-	–	–	–	–
Sakharova O V 2013 [30]	3–6	–	–	–	–	0 vs. 0	–
Kalra, 2010 [31]	6–9	4.5 vs. 6.2 episodes/patient/year	–	0.9 vs.0.9 episodes/patient/year	–	–	–
Buse, 2009 [33]	6–9	23.1 vs. 28 episodes/patient/year	0.007	11.4 vs. 8.9 episodes/patient/year	0.009	0.03 vs. 0.10 episodes/patient/year	–
Strojek, 2009 [32]	6–9	4.8 vs. 6.5 episodes/patient/year	0.034	0.5 vs. 1.1 episodes/patient/year	0.003	-	–
Schiel, 2007 [34]	3–6	59 or 72 vs. 77	–	–	–	–	–
Robbins, 2007 [35]	6–9	0.5 vs. 0.8 episodes/patient/month	–	0.3 vs. 0.2 episodes/patient/month	–	–	–
Raskin, 2007 [36]	6–9	42 vs. 68	0.0013	10 vs. 25	0.021	0 vs. 0	–

Table 5 continued

Author, year	Study duration (months)	Overall hypoglycemia[a]	Intergroup *p* value	Nocturnal hypoglycemia[a]	Intergroup *p* value	Severe hypoglycemia[a]	Intergroup *p* value
Jacober, 2006 [37]	6–9	2.57 vs. 3.98 episodes/patient/month	0.0013	1.05 vs. 0.80 episodes/patient/month	NS	0 vs. 0	-
Kazda, 2006 [10]	6–9	1 vs. 1.5 or 1.4 episode/100 patient-years	–	–	–	–	–
Bullano, 2006 [38]	-	19.1 vs. 16.5 events /100-patients/year	–	–	–	–	–
Roach, 2006 [13]	6–9	30 vs. 80	–	–	–	–	–
Janka, 2005 [39]	6–9	4.07 vs. 9.87 events per patient-years	< 0.0001	0.51 vs. 1.04 events per patient-years	0.0449	0 vs. 0.05	-
Raskin, 2005 [40]	6–9	0.7 vs. 3.4 episodes/patient/year	< 0.05	–	–	1 vs. 0	–
Malone, 2004 [41]	9–12	0.39 vs. 0.68 episodes/patient/month	0.04	0.14 vs. 0.24 episodes/patient/month	–	–	–
Gla-100 vs. second-generation basal insulins							
Bailey, 2019 [42]	6–9	9.66 vs. 12.45	–	–	–	–	–
Gupta, 2018 [43]	6–9	0.08 vs. 0.04 vs. 0.13 events / PYE	0.018	-	-	-	–
Nakanishi, 2018 [6]	3–6	–	–	–	–	–	–
Marso, 2017 [44]	> 12	–	–	–	–	3.70 vs. 6.25 episodes / 100 PYE	< 0.001

Table 5 continued

Author, year	Study duration (months)	Overall hypoglycemia[a]	Intergroup *p* value	Nocturnal hypoglycemia[a]	Intergroup *p* value	Severe hypoglycemia[a]	Intergroup *p* value
Wysham, 2017 [45]	> 12	275.1 vs. 219.9 episodes/ 100 PYE	< 0.001	88.4 vs. 72 episodes/100 PYE	< 0.001	9.4 vs. 4.4 episodes / 100 PYE	0.03
Ghosal, 2016 [47]	6–9	19.4 vs. 64.6	–	-	–	-	–
Pan, 2016 [46]	6–9	85 vs. 97 episodes/100PYE	–	22 vs. 24 episodes/100 PYE	–	2 vs. 1 episode/100 PYE	–
Terauchi, 2016 [8]	6–9	11.55 vs. 17.87 episodes / PYE	–	2.44 vs. 5.3 episodes / PYE	–	0.05 vs. 0.03 episodes / PYE	–
Bolli, 2015 [48]	6–9	6.4 vs. 8.5 events/PYE	0.042	16 vs. 17	NS	1 vs. 1 episode	–
Yki-Jarvinen, 2014 [49]	6–9	14.37 vs. 18.96 episodes / PYE	–	1.98 vs. 3.95 episodes / PYE	Not mentioned	0.03 vs. 0.06 episodes / PYE	–
Gough SC, 2013 [50]	6–9	1.22 vs. 1.42 episodes/PYE	–	0.18 vs. 0.28 episodes/ PYE	–	–	–
Meneghini L 2013 [52]	6–9	3.6 vs. 3.6 vs. 3.5 episodes/ PYE	–	0.6 vs. 0.6 vs. 0.8 episodes/PYE	–	–	–
Onishi Y 2013 [51]	6–9	3.0 vs. 3.7 episodes/PYE	–	0.8 vs. 1.2 episodes/PYE	–	–	–
Zinman B, 2012 [53]	> 12	1.52 vs. 1.85 episodes / patient/ year	–	0.25 vs. 0.39 episodes/patient/year	0.038	0.003 vs. 0.023 episodes/patient/ year	0.017
Gla-100 vs. co-formulations							
Kumar, 2017 [54]	6–9	52.6 vs. 48.1% of the patients	< 0.05	19.1 vs. 21.0% of the patients	–	–	–
Kumar, 2016 [55]	> 12	Treatment ratio is 1.86 in favor of Gla-100	< 0.0001	Treatment ratio is 10.25 in favor of IDegAsp	< 0.0001	0.01 vs. 0.01 events / PYE	-

Table 5 continued

Author, year	Study duration (months)	Overall hypoglycemia[a]	Intergroup *p* value	Nocturnal hypoglycemia[a]	Intergroup *p* value	Severe hypoglycemia[a]	Intergroup *p* value
Onishi Y 2013 [56]	6–9	1.91 vs. 2.71 episodes/ PYE	–	0.39 vs. 0.53 episodes/ PYE	–	–	–
Gla-100 vs. other basal insulins							
Cander S, 2014 [57]	3–6	0.0 vs. 0.5 vs. 0.0 episodes/patient/week	–	–	–	–	–
Wei W, 2014 [59]	3–6	0.30 vs. 0.37 vs. 0.37 vs. 0.41 vs. 0.26 vs. 0.21 episodes / PYE	–	–	–	–	–
Meneghini L, 2013 [60]	6–9	3.19 vs. 4.41 episodes / PYE	0.034	1.11 vs. 0.88episodes / PYE	–	–	–
Esposito, 2008 [61]	9–12	7.5 vs. 6.0 episodes/PYE	–	33 vs. 25	–	–	–
Rosenstock, 2008 [9]	> 12	5.8 vs. 6.2 episodes/patient-year	–	1.3 vs. 1.3 episodes/patient-year	–	0	–
Malone, 2005 [62]	9–12	0.61 vs. 0.44 episodes / patient / 30 days	–	0.14 vs. 0.34 episodes / patient / 30 months	0.002	–	–

