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Safety and efficacy of insulin glargine 300 u/mL compared with other basal insulin therapies in patients with type 2 diabetes mellitus: a network meta-analysis

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ABSTRACT

Objective: To compare the efficacy and safety of a concentrated formulation of insulin glargine (Gla-300) with other basal insulin therapies in patients with type 2 diabetes mellitus (T2DM).

Design: This was a network meta-analysis (NMA) of randomised clinical trials of basal insulin therapy in T2DM identified via a systematic literature review of Cochrane library databases, MEDLINE and MEDLINE In-Process, EMBASE and PsycINFO.

Outcome measures: Changes in HbA1c (%) and body weight, and rates of nocturnal and documented symptomatic hypoglycaemia were assessed.

Results: 41 studies were included; 25 studies comprised the main analysis population: patients on basal insulin-supported oral therapy (BOT). Change in glycated haemoglobin (HbA1c) was comparable between Gla-300 and detemir (difference: −0.08; 95% credible interval (CrI): −0.40 to 0.24), neutral protamine Hagedorn (NPH; 0.01; −0.28 to 0.32), degludec (−0.12; −0.42 to 0.20) and premixed insulin (0.26; −0.04 to 0.58). Change in body weight was comparable between Gla-300 and detemir (0.69; −0.31 to 1.71), NPH (−0.76; −1.75 to 0.21) and degludec (−0.63; −1.63 to 0.35), but significantly lower compared with premixed insulin (−1.83; −2.85 to −0.75). Gla-300 was associated with a significantly lower nocturnal hypoglycaemia rate versus NPH (risk ratio: 0.18; 95% CrI: 0.05 to 0.55) and premixed insulin (0.36; 0.14 to 0.94); no significant differences were noted in Gla-300 versus detemir (0.52; 0.19 to 1.36) and degludec (0.66; 0.28 to 1.50). Differences in documented symptomatic hypoglycaemia rates of Gla-300 versus detemir (0.63; 0.19to 2.00), NPH (0.66; 0.27 to 1.49) and degludec (0.55; 0.23 to 1.34) were not significant. Extensive sensitivity analyses supported the robustness of these findings.

Conclusions: NMA comparisons are useful in the absence of direct randomised controlled data. This NMA suggests that Gla-300 is also associated with a significantly lower risk of nocturnal hypoglycaemia compared with NPH and premixed insulin, with glycaemic control comparable to available basal insulin comparators.

Strengths and limitations of this study

- This is the first comprehensive literature review and network meta-analysis (NMA) summarising the available clinical trial literature on the clinical benefits of the newly approved basal insulin, Gla-300, and potential basal insulin comparators, and enabling comparisons between these therapies.
- The systematic literature review was limited to only English language literature; while this is likely to include all major randomised clinical trials conducted for basal insulin therapy in type 2 diabetes mellitus (T2DM), it may exclude smaller studies with no publication in English.
- The NMA was conducted in accordance with National Institute for Health and Care Excellence guidance and extensive sensitivity analyses were utilised to assess the robustness of the findings.
- While NMA enables the synthesis of available clinical information, it is not a substitute for head-to-head clinical trials to compare therapies, and such trials should be encouraged and conducted.

INTRODUCTION

Worldwide, approximately 348.3 million people are living with type 2 diabetes mellitus (T2DM).[1 2] As T2DM progresses, insulin therapy may be required to achieve glycaemic control. The 2015 ADA/EASD Position Statement on Managing Hyperglycemia in T2DM recommends initiating basal insulin in combination with oral therapy among the appropriate options for patients who are

unable to achieve their glycated haemoglobin (HbA1c) target after 3 months of metformin monotherapy.[3]

Insulin glargine 300 u/mL (Gla-300) is a new basal insulin that has recently (2015) been approved by the European Commission and the US Food and Drug Administration. Gla-300 is a concentrated formulation of insulin glargine 100 u/mL (Gla-100), developed to produce a more flat and more prolonged pharmacokinetic and pharmacodynamic profile.[4–6] Several randomised controlled clinical safety and efficacy trials comparing Gla-300 to Gla-100 have shown that Gla-300 achieves reduction in HbA1c comparable to that of Gla-100, while lowering the risk of hypoglycaemia.[6–8] Comparable HbA1c reduction is expected given that each treatment group utilised the same dose titration to achieve fasting plasma glucose of 4.4–5.6 mmol/L (ie, treat-to-target approach). The lower hypoglycaemia rates observed with Gla-300 may be due to properties inherent to the glargine molecule that lead to pharmacokinetic and pharmacodynamic differences at varying concentrations (ie, between Gla-300 and Gla-100).[4 5]

At the present time, head-to-head studies of Gla-300 with other available basal insulin options have not been conducted; however, such comparisons would help determine the place in therapy for this product. Meta-analysis enables the findings from multiple primary studies with comparable outcome measures to be combined.[9] In absence of direct head-to-head clinical trials, mixed treatment meta-analysis (also known as network meta-analysis (NMA)) may be used to estimate comparative effects of multiple interventions using indirect evidence.[9] The current report is an NMA conducted to indirectly compare the efficacy and safety of U300 versus available intermediate-acting to ultra-long-acting basal insulin formulations in the treatment of T2DM.

METHODS

Systematic literature review

A systematic literature review was conducted to identify evidence for the clinical efficacy and safety of insulin regimens in T2DM according to National Institute for Health and Care Excellence (NICE) standards.[9] The following electronic databases were searched: the Cochrane Library (eg, the Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Abstracts of Reviews of Effectiveness (DARE)), MEDLINE and MEDLINE In-Process (using Ovid platform), EMBASE (using Ovid Platform) and PsycINFO. Congresses searched were the European Association for the Study of Diabetes (EASD; 2011–2013), the American Diabetes Association (ADA; 2011–2013) and the International Diabetes Federation (IDF; 2011 and 2013). Key search terms included: 'diabetes mellitus, type 2/', 'glargine', 'detemir', 'degludec', 'NPH', 'neutral protamine hagedorn', 'biphasic', 'aspart protamine', 'novomix' and 'premix'. Searches were limited to human, English-language only articles published from 1980 onwards. The NMA focused on studies published recently (ie, based on availability of basal insulin analogues). At the time of analysis, the Gla-300 vs Gla-100 studies were only available in clinical study reports; however, these studies have subsequently been published.[6–8]

Several quality control procedures were in place to ensure appropriate study selection and data extraction. Screening of abstracts and full-text was conducted by two independent researchers (a third independent researcher made a final determination for articles for which there was uncertainty). Data extraction was also conducted by two independent researchers (with reconciliation of discrepancies). Where available, full-text versions of the article were used for data extraction (an abstract or poster was not used unless it was the terminal source document). All processes were documented by the researchers and the data extraction file was also quality checked. The source materials (abstracts, full-text articles) and data extraction files were sorted, and saved on a secure server.

Inclusion criteria

In order to be considered for the NMA, clinical studies identified by the systematic literature review had to meet the following criteria: randomised active comparator-controlled clinical studies, patient population of adults with T2DM treated with basal insulin (with or without bolus), patients could be newly initiating insulin (naïve) or already exposed to insulin, and a minimum follow-up of 20 weeks. In addition, studies were required to have patients from at least one of the following countries: the USA, France, Germany, the UK, Spain and/or Italy.

Outcome measures

Outcome measures analysed by NMA included change in HbA1c (%) from baseline, change in body weight (kg) from baseline and rates of hypoglycaemic events (documented symptomatic and/or nocturnal) per patient year. A documented symptomatic event was defined as an event during which typical symptoms of hypoglycaemia were accompanied by measured plasma glucose under a threshold value. In the EDITION trials, the results were reported using both a concentration of ≤3.0 mmol/L and of ≤3.9 mmol/L. No restriction on the threshold levels was imposed. A 3.9 mmol/L threshold for the EDITION trials was selected to be consistent with the majority of other trials in the network. Nocturnal hypoglycaemic events were defined as any event (confirmed and/or symptomatic) occurring during a period at night.

Statistical methods

All analyses were implemented using the statistical software R and OpenBUGS, specifically the packages using Markov Chain Monte Carlo (MCMC). Examples of coding used are provided in an online supplemental appendix. Randomised clinical trials that were identified

from a systematic literature review and that met the study selection inclusion criteria were analysed using a random-effect Bayesian NMA, following the UK NICE guidance.[9] Each outcome was analysed within the evidence network where it was reported. MCMC was used to estimate the posterior distribution for treatment comparison. Continuous outcomes (eg, change in HbA1c or body weight) were modelled assuming a normal likelihood and an identity link. Event rate data (eg, number of hypoglycaemic episodes per patient-year follow-up) were modelled using a Poisson mixed likelihood and log link. Non-informative priors were assumed.