Table 5 continued

Author, year	Weight change from baseline; mean	Intergroup *p* value	Baseline Insulin dose	Post-treatment insulin dose	Intergroup *p* value
Gla-100 vs. NPH insulin					
Fiesselmann, 2016 [14]	0.8 vs. 0.1	< 0.05 in favor of NPH	–	–	–
Home PD, 2014 [15]	1.26 vs. 1.05	–	0.2 vs. 0.2 U/kg/day	0.39 vs. 0.36 U/kg/day	–
Delgado E, 2012 [16]	–	–	34 vs. 34	30 vs. 36	–
Mu P, 2011 [18]	–	–	–	–	–
Hsia SH, 2011[a] [17]	-0.2 vs. 1.7 vs. 3.1	0.01 in favor of NPH	–	14.6 vs. 17.7 vs. 17.9 U/day	–
Mattia, 2009 [19]	-	-	10 vs. 10 U/day	28.8 vs. 34.7 U/day	–
Pan, 2007 [20]	-	-	9.6 vs. 9.6 U/day	32.1 vs. 32.1 U/day	–
Jarvinen, 2006 [21]	2.6 vs. 3.5	–	–	68 vs. 70	–
Eliaschewitz, 2006 [22]	–	–	16.2 vs. 14.9 U/day	32.6 vs. 31.2 U/day	–
Shi, 2004 [23]	–	–	–	–	–
Riddle, 2003 [25]	3.0 vs. 2.8	–	10 vs. 10 U/day	47.2 vs. 41.8 U/day	< 0.005 in favor of Gla-100
Benedetti, 2003 [24]	2.01 vs. 1.88	–	–	-	–
Yki-Jarvinen, 2000 [26]	2.57 vs. 2.34	–	–	23 vs. 21 U/day	–
Gla-100 vs. premixed insulin					
Petrovski, 2018 [27]	-	< 0.001 in favor of Gla-100	-	-	-
Cao Y, 2017 [29]	-0.33 vs. 1.65	< 0.05 in favor of Gla-100	-	21 vs. 58 U/day	-
Zhang, 2017 [28]	-0.2	< 0.0001 in favor of Gla-100	29.4 U/day	16.0 U/day	-

Table 5 continued

Author, year	Weight change from baseline; mean	Intergroup *p* value	Baseline Insulin dose	Post-treatment insulin dose	Intergroup *p* value
Sehgal S, 2015 [7]	1.9 vs. 1.1 vs. 0.9	-	0.2 vs. 0.2 vs. 0.3 U/kg/day	0.3 vs. 0.3 vs. 0.5 U/kg/day	NS
Sun, 2014 [11]	-	-	0.2 vs. 1.0 U/kg/day	-	-
Zhang Y, 2014 [12]	-	-	30.2 U/day	16.38 U/day	-
Sakharova O V 2013 [30]	2.4 vs. 1.7	-	-	0.4 vs. 0.3 U/kg/day	-
Kalra, 2010 [31]	0.8 vs. 1.16	-	0.2 vs. 0.2 U/kg/day	0.4 vs. 0.35 U/kg/day	NS
Buse, 2009 [33]	3.6 vs. 2.5	< 0.0001 in favor of Gla-100	-	0.47 vs. 0.40 U/kg/day	< 0.001 in favor of Gla-100
Strojek, 2009 [32]	1.74 vs. 1.67	-	0.2 vs. 0.2 U/kg/day	0.29 vs. 0.32 U/kg/day	NS
Schiel, 2007 [34]	0.77 vs. - 0.31 vs. 0.21	-	77.6 vs. 64.9 vs. 65.2 U/day	75.1 vs. 53.9 vs. 70.6 U/day	NS
Robbins, 2007 [35]	- 0.5 vs. 1.2	< 0.001	0.6 vs. 0.6 U/kg/day	0.6 vs. 0.7 U/kg/day	< 0.001 in favor of Gla-100
Raskin, 2007 [36]	5.4 vs. 3.0	0.0004 in favor of Gla-100	0.14 vs. 0.14	0.91 vs. 0.57	-
Jacober, 2006 [37]	-	-	-	0.25 vs. 0.27 U/kg/day	-
Kazda, 2006 [10]	2.3 vs. 1.8 vs. 0.7	-	0.25 vs. 0.30 vs. 0.16 U/kg/day	0.50 vs. 0.59 vs. 0.43 U/kg/day	< 0.005 in favor of Gla-100
Bullano, 2006 [38]	–	–	–	–	–
Roach, 2006 [13]	–	–	–	44 vs. 60 U/day	–
Janka, 2005 [39]	1.4 vs. 2.1	-	9.9 vs. 20.6	28.2 vs. 64.5	< 0.05 in favor of Gla-100
Raskin, 2005 [40]	5.4 vs. 3.5	< 0.01 in favor of Gla-100	0.14 vs. 0.13	0.82 vs. 0.55	< 0.05 in favor of Gla-100
Malone, 2004 [41]	2.3 vs. 1.6	0.006 in favor of Gla-100	0.39 vs. 0.39	0.62 vs. 0.57	< 0.001 in favor of Gla-100

Table 5 continued

Author, year	Weight change from baseline; mean	Intergroup *p* value	Baseline Insulin dose	Post-treatment insulin dose	Intergroup *p* value
Gla-100 vs. second-generation basal insulins					
Bailey, 2019 [42]	–	–	–	–	–
Gupta, 2018 [43]	–	–	0.339 vs. 0.331 vs. 0.73 U/kg/day	0.44 vs. 0.43 vs. 0.58 U/kg/day	–
Nakanishi, 2018 [6]	–	–	8.7 vs. 11.1 U/day	8.6 vs. 10.8 U/day	–
Marso, 2017 [44]	4.9 vs. 4.9	–	–	–	0.04 in favor of Gla-100
Wysham, 2017 [45]	0.9 vs. 0.5	–	43.0 vs. 40.0 U/day	83.0 vs. 83.0 U/day	–
Ghosal, 2016 [47]	0.85 vs. 1.65	–	–	18.61 vs. 25.68 U/day	0.002 in favor of IDeg
Pan, 2016 [46]	2.2 vs. 1.8	–	0.14 vs. 0.14 U/kg/day	0.49 vs. 0.50 U/kg/day	–
Terauchi, 2016 [8]	0.4 vs. 0.6	0.0003 in favor of Gla-100	0.23 vs. 0.24 U/kg/day	0.35 vs. 0.30 U/kg/day	–
Bolli, 2015 [48]	0.71 vs. 0.49	-	0.2 vs. 0.2 U/kg/day	0.62 vs, 0.53 U/kg/day	–
Yki-Jarvinen, 2014 [49]	0.66 vs. 0.08	0.015 in favor of Gla-300	0.64 vs. 0.66 U/kg/day	0.92 vs. 0.84 U/kg/day	< 0.05 in favor of Gla-100
Gough SC, 2013 [50]	1.9 vs. 1.5	–	11.0 vs. 10.0 U/day	0.53 vs. 0.60 U/kg/day	< 0.05 in favor of IDeg
Meneghini L 2013 [52]	1.5 vs. 1.6 vs. 1.3	–	0.2 vs. 0.2 vs. 0.2 U/kg/day	0.6 vs. 0.6 vs. 0.6 U/kg/day	–
Onishi Y 2013 [51]	1.3 vs. 1.4	–	0.14 vs. 0.14 U/kg/day	0.28 vs. 0.35 U/kg/day	0.0004 in favor of IDeg
Zinman B, 2012 [53]	2.4 vs. 2.1	–	0.12 vs. 0.11 U/kg/day	0.59 vs. 0.60 U/kg/day	-
Gla-100 vs. co-formulations					

Table 5 continued

Author, year	Weight change from baseline; mean	Intergroup *p* value	Baseline Insulin dose	Post-treatment insulin dose	Intergroup *p* value
Kumar, 2017 [54]	1.74 vs. 1.41	–	–	0.69 vs. 0.69 U/kg/day	–
Kumar, 2016 [55]	2.8 vs. 4.4	< 0.0001 in favor of Gla-100	–	0.70 vs. 0.78 U/kg/day	–
Onishi Y 2013 [56]	0.7 vs. 0.7	-	11.0 vs. 10.0 U/day	29.0 vs. 28.0 U/day	–
Gla-100 vs. other basal insulins					
Cander S, 2014 [57]	1.0 vs. 0.0 vs. 1.1	–	0.12 vs. 0.12 vs. 0.12 U/kg/day	0.25 vs. 0.22 vs. 0.19 U/kg/day	–
Wei W, 2014 [59]	–	–	46.6 vs. 45.1 vs. 41.1 vs. 40.0 vs. 49.3 vs. 51.2 U/day	47.6 vs. 48.4 vs. 41.5 vs. 42.1 vs. 54.6 vs. 53.0 U/day	–
Meneghini L, 2013 [60]	0.49 vs. 1.0	< 0.05 in favor of IDet	0.2 vs. 0.2 U/kg/day	0.70 vs. 0.61 U/kg/day	0.0119 in favor of Gla-100
Esposito, 2008 [61]	2.4 vs. 2.8	-	11.0 vs. 10.0 U/day	52.0 vs. 57.0 U/day	-
Rosenstock, 2008 [9]	2.8 vs. 3.5	< 0.05 in favor of IDeg	0.2 vs. 0.2 U/kg/day	0.78 vs. 0.44 U/kg/day	< 0.0001 in favor of Gla-100
Malone, 2005 [62]	0.82 vs. -0.06	0.001 in favor of Gla-100	0.27 vs. 0.27 U/kg/day	0.42 vs. 0.36 U/kg/day	< 0.001 in favor of Gla-100

PYE patient-years of exposure
[a]% if not mentioned

Table 6 Safety outcomes (Intensification)

Author, year	Study duration (months)	Overall hypoglycemia	Intergroup *p* value	Nocturnal hypoglycemia	Intergroup *p* value	Severe hypoglycemia[a]	Intergroup *p* value
Gla-100 vs. NPH insulin							
Betonico, 2019 [72]	9–12	4.9 vs. 6.3 events / patient	-	0.5 vs. 1.5 events / patient	0.047	0.7 vs. 1.03 events/patient	–
Rosenstock, 2001 [73]	6–9	61.4 vs. 66.8	-	31.3 vs. 40.2	0.02	6.6 vs. 10.4	–
Gla-100 vs. premixed insulin							
Aschner, 2015 [74]	6–9	1.20 vs. 3.40 episodes/ PYE	–	0.35 vs. 1.01 episodes / PYE	< 0.05	–	–
Ito H, 2014 [71]	3–6	–	–	–	–	–	–
Tinahones, 2014 [75]	6–9	16.51 vs. 13.07 episodes / PYE	–	1.54 vs. 1.82 episodes / PYE	–	0.04 vs. 0.0 episodes / PYE	–
Tentolouris N, 2013 [83]	> 12	0.705 vs. 0.757 episodes / patient/year	–	0.053 vs. 0.076 episodes / patient/year	–	0.007 vs. 0.017 episodes / patient / year	–
Jain, 2010 [67]	6–9	2.19 vs. 1.57 episodes / Patient/ month	0.022	46.7 vs. 46.9% of the population	–	2.1 vs. 3.4% of the population	–
Rosenstock, 2008 [76]	6–9	48.70 vs. 51.20	–	4.78 vs. 6.17	–	0.10 vs. 0.04	–
Joshi, 2005 [70]	3–6	58.08 vs. 16.07	< 0.05	–	–	–	–
Fritsche, 2010 [64]	> 12	13.99 events per patient-year vs. 18.54 events per patient-year	NS	2.28 vs. 2.37 events per patient-year	NS	0.11 vs. 0.22 events per patient-year	NS

Table 6 continued

Author, year	Study duration (months)	Overall hypoglycemia	Intergroup *p* value	Nocturnal hypoglycemia	Intergroup *p* value	Severe hypoglycemia[a]	Intergroup *p* value
Levin, 2011 [77]	6–9	36 vs. 42%	NS	–	–	–	–
Bowering, 2012 [78]	9–12	1.96 events per patient per 30 days vs. 1.71 events per patient per 30 days	NS	0.85 events per patient per 30 days vs. 0.67 events per patient per 30 days	NS	2.8 vs. 3.4%	NS
Miser, 2010 [63]	6–9	Intensification arm A – 11.2 (44.8) vs. 10.1 (21.8) Intensification arm B – 12.1 (28.2) vs. 11.1 (20.4) events / PYE	NS	Intensification arm A – 3 (13.6) vs. 2.5 (7.0) Intensification arm B – 2.4 (6.1) vs. 2.5 (8.1) events / PYE	NS	Intensification arm A – 3 (13.6) vs. 2.5 (7.0) Intensification arm B – 2.4 (6.1) vs. 2.5 (8.1)	
Riddle, 2014 [66]	> 12	G + 1 vs. G + 3 vs. PM (2 +) – 7.1 (0.9) vs. 7.2 (1) vs. 12.2 (1.7)	0.0013 for G + 1 vs. PM (2 +); 0.0016 for G + 3 vs. PM (2 +)	–	–	G + 1 vs. G + 3 vs. PM (2 +) – 0.1 (0) vs. 0.2 (0.1) vs. 0.2 (0.1)	NS for all comparisons
Vora, 2015 [65]	6–9	15.3 events / PYE vs. 18.2 events / PYE	NS	5.7 events / PYE vs. 3.6 events / PYE	0.019	–	–
Jia, 2015 [79]	6–9	0.41 (0.67) events / patient / 30 days vs. 0.47 (1.04) events / patient / 30 days	NS	0.05 (0.21) events / patient / 30 days vs. 0.03 (0.09) events / patient / 30 days	NS	0 vs. 0	NS
Giugliano, 2014 [68]	9–12	8.13 (13.45) events / PYE vs. 9.63 (19.31) events / PYE	NS	1.09 (3.25) events / PYE vs. 1.91 (5.20) events / PYE	0.018	0.12 (0.80) events / PYE vs. 0.09 (0.74) events / PYE	NS

Table 6 continued

Author, year	Study duration (months)	Overall hypoglycemia	Intergroup *p* value	Nocturnal hypoglycemia	Intergroup *p* value	Severe hypoglycemia[a]	Intergroup *p* value
Gla-100 vs. second-generation basal insulins							
Hollander, 2015 [80]	> 12	9.84 vs. 12.76 episodes / PYE	0.011	1.27 vs. 1.77 episodes / PYE	0.016	0.05 vs. 0.06 episodes / PYE	–
Riddle, 2014 [81]	6–9	26.37 vs. 28.08 episodes / PYE	–	3.32 vs. 4.57 episodes / PYE	0.0045	0.27 vs. 0.24 episodes / PYE	–
Gla-100 vs. co-formulations							
Philis-Tsimikas A, 2019 [82]	9–12	2.87 vs. 3.43 episodes / PYE	–	0.6 vs. 1.01 episodes / PYE	< 0.05	0.037 vs. 0.048 episodes / PYE	–
Gla-100 vs. other basal insulins							
Raskin, 2009 [84]	6–9	19.30 vs. 17.94 episodes / PYE	–	4.23 vs. 3.38 episodes / PYE	–	0.09 vs. 0.12 episodes / PYE	–
Hollander, 2008 [84]	> 12	12.55 vs. 9.30 episodes / PYE	NS	2.88 vs. 2.4 episodes / PYE	NS	–	–

Table 6 continued

Author, year	Weight change from baseline; mean	Intergroup *p* value	Baseline insulin dose	Post-treatment insulin dose	Intergroup *p* value
Gla-100 vs. NPH insulin					
Betonico, 2019 [72]	–	–	–	0.31 vs. 0.34 U/kg/day	–
Rosenstock, 2001 [73]	0.4 vs. 1.4	0.0007	–	0.75 vs. 0.75 U/kg/day	–
Gla-100 vs. premixed insulin					
Aschner, 2015 [74]	1.1 vs. 1.4	–	0.17 vs, 0.17 U/kg/day	0.60 vs. 0.81 U/kg/day	–
Ito H, 2014 [71]	–	–	26.8	25.8	–
Tinahones, 2014 [75]	1.13 vs. 0.5	0.018 in favor of basal bolus	33.8 vs. 33.5 U/day	39.8 vs. 37.4 U/day	–
Tentolouris N, 2013 [83]	0.734 vs. 0.121	–	0.61 vs. 0.56 U/kg/day	0.65 vs. 0.53 U/kg/day	< 0.001 in
Jain, 2010 [67]	3.19 vs. 3.09	–	–	0.51 vs. 0.57 U/kg/day	0.017
Rosenstock, 2008 [76]	4.0 vs. 4.5	–	52.0 vs. 55.0 U/day	123.0 vs. 146.0 U/day	0.002
Joshi, 2005 [70]	–	–	38.23 vs. 57.39 U/day	40.19 vs. 52.77 U/day	–
Fritsche, 2010 [64]	3.6 vs. 2.2	< 0.0001	52.4 vs. 58.3 U/day	98 vs. 91.3 U/day	< 0.0001
Levin, 2011 [77]	2.40 vs. 2.35	0.03	76.92 vs. 77.65 U/day	78.31 vs. 90.06 U/day	NS
Bowering, 2012 [78]	2.92 vs. 2.78	NS	–	0.71 vs. 0.71 U/kg/day	NS