Sensitivity analyses

Sensitivity analyses including meta-regression were conducted to evaluate the robustness of the findings. The base scenario included studies of patients on basal insulin-supported oral therapy (BOT; patients received basal insulin in combination with oral antihyperglycaemic drugs but with no bolus insulin; patients could be either—insulin naïve or insulin experienced). Additional scenarios were all studies (ie, patients receiving basal insulin with or without bolus), studies of patients on BOT excluding premixed studies, studies of insulin-naïve patients only, only studies with Week 24–28 results, and excluding degludec three times weekly (3TW) dosing. Meta-regression was conducted for key outcomes to account for study-level population characteristics, adjusting for the following: study-level baseline HbA1c, diabetes disease duration and basal-bolus population. In addition, broader definitions for hypoglycaemia were analysed. A comparison of NMA to classical meta-analysis in the base scenario (BOT) using an inverse variance-weighted method was also conducted.

RESULTS

Systematic literature review

Over 4000 studies were identified for screening, of which 86 were identified for data extraction; from these, 41 studies were included in the NMA (figure 1A). A brief overview of these studies is provided in table 1.

Included trials

All studies were randomised based on entry criteria, with interactive voice (or web) response system or telephone system as the main method of randomisation (n=22), followed by use of sequential numbers/codes (n=6) and electronic case record system (n=1); the method of randomisation was either not reported or not clear in the remaining studies (n=12). The majority (40/41) of studies specified an open-label in design (1 study did not specify). Loss to follow-up (ie, rates of discontinuation among randomised patients) among the studies ranged from 1.6% to 28.5%, with 10 studies reporting discontinuation rates <10%, 22 reporting 10–20% and 5 reporting >20% in at least one treatment arm (loss to follow-up was not reported in 4 studies). The baseline patient characteristics of patients in each of the 41 studies are provided in table 2.

Twenty-five of the 41 studies (61%) were of patients on BOT (main population for this analysis; n=15 746 patients). The evidence network for the BOT studies is depicted in figure 1B. Patients in the BOT studies had a mean age ranging from 52.4 to 61.7 years, duration of diabetes 8.2–13.8 years, baseline body weight 81.3–99.5 kg and HbA1c 7.8–9.8%.

Glycaemic control

In patients with T2DM on BOT (n=25 studies), the change in HbA1c was comparable between Gla-300 and insulin detemir (−0.08; −0.40 to 0.24), neutral protamine Hagedorn (NPH; 0.01; −0.28 to 0.32), degludec (−0.12; −0.42 to 0.20) and premixed insulin (0.26; −0.04 to 0.58) (figure 2A). These changes were similar to those in the overall NMA (n=41 studies) and across the various sensitivity analyses shown in table 3A.

Body weight

Change in body weight from baseline was reported in 36 trials in the NMA. Among patients with T2DM on BOT, no statistically significant difference in body weight change was observed between Gla-300 and detemir (difference: 0.69; 95% CrI −0.31 to 1.71), NPH (−0.76; −1.75 to 0.21) or degludec (−0.63; −1.63 to 0.35), whereas weight gain was significantly lower with Gla-300 compared with premixed insulin (−1.83; −2.85 to −0.75) (figure 2B). These changes were similar to those in the overall NMA (n=41 studies) and across the various sensitivity analyses (table 3A).

Hypoglycaemia events

Among the studies identified, 20 trials reported nocturnal hypoglycaemia event rate data and 16 reported documented symptomatic hypoglycaemia event rate data that met criteria for inclusion in the NMA. The hypoglycaemia event data from each of these clinical trials are summarised in table 4.

Nocturnal hypoglycaemia

In patients with T2DM on BOT, Gla-300 was associated with a significantly lower nocturnal hypoglycaemia rate compared with NPH (0.18; 0.05 to 0.55) and premixed insulin (0.36; 0.14 to 0.94) and a numerically lower rate when compared with detemir (0.52; 0.19 to 1.36) and degludec (0.66; 0.28 to 1.50) (figure 2C). These changes were similar to those in the overall NMA (n=41 studies) and across the various sensitivity analyses (table 3A).

Documented symptomatic hypoglycaemia

In patients with T2DM on BOT, Gla-300 was associated with a numerically lower rate of documented symptomatic hypoglycaemic events compared with detemir (0.63; 0.19 to 2.00), NPH (0.66; 0.27 to 1.49) and degludec (0.55; 0.23 to 1.34) (figure 2D). These changes were similar to those in the overall NMA (n=41 studies) and

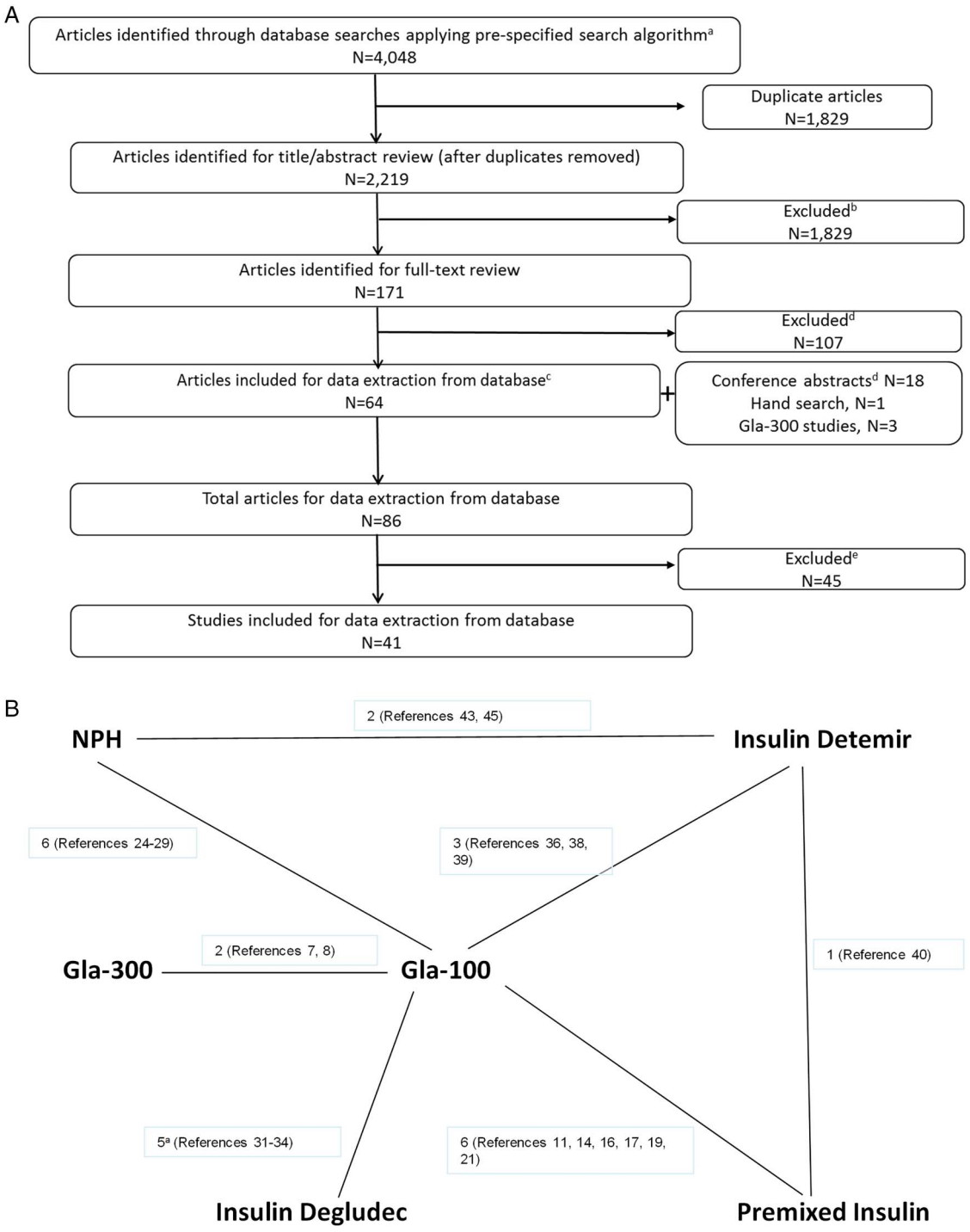


Figure 1 (A) PRISMA flow diagram for studies comparing basal insulin therapies in type 2 diabetes mellitus (T2DM; N=41). [a]Cochrane Library (eg, the Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Abstracts of Reviews of Effectiveness (DARE)), MEDLINE and MEDLINE In-Process (using Ovid platform), Embase (using Ovid Platform) and PsycINFO; If applicable, relevant results from clinical trial registry were included. Zinman *et al*[34] report 2 distinct studies within 1 publication. [b]For title/abstract and full-text review, articles were excluded based on inclusion/exclusion criteria as specified in the systematic literature review. [c]Two articles analysed the same trial. [d]Conferences searched included EASD and ADA 2011–2013, and IDF 2011. IDF 2013 was assessed when the CD-ROM became available—the end of February. Multiple abstracts examined the same trial and 14 trials were extracted. [e]Studies must include at least two treatment arms in the network, including: U300, insulin glargine, insulin detemir, insulin NPH, insulin degludec and premix insulin. (B) Evidence network diagram for BOT studies (n=25) reporting HbA1c (%) change from baseline. Each insulin treatment is a node in the network. The links between the nodes represent direct comparisons. The numbers along the lines indicate the number of trials or pairs of trial arms for that link in the network. Reference numbers indicate the trials contributing to each link. BOT, basal insulin-supported oral therapy; HbA1c, glycated haemoglobin; NPH, neutral protamine Hagedorn.

Table 1 Randomised comparative studies included in NMA of patients with T2DM on basal insulin treatment

	First author, year published (Regimen type)	Countries/ Continents	Key inclusion criteria	N*	Randomised comparator arms	Allocation method	Study duration	Discontinuation rate†	Outcomes in current NMA‡			
									A	B	C	D
Gla-300 vs Gla-100	Bolli, 2015[8]	North America, Europe, Japan	Insulin naïve OAD HbA1c 7–11%	873	Gla-300 Gla-100	IVRS	6 months	Gla-300: 62/439 (14%) Gla-100: 75/439 (17%)	✓	✓	✓	✓
	Riddle, 2014[6]	North America, Europe, South Africa	On basal bolus insulin regimen HbA1c 7–10%	806	Gla-300 + bolus Gla-100 + bolus	IVRS	6 months	Gla-300: 30/404 (7.4%) Gla-100: 31/402 (7.7%)	✓	✓	✓	✓
	Yki-Järvinen, 2014[7]	North America, Europe, Russia, South America, South Africa	On basal insulin OAD HbA1c 7–10%	809	Gla-300 Gla-100	IVRS	6 months	Gla-300: 36/404 (8.9%) Gla-100: 38/407 (9.3%)	✓	✓	✓	✓
Gla-100 vs premixed insulin	Aschner, 2013[10]	NR	Insulin naïve OAD	923	Premixed Gla-100±glulisine	NR	24 weeks	NR (meeting abstract)	✓	✓		✓
	Buse, 2009[11]	Australia, Europe, India, North America, South America	Insulin naïve OAD HbA1c >7%	2091	Lispro protamine/lispro 75/25 Gla-100	IVRS	24 weeks	Premixed insulin:145/1045 (13.9%) Gla-100: 128/1046 (12.2%)	✓	✓		
	Fritsche, 2010[12]	Europe and Australia	Premixed insulin +/- Metformin HbA1c 7.5–11.0%	310	70/30 NPH + bolus (regular or aspart) Gla-100 + glulisine	Electronic case record system	52 weeks	Premixed insulin: 28/157 (17.8%) Gla-100:25/153 (16.3%)	✓	✓	✓	
	Jain, 2010[13]	Asia, Australia, Europe, North America, Russian Federation	Insulin naïve OAD HbA1c ≥7.5–12%	484	Insulin lispro 50/50 Gla-100 + lispro	TS	36 weeks	Premixed insulin: 31/242 (12.8%) Gla-100: 27/242 (11.2%)	✓	✓		
	Kann, 2006[14]	Europe	Insulin naïve OAD HbA1c >7–12%	255	Insulin aspart 70/30+ metformin Gla-100 + glimepiride	Sealed codes	28 weeks	Premixed insulin: 13/130 (10.0%) Gla-100: 12/128 (9.4%)	✓	✓		
	Kazda, 2006[15]	Germany	Insulin naïve HbA1c 6–10.5%	159	Protaminatedlispro/ lispro 50/50 Lispro Gla-100	NR	24 weeks	Premixed insulin: 14.8%§ Bolus insulin: 7.7%§ Gla-100: 15.1%§	✓	✓		
	Ligthelm, 2011[16]	USA and Puerto Rico	On basal insulin OAD HbA1c ≥8%	279	Biphasic aspart 70/30 Gla-100	IVRS	24 weeks	Premixed insulin: 19/137 (13.9%) Gla-100: 32/143 (22.4%)	✓	✓	✓	

Continued

Table 1 Continued

	First author, year published (Regimen type)	Countries/ Continents	Key inclusion criteria	N*	Randomised comparator arms	Allocation method	Study duration	Discontinuation rate†	Outcomes in current NMA‡ A	B	C	D
	Raskin, 2005[17]	USA	Insulin naïve OAD HbA1c ≥8%	222	Biphasic aspart 70/30 Gla-100	Sequential numbers/ codes	28 weeks	Premixed insulin:17/117 (14.5%) Gla-100: 7/116 (6.0%)	✓			
	Riddle, 2011[18]	NR	OAD	572	Protamine-aspart/ aspart 70/30 Glargine + 1 prandial Glulisine Gla-100 + glulisine (stepwise addition)	NR	60 weeks	NR (meeting abstract)	✓			✓
	Robbins, 2007[19]	Australia, Europe, India, North America (USA and Puerto Rico)	OAD HbA1c 6.5–11%	315	Lispro 50/50 + metformin Gla-100+metformin	TS	24 weeks	Premixed insulin: 15/158 (9.5%) Gla-100: 22/159 (13.8%)	✓	✓		
	Rosenstock, 2008[20]	USA and Puerto Rico	On basal insulin OAD HbA1c 7.5–12%	374	Insulin lispro protamine/lispro Gla-100 + lispro	TS	24 weeks	Premixed insulin: 29/187 (15.5%) Gla-100: 29/187 (15.5%)	✓	✓		✓
	Strojek, 2009[21]	Asia, Europe, North America, South America, South Africa	Insulin naïve OAD HbA1c >7–11%	469	Biphasic aspart 70/30 + metformin/glimepiride Gla-100 +metformin/ glimepiride	IVRS	26 weeks	Premixed insulin: 26/239 (10.9%) Gla-100: 21/241 (8.7%)	✓		✓	
	Tinahones, 2013[22]	11 countries (not specified)	On basal insulin OAD HbA1c 7.5–10.5%	478	Lispro mix 25/75 Gla-100 + lispro	NR	24 weeks	NR (meeting abstract)	✓	✓		✓
	Vora, 2013[23]	NR	On basal insulin	335	Biphasic insulin aspart/ aspart protamine 30/70 Gla-100 + glulisine	NR	24 weeks	Premixed insulin: 23/165 (13.9%) Gla-100: 14/170 (8.2%)	✓			✓
Gla-100 vs NPH	Fritsche, 2003[24]	Europe	Insulin naïve OAD HbA1c 7.5–10.5%	695	NPH Gla-100 (morning) Gla-100 (bedtime)	Sequential numbers/ codes	28 weeks	NPH: 27/234 (11.5%) Gla-100 (morning): 12/ 237 (5.1%) Gla-100 (bedtime):18/229 (7.9%)	✓	✓		✓

Continued

Table 1 Continued

	First author, year published (Regimen type)	Countries/ Continents	Key inclusion criteria	N*	Randomised comparator arms	Allocation method	Study duration	Discontinuation rate†	Outcomes in current NMA‡ A	B	C	D
	Massi Benedetti, 2003[25]	Europe, South Africa	OAD	570	NPH Gla-100	Sequential numbers/ codes	52 weeks	NPH: 33/285 (11.6%) Gla-100: 16/293 (5.5%)	✓			✓
	Riddle, 2003[26]	North America	Insulin naïve OAD HbA1c 7.5–10%	756	NPH Gla-100	IVRS	24 weeks	NPH: 32/392 (8.2%) Gla-100: 33/372 (8.9%)	✓	✓		✓
	Rosenstock, 2001[27]	NR	On insulin HbA1c 7–12%	518	NPH Gla-100	NR	28 weeks	NPH: 21/259 (8.1%) Gla-100: 28/259 (10.8%)	✓	✓		✓
	Rosenstock 2009[28]	North America	OAD HbA1c 6–12%	1017	NPH Gla-100	IVRS	5 years	NPH: 145/509 (28.5%)§ Gla-100: 141/515 (27.4%)§	✓	✓		
	Yki-Järvinen, 2006[29]	Europe	Insulin naïve OAD HbA1c ≥8%	110	NPH Gla-100	NR	36 weeks	NPH: 1/49 (2.0%) Gla-100: 1/61 (1.6%)	✓	✓		✓
Degludec vs Gla-100	Garber, 2012[30]	Asia (Hong Kong), Europe, Middle East (Turkey), North America, Russia, South Africa	On insulin ±OAD HbA1c 7–10%	1004	Degludec + aspart Gla-100 + aspart	IVRS	52 weeks	Degludec: 137/755 (18.1%) Glargine:40/251 (15.9%)	✓	✓	✓	✓
	Gough, 2013[31]	Europe, North America, Russia, South Africa	Insulin naïve OAD HbA1c 7–10%	456	Degludec Gla-100	IVRS	26 weeks	NR§	✓	✓	✓	✓
	Meneghini, 2013[32]	Asia, Europe, Israel, North America, Russia, South America, South Africa	OAD HbA1c 7–11%	685	Degludec (flexible) Degludec (once daily) Gla-100	IVRS	26 weeks	Degludec (flexible): 26/229 (11.4%) Degludec(once daily): 24/228 (10.5%) Gla-100: 27/230 (11.7%)	✓	✓	✓	✓
	Zinman, 2012[33]	Europe, North America		1023	Degludec Gla-100	IVRS	52 weeks	Degludec: 166/773 (21.5%)	✓	✓	✓	✓