Table 6 continued

Author, year	Weight change from baseline; mean	Intergroup *p* value	Baseline insulin dose	Post-treatment insulin dose	Intergroup *p* value
Miser, 2010 [63]	Intensification arm A – 0 vs. 2 Intensification arm B – 0 vs. 2	NS	Intensification arm A – 41 (24.3) vs. 41.9 (24.4) Intensification arm B – 50 (24) vs. 49.9 (21.3) U/day	Intensification arm A – 69.4 (44.4) vs. 71.1 (39.4) Intensification arm B – 74.4 (36.1) vs. 73.9 (39.2) U/day	NS
Riddle, 2014 [66]	G + 1 vs. G + 3 vs. PM (2 +) – 5.0 (6.5) vs. 6.8 (7.6) vs. 6.4 (6.9)	0.024 for G + 1 and G + 3 vs. PM (2 +)	–	G + 1 vs. G + 3 vs. PM (2 +) – 0.92 (0.47) vs. 1.05 (0.73) vs. 1.04 (0.66) U/kg/day	NS for all comparisons
Vora, 2015 [65]	2.06 vs. 2.5	NS	–	–	NS
Jia, 2015 [79]	0.7 vs. 0.8	NS	0.62 (0.21) vs. 0.63 (0.20) U/kg/day	0.76 (0.27) vs. 0.74 (0.25) U/kg/day	NS
Giugliano, 2014 [68]	2.32 (3.7) vs. 2.31 (3.3)	NS	–	0.57 (0.39) vs. 0.56 (0.32) U/kg/day	NS
Gla-100 vs. second-generation basal insulins					
Hollander, 2015 [80]	4.4 vs. 4.0	–	–	0.71 vs. 0.76 U/kg/day	–
Riddle, 2014 [81]	0.9 vs. 0.9	–	0.67 (vs. 0.67 U/kg/day	0.97 vs. 0.88 U/kg/day	–
Gla-100 vs. co-formulations					
Philis-Tsimikas A, 2019 [82]	2.4 vs. 2.5	–	35.2 vs. 34.6 U/day	83.4 vs. 89.3 U/day	< 0.05 in favor of IDegAsp

Table 6 continued

Author, year	Weight change from baseline; mean	Intergroup *p* value	Baseline insulin dose	Post-treatment insulin dose	Intergroup *p* value
Gla-100 vs. other basal insulins					
Raskin, 2009 [84]	1.2 vs. 2.7	0.001 in favor of IDet	0.2 vs. 0.2 U/kg/day	0.81 vs. 0.75 U/kg/day	–
Hollander, 2008 [85]	3.8 vs. 2.8	< 0.05	–	–	NS

PYE patient-years of exposure

(*P* = 0.029) [42] (see Table S2 in the electronic supplementary material for details).

Safety Outcomes

Primary Outcomes

Hypoglycemia Events

Out of 13 studies reporting hypoglycaemia, only three studies reported significant difference between Gla-100 and second-generation basal insulins. These studies were of fair-to-good quality [43, 45, 48]. Gla-300 receiving patients exhibited significantly lower overall rate of hypoglycemia when compared with Gla-100 (6.4 vs. 8.5 events/PYE, *P* = 0.042) [48]. However, in a crossover study, IDeg followed by Gla-100 in combination to OADs led to lesser hypoglycemic events than those receiving Gla-100 followed by IDeg (219.9 episodes vs. 275.1 episodes/ 100 PYE, *P* < 0.001) [45]. Similarly, no significant difference was observed between the two groups in the rates of nocturnal hypoglycaemia, apart from the abovementioned study where IDeg followed by Gla-100 administration resulted in fewer events than the group receiving Gla-100 followed by IDeg (*P* < 0.001). In a study by Zinman et al. Gla-100 group reported significantly lower incidence of severe hypoglycemia compared with IDeg group (*P* = 0.017) [53] (Table 5).

Gla-100 vs. Co-formulations Only three studies reported the use of Gla-100 with insulin co-formulations [54–56] and were of fair-to-good quality. These co-formulations consisted of IDegAsp with various OAD combinations (including MET, DPP-4 inhibitor, SU, pioglitazone) (Table 3).

Glycemic Outcomes

Primary Outcomes

HbA1c

No significant difference was reported for HbA1c reductions between the groups receiving Gla-100 and insulin co-formulations in all the three studies [54–56] (Table 3).

Response Rates

The two groups exhibited a similar number of patients achieving target HbA1c levels. There were no data reported for the number of patients achieving FPG targets [54–56] (see Table S2 in the electronic supplementary material for details).

Safety Outcomes

Primary Outcomes

Hypoglycemia events

A study by Kumar A et al. reported significant difference ($P < 0.0001$) and a treatment ratio of 1.86 in favor of Gla-100 [55] for overall and nocturnal hypoglycaemia. Another study by Kumar S et al. reported significantly lower incidence of hypoglycemia in Gla-100 receiving group (48.1 vs. 52.3%, $P < 0.05$) [54] (Table 5).

Gla-100 vs. Other First-Generation Basal Insulins Only seven studies evaluated the effect of Gla-100 against other first-generation basal insulins in insulin-naïve patients with T2DM undergoing insulin initiation. Of these, five studies were of good quality [9, 58–61] and two were of poor quality [57, 62]. A majority of studies ($n = 6$) compared Gla-100 in combination with OADs against human NPL insulin (75/25 mix) and variants of insulin detemir (IDet, Det S compact) (Table 3).

Glycemic Outcomes

Primary Outcomes

HbA1c

Gla-100 and other first-generation basal insulins did not differ significantly with respect to HbA1c reduction in five of the seven studies [9, 57, 58, 60, 61], the majority ($n = 5$) of which were of good quality. However, Gla-100 was found to be more effective than detemir formulations ($P < 0.05$) [59]. A switch-over study conducted by Malone et al. administered lispro mix (75/25) followed by Gla-100 and compared it with the group that received Gla-100 followed by lispro mix (75/25). The study reported a greater reduction in HbA1c levels in the arm receiving Gla-100 first than those receiving lispro mix (75/25) (− 1 vs. − 0.42; $P < 0.001$) [62] (Table 3).

Response Rates

Though three studies did not report any significant difference between Gla-100 and other first-generation basal insulins, there were two studies that reported a significantly higher number of Gla-100 receiving patients achieving target HbA1c levels (53 vs. 38%, $P = 0.026$) and target FPG (58 vs. 46%, $P < 0.01$) when compared to those receiving IDet [9, 60]. Both of these studies were of good quality. Interestingly, in a switch-over study (poor quality), a greater number of patients receiving lispro mix (75/25), followed by Gla-100 achieved target HbA1c levels (30 vs. 12%, $P = 0.002$) than those receiving Gla-100 followed by lispro mix (75/25). However, the opposite was true for patients achieving FPG levels with more patients receiving Gla-100 followed by lispro mix (75/25) achieving target FPG levels (51 vs. 34%, $P = 0.01$)[62]. None of the studies reported data on treatment satisfaction (see Table S2 in the electronic supplementary material for details).