Continued

Table 1 Continued

	First author, year published (Regimen type)	Countries/ Continents	Key inclusion criteria	N*	Randomised comparator arms	Allocation method	Study duration	Discontinuation rate†	Outcomes in current NMA‡ A	B	C	D
			Insulin naïve OAD HbA1c 7–10%					Glargine:60/257 (23.3%)				
	Zinman (AM), 2013[34]	Europe, Israel, North America, South Africa	Insulin naïve OAD HbA1c 7–10%	456	Degludec Gla-100	IVRS	26 weeks	Degludec: 38/230 (16.5%) Gla-100: 24/230 (10.4%)	✓	✓	✓	
	Zinman (PM), 2013[34]	Europe, North America	Insulin naïve OAD HbA1c 7–10%	467	Degludec Gla-100	IVRS	26 weeks	Degludec: 25/233 (10.7%) Gla-100: 25/234 (10.7%)	✓	✓	✓	
Detemir vs Gla-100	Hollander, 2008[35]	Europe and the USA	OAD and/or insulin HbA1c 7–11%	319	Detemir + aspart Gla-100 + aspart	TS	52 weeks	Detemir: 43/216 (19.9%) Gla-100: 23/107 (21.5%)	✓	✓	✓	
	Meneghini, 2013[36]	Asia, South America, USA	Insulin naïve OAD HbA1c 7–9%	453	Detemir Gla-100	NR	26 weeks	Detemir: 38/228 (16.7%) Gla-100: 41/229 (17.9%)	✓	✓	✓	
	Raskin, 2009[37]	NR	OAD and/or insulin HbA1c 7–11%	387	Detemir + aspart Gla-100 + aspart	NR	26 weeks	Detemir: 46/256 (18.0%) Gla-100: 18/131 (13.7%)	✓	✓	✓	
	Rosenstock, 2008[38]	Europe and the USA	Insulin naïve OAD HbA1c 7.5–10%	582	Detemir Gla-100	TS	52 weeks	Detemir: 60/291 (20.6%) Gla-100: 39/291 (13.4%)	✓	✓	✓	
	Swinnen, 2010[39]	Asia, Australia, Europe, Middle East (Turkey), North America, Russia, South America	Insulin naïve OAD HbA1c 7–10.5%	964	Detemir Gla-100	NR	24 weeks	Detemir: 10.1%§ Gla-100:4.6%§	✓	✓		✓
Detemir vs premixed	Holman, 2007[40]	Europe	Insulin naïve OAD HbA1c 7–10%	708	Prandial insulin aspart Detemir Biphasic aspart 30	IVRS	52 weeks	Bolus: 17/239 (7.1%) Detemir: 10/234 (4.3%) Premixed insulin:13/235 (5.5%)	✓	✓		

Continued

Table 1 Continued

	First author, year published (Regimen type)	Countries/ Continents	Key inclusion criteria	N*	Randomised comparator arms	Allocation method	Study duration	Discontinuation rate†	Outcomes in current NMA‡ A	B	C	D
	Liebl, 2009[41]	Europe	OAD HbA1c 7–12%	715	Detemir + aspart Soluble aspart/ protamine-crystallised aspart 30/70	Codes	26 weeks	Detemir: 44/541 (8.1%) Premixed insulin: 17/178 (9.6%)	✓	✓		
Detemir vs NPH	Haak, 2005[42]	Europe	HbA1c ≤12%	505	Detemir + aspart NPH + aspart	NR	26 weeks	Detemir: 26/341 (7.6%)§ NPH: 8/164 (4.9%)§	✓	✓		
	Hermansen, 2006[43]	Europe	Insulin naïve OAD HbA1c 7.5–10%	475	Detemir NPH	TS	24 weeks	Detemir: 4%§ NPH: 5%§	✓	✓	✓	
	Montañana, 2008[44]	Spain	On insulin± metformin HbA1c 7.5–11%	271	Detemir + aspart NPH + aspart	Codes	26 weeks	Detemir:7/126 (5.6%) NPH: 12/151 (7.9%)	✓	✓	✓	
	Philis-Tsimakas, 2006[45]	North America and Europe	Insulin naïve OAD HbA1c 7.5–11%	498	Detemir morning Detemir evening NPH	IVRS	20 weeks	Detemir (morning): 19/168 (11.3%) Detemir (evening): 16/170 (9.4%) NPH: 17/166 (10.2%)	✓		✓	
	Raslová, 2004[46]	8 Countries (not specified)	On insulin ±OADs HbA1c <12%	394	Detemir + insulin aspart NPH + human soluble insulin	NR	22 weeks	Detemir: 10/195 (5.1%)§ NPH: 6/199 (3.0%)§	✓	✓		

All the studies were open-label, with the exception of Liebl *et al*[1] (not reported).
*Safety population; exceptions: efficacy population for Buse *et al*,[11] Raslová *et al*,[46] Riddle *et al*,[18] Tinahones *et al*[22] and Vora *et al*.[23]
†Numerator for discontinuation rate=randomised patients−patients completing the study; denominator for discontinuation rate=randomised patients. Exceptions noted in footnote (§).
‡A=change in HbA1c, B=change in body weight, C=nocturnal hypoglycaemia rate, D=documented symptomatic hypoglycaemia rate.
§Exceptions to definition of discontinuation rate/or discontinuation rate not calculable with information available: Gough 2013 reported that 460 were randomised 1:1 (3 were randomised in error and were withdrawn, 1 withdrew consent (all prior to treatment)) and 228 and 229 received detemir and Gla-100, respectively, however, completion/withdrawal not described; Kazda *et al*[15] reported 'drop-out' rates (however, numbers randomised to each group not provided and denominator may have been exposed rather than randomised patients); Swinnen *et al*'s[39] brief report does not make clear what the denominator was for completion rate provided (did not report number randomised to each group, only total randomised; did not report numbers of patients completing the study—only the percentages); Hermansen *et al*:[43] denominator may be ITT population—475 were randomised but the breakdown between treatment arms is not clear; Haak *et al*,[42] reported rates based on patients receiving treatment rather than randomised patients; Raslová *et al*[46] reported rates reported based on ITT rather than randomised patients (ITT only 1 less than randomised, but number randomised to each treatment arm not provided in publication). In addition, Rosenstock *et al*[28] reported data over 5 years; however, only the first year data were included in this NMA.
HbA1c, glycated haemoglobin; ITT, intention to treat; IVRS, interactive voice (or web) response system; NMA, network meta-analysis; NPH, neutral protamine Hagedorn; NR, not reported; OAD,oral antidiabetic medication; T2DM, type 2 diabetes mellitus; TS, telephone system.

Table 2 Patient baseline characteristics for trials included in the NMA (N=41)