Safety Outcomes

Primary Outcomes

Hypoglycemia Events

No significant difference was observed in hypoglycemic events between patients receiving Gla-100 and other first-generation basal insulins in five studies reporting hypoglycemia events; of which three were of good quality and two were of poor quality. However, one study of good quality reported that Gla-100 was associated with a significantly higher number of hypoglycemic episodes per patient-year when compared to those receiving IDet (4.41 vs. 3.19 patient-years, $P = 0.034$) [60]. Similarly, a significantly higher number of nocturnal events were observed in patients receiving Gla-100 followed by lispro mix (75/25) than those receiving lispro mix (75/25) followed by Gla-100 ($P = 0.002$) [62] (Table 5).

Other Outcomes *Gla-100 vs. NPH*

Other Glycemic Outcomes

BG Profile

Of the six studies reporting the difference between FPG levels at baseline and at study endpoint, five studies were of good-to-fair quality [15, 17, 19, 22, 25] and one study was of poor quality [20]. Out of these eight studies, Gla-100 resulted in significant FPG reduction in four studies [14–16, 24] (Table 3).

Glycemic Variability

Total seven studies reported glycemic variability, either in terms of coefficient of variation (CV) [18, 21] or reduction in mean blood glucose values [15, 19, 20, 24, 25]. Of these, four studies were of fair-to-good quality [15, 19, 21, 25], while the remaining three were

of poor quality [18, 20, 24]. The study by Mu et al. reported that Gla-100 exhibited better reduction in CV [13.4 (3.6) at baseline to 10.2 (4.2) at the end of study] when compared with NPH (12.9 [4] at baseline to 19.6 [6.1]; $P < 0.05$) [18]. In a study by Mattia et al., when Gla-100 was followed by NPH, Gla-100 exhibited not only lower BG excursion at 5-h (129.1 vs. 152.8 mg/dL; $P < 0.05$) but also at 6-h post-meal test (108.5 vs. 154.6 mg/dL; $P < 0.01$) when compared with NPH insulin [19]. When NPH was followed by Gla-100 in the same study, Gla-100 offered significantly efficient post-prandial glucose control (146.5 [16.7] mg/dL) when compared with NPH (171.2 [24.7] mg/dL) ($P < 0.02$) [19]. However, the study by Yki-Jarvinen et al. reported no significant difference between CVs of FPG for Gla-100 and NPH [21] (See Table S4 in the electronic supplementary material for details).

Other Safety Outcomes

Weight Change and Insulin Dose Change

Out of the nine studies reporting weight change, seven were of good-to-fair quality [14–17, 19, 21, 25]. It was observed that Gla-100 and NPH did not differ significantly with respect to weight gain, and the difference was statistically non-significant in five studies. However, significant change in weight gain was reported by two studies and both demonstrated that NPH effectively controls weight gain in insulin-naïve patients with diabetes ($P < 0.05$; $P = 0.01$) [14, 17] (Table 5).

Most of the studies ($n = 8$) did not differ significantly with respect to change in insulin dose between baseline and study endpoint [15, 17, 19–22, 26]; of which six studies were of fair-to-good quality. However, one study of fair quality reported significant increase in insulin dose from baseline (10 U/day for Gla-100 and NPH) to 47.2 (1.3) U/day for Gla-100 compared with 41.8 (1.3) U/day for NPH ($P < 0.005$) [25] (Table 5).

Treatment Satisfaction

Eliaschewitz et al. reported a significantly better treatment satisfaction with Gla-100 vs. NPH insulin ($P < 0.02$). The same study also reported that fewer patients receiving Gla-100 lost time from work or normal activities due to diabetes when compared with those receiving NPH (1.8 vs. 3.3%) [22] (See Table S2 in the electronic supplementary material for details).

Gla-100 vs. Premixed Insulin

Other Glycemic Outcomes

BG Profile

In total, 19 studies reported either FPG or PPG levels at baseline, endpoint, and the mean change values. Gla-100 was found to provide better glucose control for FPG and reported statistically significant reduction in FPG levels in six studies of fair-to-good quality when compared to other premixed insulin regimens ($P < 0.0001$ to < 0.01) [12, 27, 28, 33, 39, 41]. Significant improvements in the PPG levels were also observed in patients receiving Gla-100 compared to those receiving premixed insulin regimens ($P < 0.0001$ and < 0.01) in two studies of fair quality [12, 28]. However, a single study (which was of poor quality) reported significantly improved PPG levels with premixed insulin (twice daily) compared with Gla-100 (once daily) ($P = 0.001$) [30] (Table 3).

Glycemic Variability

Out of six studies reporting insulin initiation comparing treatment difference between Gla-100 and premixed insulins, five were of fair-to-good quality [13, 29, 35, 39, 40]. It was reported that though Gla-100 offers better blood glucose control than human premixed insulin (30% regular, 70% NPH insulin; insulin actraphane HM 30/70) [39], it did not provide as much insulin sensitivity when compared to that of insulin lispro 25/75 BID (9.3 [6.6] vs. 14.4 [10.8], $P = 0.020$) [13]. Likewise, premixed insulin seemed to offer better postprandial glycemic exposure ($\sim$ 25% less for the BIAsp 70/30 group than for the Gla-100 group, 97.4 [90.4] vs. 129.6 [102] mg/dL, $P < 0.05$) [40] (see Table S4 in the electronic supplementary material for details).

Other Safety Outcomes

Weight Change and Insulin Dose Change

In total, 19 studies reported the body weight either at baseline, post-treatment, or the difference in weights. However, only six have reported a statistical difference between Gla-100 vs. premixed insulins, with Gla-100 unanimously found to be associated with significantly less weight gain ($P < 0.001$ to < 0.05) in six studies.

These studies were of fair-to-good quality [28, 29, 33, 36, 40, 41] (Table 4).

Six studies reporting significantly lesser change in the insulin dose from baseline to endpoint for Gla-100 compared with premixed insulin regimens ($P < 0.005$ to < 0.05) were of fair-to-good quality; except Kazda et al., which was of poor quality [10, 33, 35, 39–41]. On the contrary, four studies reported no statistical difference between Gla-100 and premixed insulin dose increment, of which three were of fair-to-good quality [7, 31, 32, 34] (Table 4).

Treatment Satisfaction

Gla-100 exhibited better treatment satisfaction scores than premixed insulins ($P < 0.0001$ to < 0.05) in three studies that were of fair-to-good quality [12, 28, 29] (see Table S2 in the electronic supplementary material for details).

Gla-100 vs. Second-Generation Basal Insulin

Other Glycemic Outcomes

BG Profile

In total, nine studies comparing second-generation insulin regimens with Gla-100 did not show any statistical difference in reduction in FPG levels. However, one study by Marso et al. [44] reported that in comparison to Gla-100, IDeg caused a significant reduction in FPG levels ($P < 0.0001$) [44]. None of the studies reported any data regarding PPG levels (Table 3).

Glycemic Variability

Only three studies, which were of good quality, reported data on glycemic variability [46, 48, 51]. Compared to Gla-300, Gla-100 provided lower CV (%) (18.7 [0.5] vs. 18.3 [0.5]) [48]. Similar results were reported in another study wherein lower CV was reported in the Gla-100 group (12.9%) when compared with theIDeg-100 group (14.2%) [46] (see Table S4 in the electronic supplementary material for detail). However, these differences did not reach any statistical significance.

Other Safety Outcomes

Weight Change and Insulin Dose Change

In total, 13 studies reporting changes in body weight for patients receiving either Gla-100 or a second-generation basal insulin were of fair-to-good quality. Nine studies showed no statistical difference between the groups [44–48, 50–53]. However, two studies reported that Gla-300 was associated with significantly lower weight gain than Gla-100 ($P = 0.003$ and 0.015) [8, 49] (Table 5).

Of all the 13 studies reporting a change in insulin dose, only two studies of fair-to-good quality exhibited a significant difference in favor of Gla-100 ($P = 0.04$ and < 0.05) [44, 49]; whereas three studies reported increased dose of IDeg at the endpoint ($P < 0.05$) [47, 50, 51] (Table 5).

Treatment Satisfaction

No study exhibited significant difference in the treatment satisfaction scores.