	First author	Year	Age Mean±SD	Male (%)	Diabetes duration (years) Mean±SD	HbA1c (%), Mean±SD	Body weight (kg) Mean±SD
Gla-100 vs Gla-300	Bolli[8]	2015	57.7±10.1	57.8	9.8±6.4	8.5±1.1	95.4±23.0
	Riddle[6]	2014	60.0±8.6	52.9	15.9±7.5	8.1±0.8	106.3±20.8
	Yki-Järvinen[7]	2014	58.2±9.2	45.9	12.6±7.1	8.3±0.8	98.4±21.6
Gla-100 vs premixed	Aschner[10]	2013	NA	NA	NA	8.7±0	NA
	Buse[11]	2009	57.0±10	52.80	9.5±6.1	9.1±1.3	88.50±21.0
	Fritsche[12]	2010	60.6±7.7	50.91	12.7±6.3	8.6±0.9	85.61±15.1
	Jain[13]	2010	59.4±9.2	48.78	11.7±6.5	9.4±1.2	78.5±15.3
	Kann[14]	2006	61.3±9.1	51.4	10.25±7.1	9.1±1.4	85.4±15.5
	Kazda[15]	2006	59.4±9.5	54.7	5.6±2.9	8.1±1.2	NA
	Ligthelm[16]	2011	52.7±10.4	56.66	11.15±6.4	9.0±1.1	97.9±20.5
	Raskin[17]	2005	52.5±10.2	54.5	9.2±5.3	9.8±1.5	90.2±18.9
	Riddle[18]	2011	NA	NA	NA	NA	NA
	Robbins[19]	2007	57.8±9.1	49.9	11.9±6.3	7.8±1.0	88.6±19.7
	Rosenstock[20]	2008	54.7±9.5	52.5	11.1±6.3	8.9±1.1	99.5±20.6
	Strojek[21]	2009	56.0±9.9	43.96	9.3±6.0	8.5±1.1	NA
	Tinahones[22]	2013	NA	NA	NA	8.6±0.8	NA
	Vora[23]	2013	NA	NA	NA	NA	NA
Gla-100 vs NPH	Fritsche[24]	2003	61.0±9.0	53.7	NA	9.1±1.0	81.3±14.8
	MassiBenedetti[25]	2003	59.5±9.2	53.7	10.35±6.1	9.0±1.2	NA
	Riddle[26]	2003	55.5±9.2	55.5	8.71±5.56	8.6±0.9	NA
	Rosenstock[27]	2001	59.4±9.8	60.1	13.75±8.65	8.6±1.2	90.2±17.6
	Rosenstock[28]	2009	55.1±8.7	53.9	10.75±6.8	8.4±1.4	99.5±22.5
	Yki-Järvinen[29]	2006	56.5±1	63.3	9±1	9.5±0.1	93.1±2.5
Degludec vs Gla-100	Garber[30]	2012	58.9±9.3	54.0	13.6±7.3	8.3±0.8	92.5±17.7
	Gough[31]	2013	57.6±9.2	53.2	8.2±6.2	8.3±1.0	92.5±18.5
	Meneghini[32]	2013	56.5±9.6	53.7	10.6±6.7	8.4±0.9	81.7±16.7
	Zinman[33]	2012	59.2±9.8	61.9	9.2±6.2	8.2±0.8	90.0±17.3
	Zinman (PM)[34]	2013	57.4±10.2	57.2	8.8±3.4	8.3±0.8	91.9±18.5
	Zinman (AM)[34]	2013	58.2±9.8	56.9	8.9±6.1	8.3±0.9	93.3±18.8
Detemir vs Gla-100	Hollander[35]	2008	58.7±11	58.0	13.5±8.0	8.7±1.0	92.7±17.6
	Meneghini[36]	2013	57.3±10.3	56.5	8.2±6.1	7.91±0.6	82.3±16.7
	Raskin[37]	2009	55.8±10.3	54.6	12.3±7.0	8.4±1	95.6±18.2
	Rosenstock[38]	2008	58.9±9.9	57.9	9.1±6.3	8.6±0.8	87.4±17.0
	Swinnen[39]	2010	58.4±8.3	54.7	9.9±5.8	8.7±0.9	83.9±17.1
Detemir vs premixed	Holman[40]	2007	61.7±9.8	64.1	NA	8.5±0.8	85.8±15.9
	Liebl[41]	2009	60.7±9.2	58.5	9.3±6.4	8.5±1.1	NA
Detemir vs NPH	Haak[42]	2005	60.4±8.6	51.1	13.2±7.6	7.9±1.3	86.9±15.8
	Hermansen[43]	2006	60.9±9.2	53.1	9.7±6.4	8.6±0.8	82.6±13.8
	Montañana[44]	2008	61.9±8.8	40.6	16.3±8.0	8.85±1.0	81.0±12.1
	Philis-Tsimakas[45]	2006	58.5±10.5	56.8	10.3±7.2	9.0±1.0	NA
	Raslová[46]	2004	58.3±9.3	42.1	14.1±7.8	8.1±1.3	80.8±12.7

HbA1c, glycated haemoglobin; NA, not applicable; NMA, network meta-analysis; NPH, neutral protamine Hagedorn.

across the various sensitivity analyses (table 3A). In the BOT population, comparative data for premixed insulin were not available for this particular outcome.

Comparison of NMA to classic meta-analysis findings

The comparison of NMA results that integrate all available evidence versus those from classical meta-analysis solely based on direct evidence in the base scenario (BOT) found generally consistent effect size across all four outcomes and tighter 95% CIs with the classical meta-analysis (table 3B).

DISCUSSION

In this NMA of randomised clinical studies comparing various basal insulin therapies in patients with T2DM, the new concentrated formulation, Gla-300, demonstrated change in HbA1c that was comparable to the change reported in studies of insulin detemir, degludec, NPH and premixed insulin. Change in body weight with Gla-300 was significantly less than that with premixed insulin and comparable to the other basal insulin. Hypoglycaemia rates appeared lower with Gla-300 and the comparator basal insulin. The rate of documented symptomatic hypoglycaemia associated with Gla-300 was