Gla-100 vs. Co-Formulations

Other Glycemic Outcomes

BG Profile

No significant difference was reported for FPG levels between the groups receiving Gla-100 and insulin co-formulations. No data on PPG levels were reported in these studies [54–56] (Table 3).

Glycemic Variability

Only one study of fair quality reported significantly lower prandial glucose increments, overall and at main evening meal, with IDegAsp once daily than with Gla-100 once daily ($P < 0.001$) [54] (see Table S4 in the electronic supplementary material for details).

Other Safety Outcomes

Weight Change and Insulin Dose Changes

One study of good quality reported significant weight gain in patients receiving Gla-100 when compared with those receiving insulin co-formulations (4.4 vs. 2.8 kg, $P < 0.0001$) [55] (Table 5).

The insulin dose changes were similar between the groups receiving Gla-100 and co-formulation groups [54–56] (Table 5).

Treatment Satisfaction No data were reported regarding treatment satisfaction.

Gla-100 vs. Other First-generation Basal Insulins

Other Glycemic Outcomes

BG Profile

A total of four studies reported FPG reductions; of which three studies were of good quality [9, 60, 61] and one of poor quality [62]. The majority of studies ($n = 3$) comparing Gla-100 and other first-generation basal insulins did not report significant difference with respect to

reduction in FPG levels. The study conducted by Malone et al. administered lispro mix (75/25) followed by Gla-100 and compared it with the group that received Gla-100 followed by lispro (75/25). The study reported a significant difference in favor of the group receiving Gla-100 followed by lispro mix (75/25) ($P < 0.007$) [62] (Table 3).

Glycemic Variability One study of poor-quality reported data on glycemic variability comparing Gla-100 with other first-generation basal insulins. Compared to Gla-100, the measure of insulin sensitivity was found to be lower with the insulin lispro mixture (23.18 [20.92] vs. 31.44 [23.93]; $P = 0.001$) in patients receiving Gla-100 followed by lispro mix [62] (see Table S4 in the electronic supplementary material for details).

Other Safety Outcomes

Weight Change and Insulin Dose Change

Out of five studies reporting weight changes, three were of good quality [9, 60, 61] and two were of poor quality [57, 62]. The weight gain was significantly lower in patients receiving Gla-100, as reported in one study ($P = 0.001$) [62], while the other two studies reported significantly lower weight gain in the IDet group ($P < 0.05$) [9, 60] (Table 5).

Of the three studies reporting significant differences in increased insulin doses, two were of good quality [9, 60] and one was of poor quality [62]. However, these changes were in favor of Gla-100, which exhibited lower dose change than other insulins ($P < 0.0001$ to $P = 0.0119$) [9, 60, 62] (Table 5).

Treatment Satisfaction None of the studies reported data on treatment satisfaction.

Insulin Intensification

Gla-100 vs. NPH Insulin

Glycemic Outcomes

Primary Outcome

HbA1c

Two studies of fair quality reported data on the change in HbA1c levels. The study by Rosenstock et al. did not report any significant difference in groups receiving Gla-100 along with regular pre-meal insulin, and those taking NPH insulin along with regular insulin. However, a study by Betonico et al. included patients taking two different insulin regimens: Gla-100 OD followed by NPH, both administered along with insulin lispro (group A); and Insulin NPH followed by Gla-100, both co-administered with insulin lispro (group B). The patients in group A reported a significant reduction in HbA1c levels post treatment ($P = 0.028$) [72, 73] (Table 4).

Response Rates

One study reported the proportion of patients achieving target FPG levels and there was no significant difference in the proportion of patients receiving either Gla-100 (23.6%) or NPH insulin (27.1%) [73] (see Table S3 in the electronic supplementary material for details).

Safety Outcomes

Primary Outcome

Hypoglycemia Events

Both studies reporting hypoglycemia events were of fair quality. Similar proportions of overall hypoglycemic events were observed in patients receiving either Gla-100 or NPH. On the contrary, Gla-100 exhibited a significantly lower number of confirmed nocturnal hypoglycemic events than those receiving NPH (31.3 vs. 40.2%, $P = 0.02$ and 0.5 vs. 1.5 events/patient, $P = 0.047$) [72, 73]. Compared to NPH, overall hypoglycemic events and severe hypoglycemia events were relatively fewer in patients receiving Gla-100, but the difference was statistically insignificant (Table 6).

Gla-100 vs. Premixed Insulin

Glycemic Outcomes

Primary Outcome

HbA1c

Out of 15 studies reporting the change in HbA1c levels from baseline to the endpoint in patients receiving either Gla-100 or premixed insulins, six were of fair-to-good quality [70, 71, 74–77]. Three of these 15 studies reported that premixed insulin was able to significantly reduce the HbA1c level towards the endpoint when compared to those receiving Gla-100 [70, 74, 75]; however, in five studies, Gla-100 significantly reduced HbA1c levels [64, 66, 76, 77, 83] (Table 4).

Response Rates

Of the six studies reporting response rates, fourreported statistically significant outcomes. Three of these were of good quality. In two of

these studies, significantly fewer patients receiving Gla-100 were able to achieve target HbA1c levels when compared to those receiving premixed mixture ($P < 0.005$, each) [70, 74]. However, in the remaining two studies, a significantly higher number of patients receiving Gla-100 achieved target HbA1c levels [64, 76] (see Table S3 in the electronic supplementary material for details).

Safety Outcomes

Primary Outcome

Hypoglycemia Events

Out of 14 studies reporting hypoglycemia events, five were of good quality [70, 74–76, 83]. Only two studies reported statistically significant differences, with a higher ($P < 0.05$) proportion of overall hypoglycemia events in Gla-100 intensified arm as compared to the group receiving premixed insulin[67, 70]. Further, only two studies showed statistically significant difference in terms of nocturnal hypoglycemia with the patients receiving Gla-100 intensified regimen exhibiting fewer confirmed events of nocturnal hypoglycemia than those receiving premixed insulin [68, 74] (Table 6).

Gla-100 vs. Second-Generation Basal Insulins

Glycemic Outcomes

Primary Outcome

HbA1c

Of the two insulin intensification studies evaluating Gla-100 vs. second-generation basal insulin, only one study reporting the effect on HbA1c reduction between Gla-100 and second-generation basal insulin (Gla-300) was of good quality. Interestingly, both study groups exhibited a similar reduction in HbA1c at study endpoint and the difference was not statistically significant [81]. Further, the study by Hollander et al., which was of poor quality, showed similar HbA1c reduction in both Gla-100 and IDeg treatment arms; the estimated treatment difference was non-significant between Gla-100 and IDeg, suggesting that similar glycemic control can be achieved with Gla-100 and IDeg [80] (Table 4).

Response Rates

Three studies reported data comparing Gla-100 and its second-generation analogues including Gla-300 and IDeg. No difference was observed between groups with respect to number of patients achieving target HbA1c and FPG levels, either with or without hypoglycemic events (see Table S3 in the electronic supplementary material for details).

Safety Outcomes

Primary Outcome

Hypoglycemia Events

No differences were observed in the number of overall hypoglycemic events and severe hypoglycemia between patient groups receiving Gla-100 and Gla-300. However, Gla-100 exhibited more episodes of nocturnal hypoglycemia than corresponding Gla-300 (4.57 vs. 3.32 episodes/patient-year) and the difference was statistically significant ($P = 0.0045$) [81]. On the contrary, Hollander et al. reported significantly reduced risk of hypoglycemia (overall rate of hypoglycemia: 24% lower; $P = 0.011$ and nocturnal hypoglycemia: 31% lower; $P = 0.016$) with IDeg use than with Gla-100 [80] (Table 6).

Gla-100 vs. Co-Formulations

Glycemic Outcomes

Primary Outcome

HbA1c

Only one insulin intensification study comparing Gla-100 vs. co-formulations reported HbA1c reduction; the study was of fair quality. Both Gla-100 and insulin co-formulations (IDegAsp, aspart) exhibited similar HbA1c reduction profiles, and no significant difference was observed between treatment groups [82] (Table 4).