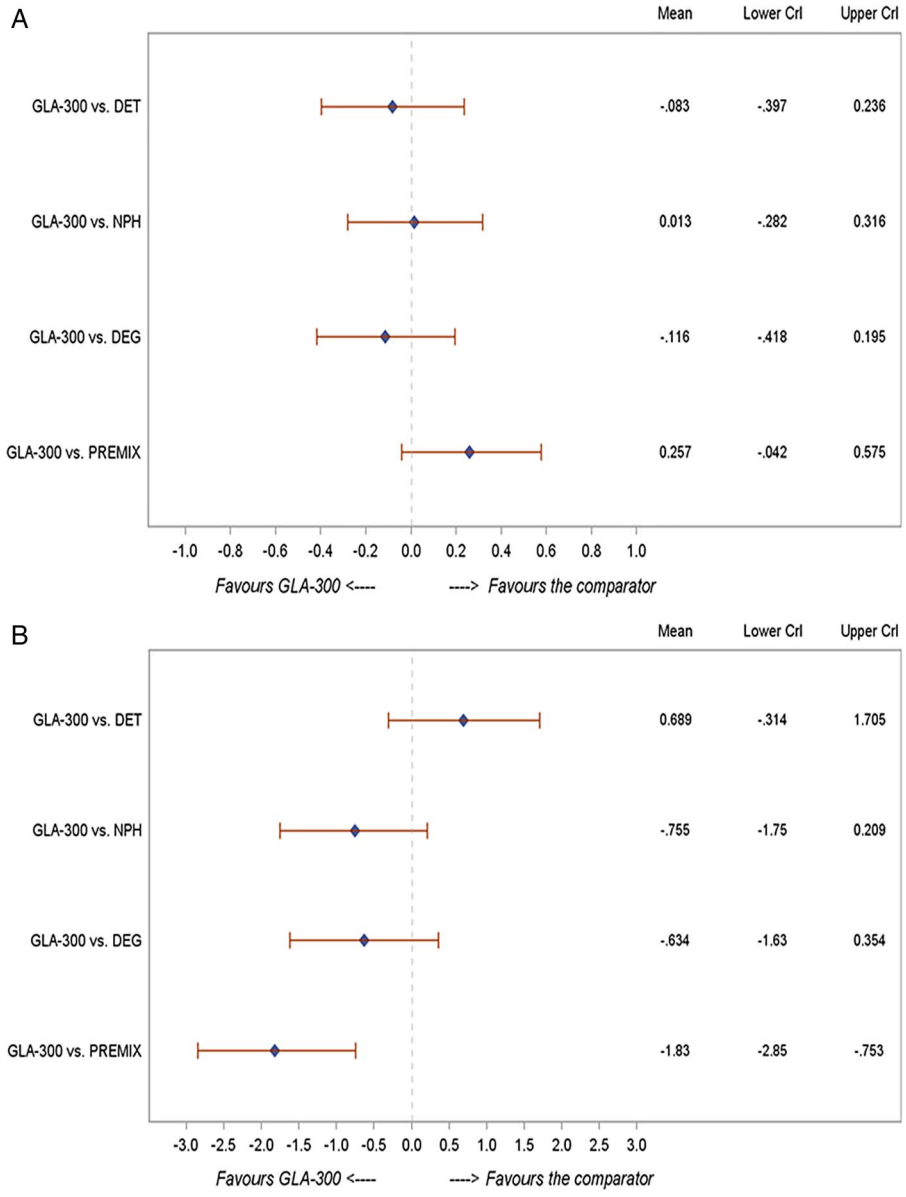


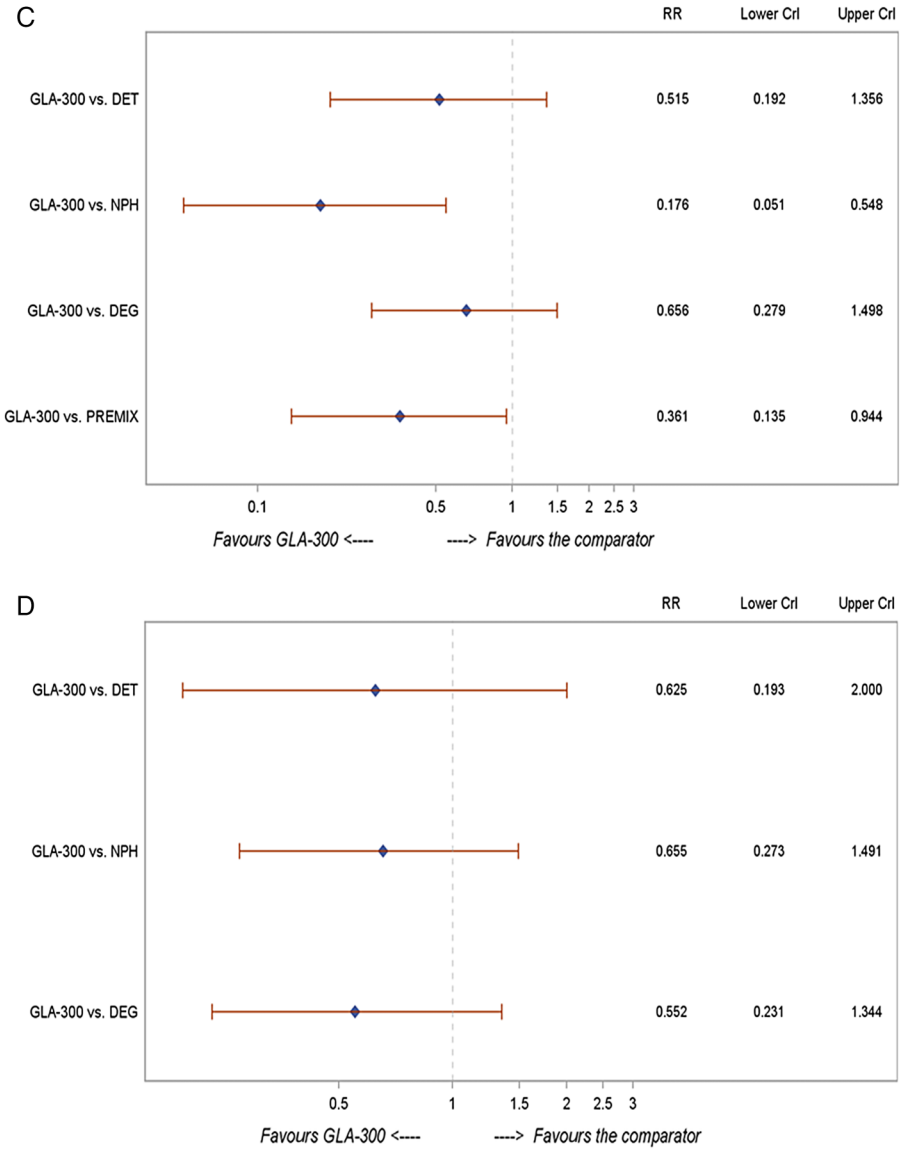
Figure 2 NMA findings for Gla-300 versus other basal insulins in the BOT population: (A) change in HbA1c (%); (B) change in body weight (kg); (C) risk of nocturnal hypoglycaemia; (D) risk of documented symptomatic hypoglycaemia. BOT, basal insulin-supported oral therapy; CrI, credible interval; DET, =insulin detemir; DEG, insulin degludec; HbA1c, glycated haemoglobin; NMA, network meta-analysis; NPH, neutral protamine Hagedorn; PREMIX, premixed insulin; RR, risk ratio.

numerically but not significantly different from that of other basal insulin therapies. A notable difference was that Gla-300 was associated with a significantly lower risk of nocturnal hypoglycaemia (ranging from approximately 64% to 82% lower) compared with premixed insulin and NPH.

These NMA data extend our current knowledge regarding Gla-300. Based on direct comparisons in the EDITION studies, Gla-300 was associated with comparable glycaemic control, but had a significantly lower rate of nocturnal hypoglycaemia compared with Gla-100.[6–8] The more flat and more prolonged pharmacokinetic profile associated with Gla-300 compared with Gla-100 may contribute to the reduced rate of nocturnal hypoglycaemia that is observed clinically. Reasons for the difference in pharmacokinetic profile between Gla-100 and Gla-300 are not known, but may be due to factors inherent to the retarding principle of the insulin glargine molecule and a phenomenon of surface-dependent release.[4 5] Gla-300 has a pH of approximately 4, at which it is completely soluble; however, once injected subcutaneously, the solution is neutralised and forms a precipitate allowing for the slow release of small amounts of insulin glargine. It has been suggested that the size (ie, surface area) of the subcutaneous deposit may determine the redissolution rate.[51]

The finding of a significantly lower rate of nocturnal hypoglycaemia associated with a basal insulin analogue compared with NPH is consistent with previous meta-analyses. For example, a meta-analysis of randomised clinical trials comparing long-acting basal insulin analogues (Gla-100 or detemir) with NPH showed that, among 10 studies reporting data for nocturnal hypoglycaemia, both analogues were associated with a reduced risk of nocturnal events, with an OR of 0.46 (95% CI 0.38 to 0.55) compared with NPH.[52] Similarly, in the pivotal Treat-to-Target study comparing Gla-100 to NPH, the risk reduction with Gla-100 ranged from 42% to

Figure 2 Continued



48% for different categories of nocturnal hypoglycaemic events.[26] A subsequent meta-analysis of individual patient data from 5 randomised clinical trials comparing Gla-100 to NPH, reported reductions of approximately 50% in nocturnal hypoglycaemia with Gla-100.[53] Given these data, along with patient-level data from the EDITION trials,[6–8] which when pooled[54] demonstrated a 31% lower relative difference in the annualised rate of nocturnal events over the 6-month study period for Gla-300 compared with Gla-100, the even more pronounced difference in the rate of nocturnal events between Gla-300 and NPH in this NMA is expected.

The finding of fewer nocturnal hypoglycaemic events with Gla-300 compared with premixed insulin in this NMA is in line with 'real-world' data from the Cardiovascular Risk Evaluation in people with type 2 Diabetes on Insulin Therapy (CREDIT) study, an international observational study that provided insights on outcomes following insulin initiation in clinical practice.[55] In CREDIT study, propensity-matched groups were evaluated 1 year after initiating insulin treatment and showed that basal insulin was associated with significantly lower rates of nocturnal hypoglycaemia compared with premixed insulin. This also held true for propensity-matched analysis of basal plus mealtime insulin versus premixed insulin groups.

The substantially lower risk of nocturnal hypoglycaemia associated with Gla-300 is an important finding given the clinical burden associated with such events.[56] In a multination survey of 2108 patients with diabetes (types 1 and 2) who had recently experienced nocturnal hypoglycaemia, patients reported a negative impact on their sleep quality as well as their functioning, the day after a nocturnal hypoglycaemic event.[57] Nocturnal events were associated with increased self-monitoring of blood glucose, and approximately 15% of patients reported temporary reductions in insulin dose. An economic evaluation of these data found that nocturnal hypoglycaemic events were associated with lost work productivity and increased healthcare utilisation.[58]