Response Rates

No studies comparing Gla-100 and insulin co-formulations (IDegAsp, aspart) reported data on the response rate.

Safety Outcomes

Primary Outcome

Hypoglycemia Events

No differences were observed in the number of overall hypoglycemic events or severe hypoglycemia events between patient groups receiving Gla-100 and IDegAsp. However, Gla-100 exhibited higher number of confirmed nocturnal hypoglycemia events than corresponding insulin co-formulation group (1.01 vs. 0.6 episodes/patient-year) and the difference was statistically significant ($P < 0.05$) [82] (Table 6).

Gla-100 vs. other First-Generation Basal Insulins

Glycemic Outcomes

Primary Outcome

HbA1c

Only one study reported HbA1c reduction and the study was of fair quality. A study by Raskin et al. reported that patients receiving Gla-100 in combination with insulin aspart and other OADs were able to significantly reduce the HbA1c levels when compared to patients receiving other basal insulins like IDet with insulin aspart and other OADs (− 1.28 vs. − 1.08, $P = 0.035$) [78] (Table 4).

Response Rates

No studies comparing Gla-100 and other first-generation basal insulins reported data on response rate.

Safety Outcomes

Primary Outcome

Hypoglycemia Events

Incidence of hypoglycemic events (17.94 vs. 19.30 episodes/PYE) and confirmed nocturnal hypoglycemia (3.38 vs. 4.23 episodes/PYE) and severe hypoglycemic events (0.12 vs. 0.09 episodes/PYE) were comparable between patients receiving IDet and those receiving Gla-100 [78] (Table 6).

Other Outcomes *Gla-100 vs. NPH*

Other Glycemic Outcomes

BG Profile

None of the insulin intensification studies reported any data comparing the effect on FPG and PPG levels after administering Gla-100 with NPH.

Glycemic Variability

Glycemic variability was reported in one study of fair quality. No significant difference in glycemic variability was reported in patients taking Gla-100 followed by NPH co-administered with insulin lispro vs. those receiving NPH, followed by Gla-100 co-administered with insulin lispro [72]. However, it was observed that Gla-100 receiving patients spent lower average daily time in hypoglycemia than those receiving NPH. On the other hand, no significant differences were observed in the risk of hypoglycemia between the two groups (see Table S5 in the electronic supplementary material for details).

Other Safety Outcomes

Weight Change and Insulin Dose Change

The study by Rosenstock et al. (2001) (fair quality study) reported a significantly lower weight change in patients receiving Gla-100 when compared to those receiving NPH insulin (0.4 vs. 1.4 kg, $P = 0.0007$) when administered with regular pre-meal insulins [73] (Table 6).

Change in the insulin dose from baseline to the endpoint was similar in Gla-100 and NPH groups, and no statistical difference was observed in both the studies [72, 73] (Table 6).

Treatment Satisfaction

No data on treatment satisfaction were reported.

Gla-100 vs. Premixed Insulin

Other Glycemic Outcomes

BG Profile

Only three studies, which were of good quality, reported data on FPG profiles [70, 74, 83]. Compared to their premixed counterparts, Gla-100 was found to be associated with significant reduction in the FPG levels from the baseline values in three studies ($P < 0.001$ each) [66, 74, 83]. Only one study reported PPG profile, which indicated reduction in PPG levels in both the treatment arms (premixed insulin: 287.29–171.54; Gla-100: 281.42–177.52), but the difference was not significant [67] (Table 4).

Glycemic Variability

The BG profile improved in both groups at study end, with more pronounced decline in BG observed in the group receiving premixed insulin than the one receiving Gla-100 (LS mean difference: 3.6 mg/dL [95% CI 0.03–0.4]; $P = 0.024$) [74] (see Table S5 in the electronic supplementary material for details).

Other Safety Outcomes

Weight Change and Insulin Dose Change

Patients receiving Gla-100 or other premixed insulin formulations exhibited similar weight change in a majority of studies; of which three studies were of good quality and one was of poor quality [67, 74, 76, 83]. However, a study conducted by Tinahones et al. reported significantly lower weight change in the Gla-100 group compared to the lispro mix group (0.5 vs.

1.13 kg, $P = 0.018$), with simultaneous oral administration of OADs [75] (Table 6). Out of 15 studies, two of fair-to-good quality reported no significant change in insulin dose from baseline [71, 75] (Table 6).

Treatment Satisfaction

No data on treatment satisfaction were reported.

Gla-100 vs. Second-generation Basal Insulin

Other Glycemic Outcomes

BG Profile

A study by Riddle et al. reported the effect on FPG levels between Gla-100 and Gla-300. Both groups exhibited similar reduction in FPG levels at study endpoint and the difference was not statistically significant [81]. Another study reporting the effect on FPG levels between Gla-100 and IDeg showed similar reduction in FPG levels [64] (Table 4).

Glycemic Variability

There was no difference in the change of day-to-day variability of pre-injection SMPG between Gla-100 and Gla-300 study groups [81] (see Table S5 in the electronic supplementary material for details).

Other Safety Outcomes

Weight Change and Insulin Dose Change

Similar weight gain was observed in Gla-100 and Gla-300 or IDeg groups at the study endpoint [64, 81]. A gradual increase in insulin dosing was observed in Gla-100 and Gla-300 regimens by the same extent, and no significant difference was observed between the two groups [81]. Hollander et al. reported similar insulin doses in IDeg and Gla-100 groups [80] (Table 6).

Treatment Satisfaction No data on treatment satisfaction were reported.

Gla-100 vs. Coformulation Insulin

Other Glycemic Outcomes

BG Profile

Gla-100 and IDegAsp exhibited similar FPG reduction profiles, and no significant difference was observed between treatment groups [82] (Table 4).

Glycemic Variability

No studies comparing Gla-100 and insulin co-formulations (IDegAsp) reported data on glycemic variability.

Other Safety Outcomes

Weight Change and Insulin Dose Change

Both Gla-100 and IDegAsp exhibited similar weight gain profiles, and no significant differences were observed between the treatment groups (Table 6).

One study reported data representing the increase in insulin dose between groups receiving Gla-100 and insulin aspart, and compared it with those receiving IDegAsp in combination with other OADs. The insulin dose gradually increased in both the groups. However, a significant increase in insulin dose was observed in patients receiving Gla-100 (34.6–89.3 U/day) than those receiving IDegAsp (35.2–83.4 U/day), and the difference was statistically significant ($P < 0.05$) [82] (Table 6).

Treatment Satisfaction No studies comparing Gla-100 and insulin co-formulations (IDegAsp) reported data on treatment satisfaction.

Gla-100 vs. Other First-Generation Basal Insulins

Other Glycemic Outcomes

BG Profile

In BG profile, Gla-100 and IDet exhibited similar FPG profile and no significant difference was observed between the two treatment groups. No studies reported data on the PPG profile (Table 4).

Glycemic Variability

No studies comparing Gla-100 and other first-generation basal insulin reported data on glycemic variability between the two treatment groups.

Other Safety Outcomes

Weight Change and Insulin Dose Change Patients receiving Gla-100 in combination with insulin aspart and OADs exhibited significantly higher weight gain than those receiving IDet along with insulin aspart and OADs (2.7 vs. 1.2, $P = 0.001$) [78] (Table 6).

Both Gla-100 and IDet exhibited significant increase in insulin dose from the baseline to the endpoint. However, the increase in insulin dose was not statistically significant between the two treatment groups [78] (Table 6).

Treatment Satisfaction

No studies comparing Gla-100 and other basal insulin reported data on treatment satisfaction.

Quality of Studies

Out of 63 RCTs, 22 were of good quality, 18 of fair, and 23 of poor quality. Six observational studies were of good quality and ten observational studies were fair in quality (see Table S6 and S7 in the electronic supplementary material for details).