Table 3 Additional analyses

(A) Sensitivity analyses

Outcome	Comparator				
	Gla-100	Detemir	NPH	Degludec	Premix
Change in HbA1c*					
BOT, insulin naïve	0.01 (−0.27 to 0.29)	−0.14 (−0.47 to 0.19)	−0.09 (−0.43 to 0.25)	−0.12 (−0.45 to 0.21)	0.08 (−0.23 to 0.39)
Adjusting for Bolus Insulin Trials	−0.01 (−0.44 to 0.42)	−0.10 (−0.55 to 0.36)	−0.05 (−0.51 to 0.41)	−0.14 (−0.60 to 0.33)	0.07 (−0.37 to 0.51)
Insulin naïve	0.04 (−0.41 to 0.48)	−0.09 (−0.59 to 0.40)	−0.06 (−0.55 to 0.43)	−0.12 (−0.62 to 0.37)	0.24 (−0.22 to 0.72)
T2DM overall	0.01 (−0.23 to 0.25)	−0.08 (−0.37 to 0.21)	−0.03 (−0.32 to 0.26)	−0.12 (−0.42 to 0.18)	0.09 (−0.18 to 0.35)
Studies reporting hypoglycaemia data	0.01 (−0.23 to 0.25)	−0.18 (−0.51 to 0.14)	−0.09 (−0.57 to 0.38)	−0.12 (−0.42 to 0.18)	0.18 (−0.12 to 0.51)
Studies with 24–28-week results	0.01 (−0.24 to 0.26)	−0.04 (−0.36 to 0.27)	−0.03 (−0.35 to 0.30)	−0.14 (−0.47 to 0.19)	0.17 (−0.10 to 0.45)
Excluding Degludec 3TW	0.02 (−0.22 to 0.28)	−0.08 (−0.37 to 0.22)	0.01 (−0.26 to 0.30)	−0.01 (−0.32 to 0.31)	0.26 (−0.02 to 0.55)
Adjusting for baseline HbA1c	0.05 (−0.49 to 0.63)	−0.03 (−0.60 to 0.56)	0.02 (−0.56 to 0.61)	−0.07 (−0.65 to 0.53)	0.13 (−0.42 to 0.72)
Adjusting for disease duration	0.03 (−0.29 to 0.34)	−0.06 (−0.41 to 0.29)	−0.01 (−0.37 to 0.35)	−0.10 (−0.46 to 0.26)	0.11 (−0.23 to 0.44)
Change in body weight					
BOT, insulin naïve	−0.44 (−1.67 to 0.81)	0.58 (−0.85 to 2.03)	−0.22 (−1.68 to 1.25)	−0.52 (−1.93 to 0.92)	−1.09 (−2.44 to 0.29)
Adjusting for Bolus Insulin Trials	−0.58 (−2.54 to 1.37)	0.11 (−1.98 to 2.20)	−0.63 (−2.75 to 1.45)	−0.66 (−2.78 to 1.45)	−1.13 (−3.18 to 0.91)
Insulin naïve	−0.30 (−1.44 to 0.82)	1.18 (−0.12 to 2.47)	−0.12 (−1.39 to 1.10)	−0.46 (−1.71 to 0.80)	−1.12 (−2.39 to 0.15)
T2DM overall	−0.27 (−1.28 to 0.73)	0.42 (−0.78 to 1.62)	−0.32 (−1.54 to 0.89)	−0.35 (−1.58 to 0.88)	−0.81 (−1.96 to 0.32)
Studies reporting hypoglycaemia data	−0.28 (−1.28 to 0.71)	1.01 (−0.29 to 2.31)	0.89 (−0.90 to 2.70)	−0.36 (−1.58 to 0.86)	−1.24 (−2.59 to 0.09)
Studies with 24–28-week results	−0.28 (−1.28 to 0.74)	0.26 (−1.05 to 1.57)	−0.15 (−1.45 to 1.16)	−0.42 (−1.76 to 0.92)	−1.01 (−2.19 to 0.18)
Excluding Degludec 3TW	−0.46 (−1.34 to 0.43)	0.68 (−0.38 to 1.76)	−0.76 (−1.82 to 0.27)	−0.79 (−1.90 to 0.33)	−1.83 (−2.89 to −0.68)
Adjusting for baseline HbA1c	−0.27 (−2.03 to 1.25)	0.43 (−1.46 to 2.12)	−0.32 (−2.23 to 1.39)	−0.34 (−2.26 to 1.38)	−0.81 (−2.68 to 0.82)
Adjusting for disease duration	−0.44 (−1.91 to 1.00)	0.25 (−1.38 to 1.87)	−0.49 (−2.15 to 1.13)	−0.52 (−2.20 to 1.13)	−0.99 (−2.58 to 0.58)
Nocturnal hypoglycaemia event rate					
BOT, insulin naïve	0.57 (0.33 to 0.98)	0.53 (0.28 to 1.01)	0.21 (0.10 to 0.44)	0.68 (0.36 to 1.25)	0.42 (0.21 to 0.81)
BOT, premixed excluded	0.62 (0.37 to 1.17)	0.56 (0.30 to 1.21)	0.16 (0.08 to 0.41)	0.79 (0.42 to 1.64)	N/A
Adjusting for Bolus Insulin Trials	0.56 (0.24 to 1.29)	0.52 (0.21 to 1.32)	0.20 (0.07 to 0.57)	0.66 (0.26 to 1.61)	0.50 (0.19 to 1.26)
Insulin naïve patients only	0.58 (0.12 to 2.77)	0.51 (0.07 to 3.38)	0.17 (0.02 to 1.37)	0.61 (0.10 to 3.48)	0.26 (0.03 to 2.35)
T2DM overall	0.64 (0.39 to 1.03)	0.60 (0.32 to 1.11)	0.23 (0.11 to 0.50)	0.75 (0.41 to 1.34)	0.57 (0.31 to 1.05)
Studies with 24–28-week results	0.64 (0.37 to 1.10)	0.51 (0.22 to 1.18)	0.24 (0.08 to 0.70)	0.67 (0.32 to 1.37)	0.55 (0.26 to 1.17)
Excluding Degludec 3TW	0.57 (0.33 to 0.98)	0.51 (0.24 to 1.07)	0.19 (0.07 to 0.45)	0.83 (0.42 to 1.69)	0.36 (0.17 to 0.74)
2.8–4.2 mmol/L	0.64 (0.37 to 1.11)	0.68 (0.35 to 1.34)	0.31 (0.15 to 0.63)	0.75 (0.38 to 1.46)	0.68 (0.35 to 1.29)
Adjusting for baseline HbA1c	0.37 (0.18 to 0.90)	0.35 (0.15 to 0.91)	0.13 (0.05 to 0.39)	0.43 (0.19 to 1.12)	0.33 (0.14 to 0.86)
Adjusting for disease duration	0.60 (0.31 to 1.13)	0.56 (0.26 to 1.19)	0.22 (0.09 to 0.53)	0.71 (0.34 to 1.46)	0.54 (0.25 to 1.14)
Documented symptomatic hypoglycaemia event rate					
BOT, insulin naïve	0.72 (0.40 to 1.30)	0.63 (0.22 to 1.73)	0.58 (0.26 to 1.24)	0.59 (0.29 to 1.20)	0.50 (0.24 to 1.01)
BOT, premixed excluded	0.75 (0.55 to 1.05)	0.69 (0.42 to 1.23)	0.55 (0.36 to 0.91)	0.66 (0.46 to 1.01)	N/A
Adjusting for Bolus Insulin Trials	0.83 (0.35 to 1.83)	0.72 (0.22 to 2.31)	0.76 (0.28 to 1.86)	0.68 (0.26 to 1.67)	0.57 (0.22 to 1.41)
Insulin naïve patients only	0.62 (0.21 to 1.77)	0.54 (0.12 to 2.36)	0.50 (0.14 to 1.63)	0.61 (0.17 to 2.25)	0.24 (0.05 to 1.09)
T2DM overall	0.78 (0.50 to 1.23)	0.68 (0.27 to 1.70)	0.71 (0.38 to 1.30)	0.64 (0.36 to 1.16)	0.54 (0.30 to 0.98)

Continued

Table 3 Continued

(A) Sensitivity analyses

Outcome	Comparator				
	Gla-100	Detemir	NPH	Degludec	Premix
Studies with 24–28-week results	0.78 (0.45 to 1.34)	0.68 (0.23 to 2.01)	0.75 (0.36 to 1.60)	0.53 (0.23 to 1.20)	0.58 (0.27 to 1.25)
Adjusting for baseline HbA1c	0.71 (0.44 to 1.13)	0.61 (0.25 to 1.51)	0.64 (0.34 to 1.19)	0.58 (0.32 to 1.05)	0.49 (0.27 to 0.89)
Adjusting for disease duration	0.57 (0.32 to 0.99)	0.50 (0.18 to 1.33)	0.52 (0.25 to 1.04)	0.47 (0.23 to 0.92)	0.40 (0.19 to 0.78)

(B) Comparison of NMA to classic meta-analysis for base scenario (BOT)

Outcome	Difference	NMA: point estimate (95% CrI)	Meta-analysis (direct evidence): point estimate (95% CI)
Change in HbA1c†	Gla-300 vs Gla-100	0.01 (−0.27 to 0.29)	0.02 (−0.08 to 0.11)
	Insulin detemir vs Gla-100	0.10 (−0.07 to 0.28)	0.04 (−0.05 to 0.13)
	NPH vs Gla-100	0.01 (−0.14 to 0.16)	0.02 (−0.05 to 0.09)
	Insulin degludec vs Gla-100	0.14 (−0.03 to 0.30)	0.13 (0.06 to 0.20)
	Premixed vs Gla-100	−0.24 (−0.40 to −0.08)	−0.15 (−0.21 to −0.10)
Change in body weight	Gla-300 vs Gla-100	−0.44 (−1.67 to 0.81)	−0.48 (−0.83 to −0.13)
	Insulin detemir vs Gla-100	−1.15 (−1.73 to −0.58)	−0.98 (−1.20 to −0.76)
	NPH vs Gla-100	0.30 (−0.21 to 0.84)	0.01 (−0.22 to 0.25)
	Insulin degludec vs Gla-100	0.18 (−0.35 to 0.70)	0.21 (0.03 to 0.38)
	Premixed vs Gla-100	1.37 (0.72 to 1.97)	1.70 (1.69 to 1.71)
Nocturnal hypoglycaemia event rate	Gla-300 vs Gla-100	0.57 (0.33 to 0.98)	0.59 (0.38 to 0.90)
	Insulin detemir vs Gla-100	1.11 (0.58 to 2.10)	1.06 (0.93 to 1.21)
	NPH vs Gla-100	3.04 (1.24 to 7.80)	NA†
	Insulin degludec vs Gla-100	0.88 (0.57 to 1.38)	0.79 (0.67 to 0.93)
	Premixed vs Gla-100	1.60 (0.84 to 3.10)	1.39 (1.19 to 1.62)
Documented symptomatic hypoglycaemia event rate	Gla-300 vs Gla-100	0.72 (0.40 to 1.30)	0.75 (0.61 to 0.92)
	Insulin detemir vs Gla-100	1.15 (0.44 to 2.96)	1.15 (1.07 to 1.24)
	NPH vs Gla-100	1.10 (0.68 to 1.89)	1.04 (1.00 to 1.09)
	Insulin degludec vs Gla-100	1.30 (0.75 to 2.24)	1.35 (1.27 to 1.44)
	Premixed vs Gla-100	NA†	NA†

*Four additional studies were included in sensitivity analyses for HbA1c and/or body weight, but were not in the main NMA.[47–50]
†No direct evidence for specific comparison.
BOT, basal insulin-supported oral therapy (ie, no bolus insulin); CrI, Credible interval; HbA1c, glycated haemoglobin; NA, not applicable; NMA, network meta-analysis; NPH, neutral protamine Hagedorn; T2DM, type 2 diabetes mellitus.

Table 4 Hypoglycaemia outcomes for trials included in the NMA

Study	Year	Arm	Total exposure*	Documented symptomatic	Nocturnal	Severe†
Gla-100 vs Gla-300						
Bolli *et al*[8]	2013	Gla-100	218	821	41	4
		Gla-300	217	505	24	4
Riddle *et al*[6]	2014	Gla-100	200	2957	162	48
		Gla-300	201	2714	127	54
Yki-Järvinen *et al*[7]	2014	Gla-100	202	1641	140	12
		Gla-300	201	1357	78	6
Gla-100 vs premixed insulin						
Aschner *et al*[10]	2013	Gla-100	213	249		5
		Premixed insulin	212	632		3
Fritsche *et al*[12]	2010	Gla-100	141		321	16
		Premixed insulin	149		353	33
Ligthelm *et al*[16]	2011	Gla-100	65		233	6
		Premixed insulin	63		273	0
Raskin *et al*[17]	2005	Gla-100	61			1
		Premixed insulin	58			0
Riddle *et al*[18]	2011	Gla-100 (plus step-wise glulisine)	220	1559		
		Gla-100 (plus 1 prandial dose)	217	1565		
		Premixed insulin	221	2694		
Robbins *et al*[19]	2007	Gla-100	73			4
		Premixed insulin	72			8
Rosenstock *et al*[20]	2008	Gla-100	86	3866		3
		Premixed insulin	86	4000		9
Strojek *et al*[21]	2009	Gla-100	114		57	3
		Premixed insulin	110		120	3
Tinahones *et al*[22]	2013	Gla-100	111	859		
		Premixed insulin	109	783		
Vora *et al*[23]	2013	Gla-100	78		446	
		Premixed insulin	76		273	
Gla-100 vs NPH						
Fritsche *et al*[24]	2003	Gla-100 (morning dosing)	109	710		6
		Gla-100 (evening dosing)	104	467		4
		NPH	107	583		13
Riddle *et al*[26]	2003	Gla-100	169	1553		14
		NPH	179	2308		9
Rosenstock *et al*[27]	2001	Gla-100	139	2012		
		NPH	139	1577		
Rosenstock *et al*[28]	2009	Gla-100	2556			102
		NPH	2511			151
Yki-Järvinen *et al*[29]	2006	Gla-100	42	5		0
		NPH	34	8		0
Degludec vs Gla-100						
Garber *et al*[30]	2012	Degludec	671	13 821	932	40
		Gla-100	229	5361	421	11
Gough *et al*[31]	2013	Degludec	106	357	19	0
		Gla-100	107	389	30	0
Meneghini *et al*[32]	2013	Degludec (flexible dosing)‡	108	851	65	2
		Degludec (evening dosing)	105	776	63	2
		Gla-100	105	383	84	2
Zinman *et al*[33]	2012	Degludec	667	2675	167	2
		Gla-100	218	806	85	5
Zinman (AM) *et al*[34]	2013	Degludec	105		42	1
		Gla-100	106		21	1
Zinman (PM) *et al*[34]	2013	Degludec	109		22	1
		Gla-100	110		22	0

Continued

Table 4 Continued

Study	Year	Arm	Total exposure*	Documented symptomatic	Nocturnal	Severe†
Detemir vs Gla-100						
Hollander *et al*[35]	2008	Detemir	187		449	17
		Gla-100	92		265	6
Meneghini *et al*[36]	2013	Detemir	103		115	0
		Gla-100	104		91	2
Raskin *et al*[37]	2009	Detemir	128		540	11
		Gla-100	65		221	8
Rosenstock *et al*[38]	2008	Detemir	262		341	0
		Gla-100	269		350	0
Swinnen *et al*[39]	2010	Detemir	224	1491		18
		Gla-100	220	1273		35
Detemir vs premixed insulin						
Holman *et al*[40]	2007	Detemir	233			4
		Premixed insulin	234			11
		Aspart	238			16
Detemir vs NPH						
Hermansen *et al*[43]	2006	Detemir	106		160	1
		NPH	106		349	8
Montañana *et al*[44]	2008	Detemir	62		46	0
		NPH	73		107	3
Philis-Tsimikas *et al*[45]	2006	Detemir (morning dosing)	63		6	0
		Detemir (evening dosing)	65		19	2
		NPH	63		47	0

*Total exposure indicates the number of patient-years over which the rate for hypoglycaemic events is determined.
†Although severe events were not analysed in the NMA due to small numbers of events, they are included in the table if reported within the publication.
‡Rotating morning and evening dosing schedule (ie, 8–40 h intervals between doses).
NMA, network meta-analysis; NPH, neutral protamine Hagedorn.

Utilisation costs were estimated to be higher among patients who injured themselves due to a trip or fall associated with their nocturnal hypoglycaemia episode (approximately $2000 per person annually).

While the findings of this NMA are promising for Gla-300, several limitations are evident. The studies included in this NMA were of open-label design, which is inherently subject to bias; however, this type of methodology is typically used in trials comparing insulin therapies due to visible differences between insulin products and/or differences in injection devices. A potential issue is that there was no multiplicity adjustment, and given that there were multiple comparisons, it is possible that positive findings were due to chance. In addition, trial-level summary data may not have been adequately powered to detect differences between products—for example, while randomised controlled studies of Gla-100 versus Gla-300 and pooled patient level data from these studies have shown that Gla-300 is associated with a significantly lower rate of nocturnal hypoglycaemia, the trial-level data comparisons in this NMA did not achieve significance for this end point. Finally, a well-recognised limitation of any NMA is that, by design, these are not randomised comparisons; however, these data can aid the decision-making process until prospective randomised comparative clinical trial data become available.

Strengths of the current NMA include that it was conducted in accordance with established NICE guidelines and that the estimates reported are in line with those in previous meta-analyses of comparative basal insulin studies.[52 53 59 60] NMA provides the capability of considering different pathways simultaneously rather than simple indirect pairwise comparison through multiple pathways. Another strength is the quality of studies included in the NMA (ie, the majority had discontinuation rates <20%). The studies included were similar in design and, from a clinical standpoint, heterogeneity of the patient population was not considered an issue. Results of the NMA were internally consistent with what was reported in individual RCTs. Finally, extensive sensitivity analyses considering subsets of studies, different hypoglycaemia definitions and adjusting for trial-level characteristics, supported the robustness of the findings.

In conclusion, clinical trial findings and the results from this NMA suggest that Gla-300 in the treatment of T2DM is associated with a lower rate of nocturnal hypoglycaemia than treatment with premixed insulin and NPH, while demonstrating comparable glycaemic control versus all comparators. Change in body weight was significantly lower for Gla-300 versus premixed insulin, and comparable with other basal insulin. These NMA data, along with randomised clinical trial findings

of reduced nocturnal hypoglycaemia and comparable clinical benefits for Gla-300 versus Gla-100, suggest that this new basal insulin represents an important advance in insulin treatment for patients with T2DM.

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Competing interests NF reports personal fees from Sanofi Aventis, during the conduct of the study and personal fees from Novo Nordisk, outside the submitted work. EC and HW are employees of Sanofi. CF, DZ and EW report grants from Sanofi, during the conduct of the study; and the Employer (Analysis Group) has received other grants from Sanofi to fund other research (eg, in different therapeutic areas); the Employer has similar arrangements with other drug and medical device manufacturers. WL received honoraria and compensation for travel and accommodation costs for attending advisory boards from Sanofi Aventis. AV is an employee of Sanofi and owner of Sanofi shares. QZ is a former employee of Sanofi, and owner of Sanofi shares. CG is a former employee of Sanofi.

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