Primary Outcome Data Summary of Good-Quality Studies

Primary outcome data of the 22 RCTs and six observational studies of good quality have been summarized in Table S8 (see electronic supplementary material for details).

DISCUSSION OF EVIDENCE: IMPLICATIONS FOR CLINICAL PRACTICE

The present systematic review reflects the current evidence base with regard to the use of Gla-100 in initiation and intensification of insulin therapy, wherein majority of the studies had compared Gla-100 with NPH, premixed and second-generation basal insulins. Overall, the data presented in this review, which included evidence from 79 studies, demonstrated that the initiation or intensification of Gla-100 in patients failing oral or other insulin therapies resulted in improved glycemic outcomes from baseline, with a low risk of hypoglycemia. In the subsequent section, we have tried to appraise the data discussed in this review to address important and practical clinical considerations with the use of Gla-100 in T2DM management.

Glucose-Lowering Ability of Gla-100 vs. Premixed Insulins in Insulin-Naïve Patients with T2DM

The majority of studies in the present review suggested that Gla-100 was better than premixed insulins and comparable to co-formulations in terms of HbA1c-lowering ability. Similar findings were reported in a systematic review and meta-analysis by Rys et al., which revealed a greater mean HbA1c reduction with Gla-100 + OADs vs. premixed insulins twice daily with a weighted mean difference (WMD) of − 0.36% [− 0.54, − 0.18] (− 3.9 mmol/mol [− 5.9; − 2.0])) and associated with a higher chance of reaching target HbA1c (RR = 1.49) [86]. Further, in all six studies that reported statistically significant differences in terms of FPG reduction, Gla-100 was associated with a greater FPG reduction compared to premixed insulins in insulin-naïve T2DM patients ($P < 0.0001$ to < 0.01) [12, 27, 28, 33, 39, 41]. Though PPG reduction was recorded in three of the head-to-head studies comparing Gla-100 vs. premixed insulins [10, 11, 30], only one showed a statistically significant difference in favor of premixed insulins [30]. The remaining two studies did not detect any statistical difference between either Gla-100 and premixed arms in terms of PPG reduction [11, 30]. Further, our analysis revealed that when patients receiving premixed insulin analogue were switched to Gla-100, there was a significant improvement in all the three glycemic parameters [12, 28]. This would indicate the glucose-lowering ability of Gla-100 in improving overall glycemic control. This evidence belonged to fair-quality studies [12, 28]. These results suggest that targeting basal normoglycemia with Gla-100 ± OADs leads to greater HbA1c and FPG reductions vs. premixed insulins along with mitigating PPG excursions in T2DM patients who are uncontrolled on OADs.

Gla-100 vs. Second-Generation Basal Insulin in Insulin-Naïve Patients with T2DM

When glucose-lowering efficacy was compared between Gla-100 and Gla-300, the majority of studies demonstrated comparability between these two basal insulins in achieving HbA1c and FPG reductions [6, 8, 43, 48, 49]. The data from the EDITION trials revealed comparable glucose-lowering efficacy for Gla-100 and Gla-300, but a significantly lower risk of hypoglycemia, particularly for nocturnal hypoglycemia associated with Gla-300 [69]. Similar observations were revealed in the trial-level meta-analysis

conducted by Roussel et al. to obfuscate the limitations of individual trials and facilitate a better understanding of results across the multiple individual trials [69]. In this analysis, the EDITION trials meta-analysis revealed comparable reductions in HbA1c, FPG, and average 24-h SMPG. The risk of confirmed or severe hypoglycemia events was significantly lower with Gla-300 vs. Gla-100, both nocturnally as well as throughout the daytime ($P = 0.007$ for both) [69]. The recent report from DELIVER 3 study, which was a good-quality evidence, showed a contrasting observation indicating superiority of Gla-300 over Gla-100 in achieving glycemic (HbA1c) reduction [42].

Compared to IDeg, HbA1c-lowering efficacy was comparable with Gla-100 across all studies [44–47, 50–53]. However, the trial-level meta-analysis revealed a greater HbA1c reduction with Gla-100 vs. IDeg ($P = 0.024$) [69]. Further, this trial-level meta-analysis showed a lower risk of confirmed or severe hypoglycemia nocturnally ($P = 0.007$) and not throughout the day ($P = 0.49$) with IDeg vs. Gla-100 [69].

Hence, in summary, evidence presented in this review pertaining to the second-generation basal insulins would suggest that their benefit over Gla-100 would only extend to a lower hypoglycemia risk (both nocturnal and anytime) with Gla-300 and a lower nocturnal hypoglycemia risk with IDeg, with a comparable glucose-lowering benefit to Gla-100.

Basal Prandial vs. Premixed Intensification Strategy

As T2DM is a progressive disease, intensification of insulin therapy is inevitable. There exists a wide variation in the guidelines' recommendations with respect to insulin intensification strategies, which is a challenge for physicians and a major barrier in their decision-making [87, 88]. The data presented in this review revealed that five studies showed significant reduction with Gla-100 than premixed regimens, whereas three out of the 15 intensification studies comparing premixed regimens vs. Gla-100-based insulin regimens revealed a significantly greater HbA1c reduction with premixed intensification regimens. However, two of the nine studies reported a statistically significant higher risk of overall hypoglycemia with premixed intensification regimen vs. Gla-100 intensification regimens, one study reported lower risk of overall hypoglycemia, seven did not show any difference, and the remaining studies did not mention the same. This is in line with the findings of the systematic review and meta-analysis by Rys et al., which have shown that Gla-100-based intensification strategy is similar to premixed intensification regimens both in terms of its HbA1c-lowering ability and hypoglycemia risk [86]. However, the gradual intensification of insulin therapy with basal-plus followed by basal-bolus is considered to mimic physiological insulin secretion more closely compared to premixed regimens [68, 80, 83]. Further, such an approach also helps in acclimatizing patients better to insulin regimens, which in turn may lead to a better chance of acceptance by the patients and therebymore success in routine clinical practice [89–92].

Strengths and Limitations

Strengths

Previously published secondary studies did not provide a full picture of clinical efficacy and safety of Gla-100 since they were focused exclusively on certain aspects of insulin therapy (for example, only insulin initiation or intensification of insulin treatment) and did not attempt to accrue all the included studies with Gla-100. This review includes a comprehensive and updated list of studies on Gla-100 vs. other insulin formulations for both initiation and intensification, is not limited by study design, and seeks to include a wide range of study designs including RCTs, and prospective and retrospective cohort and observational studies. This provides a comprehensive and up-to-date picture of Gla-100's use in T2DM management. Additionally, the evidence presented forth in this review has been appraised qualitatively with the intention of drawing the reader's focus on the fair-to-good quality of evidence with Gla-100.

Limitations
The heterogeneity of the clinical characteristics, complexities of the different insulin treatments, and study designs can confound the conclusions drawn from the data presented here. Moreover, this systematic review did not attempt to quantitatively appraise the data in the form of forest plots, which significantly limits the accuracy and precision of the conclusions.

CONCLUSIONS

In conclusion, this systematic literature review revealed that for the primary efficacy parameters studied in this review, Gla-100 insulin regimens may be a better insulin-initiation option compared to premixed insulins and comparable to NPH insulin, other first-generation basal insulins, co-formulations, and second-generation basal insulins. Overall, hypoglycemia risk with Gla-100 insulin (initiation regimens) was lower compared with NPH, premixed, co-formulations, and other first-generation basal insulins, but higher compared to second-generation basal insulins. For intensification of insulin therapy, Gla-100-based stepwise intensification strategy (basal plus to basal bolus) was better compared to other first-generation basal insulin; similar compared to NPH, co-formulations, second-generation basal insulins, and premixed insulins for the primary efficacy parameters. Further in intensification studies, overall hypoglycemia risk with Gla-100 was significantly lower compared with other first-generation basal insulins and comparable to NPH, premixed insulins, co-formulations, and second-generation basal insulins.

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