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Comparative Benefits and Harms of Basal Insulin Analogues for Type 2 Diabetes

A Systematic Review and Network Meta-analysis

Anastasia-Vasiliki Madenidou, MD, MSc; Paschalis Paschos, MD, MSc; Thomas Karagiannis, MD, MSc; Anastasia Katsoula, MD, MSc; Eleni Athanasiadou, MSc; Konstantinos Kitsios, MD, PhD; Eleni Bekiari, MD, PhD, MSc; David R. Matthews, MD, DPhil; and Apostolos Tsapas, MD, PhD, MSc

Background: Basal insulin analogues aim for protracted glycemic control with minimal adverse effects.

Purpose: To assess the comparative efficacy and safety of basal insulin analogues for adults with type 2 diabetes mellitus (T2DM).

Data Sources: Several databases from inception to April 2018 without language restrictions, ClinicalTrials.gov to April 2018, references of reviews, and meeting abstract books.

Study Selection: Randomized trials lasting at least 12 weeks that compared efficacy (change in hemoglobin A_{1c} [HbA_{1c}] level from baseline [primary outcome]; percentage of patients with HbA_{1c} level <7% at end of study and change in body weight [secondary outcomes]) and safety (hypoglycemia) of basal insulin analogues.

Data Extraction: Two authors independently extracted data and assessed risk of bias for each outcome. All authors evaluated overall confidence in the evidence.

Data Synthesis: Thirty-nine trials (26 195 patients) assessed 10 basal insulin analogues. Low- to very-low-quality evidence indicated that thrice-weekly degludec (Deg-3TW) was inferior to most other regimens for reducing HbA_{1c} level, with mean differences ranging from 0.21% (vs. degludec, 100 U/mL [Deg-100]) to 0.32% (vs. glargine, 300 U/mL [Glar-300]). High- to moderate-quality evidence suggested that detemir had a favorable weight profile versus all comparators, and Glar-300 was associated with less weight gain than glargine, 100 U/mL (Glar-100); Deg-100; degludec, 200 U/mL (Deg-200); Deg-3TW; and LY2963016. Low- and very-low-quality evidence suggested that Deg-100, Deg-200, and Glar-300 were associated with lower incidence of nocturnal hypoglycemia than detemir, Glar-100, LY2963016, and neutral protamine lispro (NPL). Incidence of severe hypoglycemia did not differ among regimens, except NPL, which was associated with increased risk versus Deg-100, detemir, Glar-100, and Glar-300.

Limitations: Results are based mostly on indirect comparisons. Confidence in summary estimates is low or very low due to individual-study limitations, imprecision, or inconsistency.

Conclusion: Low-quality evidence suggests that basal insulin analogues for T2DM do not substantially differ in their glucose-lowering effect. Low- and very-low-quality evidence suggests some regimens may be associated with lower risk for nocturnal hypoglycemia (Deg-100, Deg-200, and Glar-300) or less weight gain (detemir and Glar-300).

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For author affiliations, see end of text.
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Insulin replacement therapy is one of the main components of pharmacologic treatment of type 2 diabetes mellitus (T2DM). Guidance supports initiation of basal insulin therapy with oral medications in patients with inadequate disease control (1). Traditionally, this was accomplished with intermediate-acting neutral protamine Hagedorn (NPH) insulin. Insulin glargine (100 U/mL) and insulin detemir are long-acting basal insulin analogues that offer better metabolic control than NPH by providing consistent and protracted control of basal insulin levels while reducing risk for hypoglycemia (2).

Recently, a new generation of long-acting insulin analogues has been developed that aims for a more stable and prolonged action along with minimal risk for hypoglycemia and weight gain (3, 4). However, conclusive evidence about their comparative efficacy and safety is lacking because they have mostly been compared with insulin glargine. In the absence of adequate data on direct comparisons, network meta-analysis can be used to synthesize evidence from direct and indirect comparisons of multiple interventions and determine the best available treatment option (5). The comparative efficacy and safety of basal insulin regimens have recently been evaluated in a network meta-analysis for type 1 diabetes but not for T2DM (6). We performed a network meta-analysis of randomized controlled trials to assess the efficacy and safety of available basal insulin analogues for treatment of T2DM.

METHODS

We report our systematic review and meta-analysis in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) extension statement for network meta-analyses (7). We followed a prespecified protocol registered at PROSPERO (CRD42016037055) (8).

See also:

Web-Only
Supplement

Data Sources and Searches

We searched MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials from inception to April 2018 with no language or date restrictions and using relevant free-text terms, controlled vocabulary, and a filter for randomized controlled trials. The MEDLINE search is presented in Supplement Table 1 (available at Annals.org). We also searched ClinicalTrials.gov to April 2018, reference lists of relevant reviews, and the annual meeting abstract books of the American Diabetes Association and the European Association for the Study of Diabetes from 2011 to 2018.

Study Selection

We included randomized controlled trials of at least 12 weeks' duration that compared basal insulin analogues in adults with T2DM, regardless of study design (parallel or crossover) or reported outcomes. Eligible interventions included degludec, 100 U/mL (Deg-100); degludec, 200 U/mL (Deg-200); thrice-weekly degludec (Deg-3TW); detemir; glargine, 100 U/mL (Glar-100); glargine, 300 U/mL (Glar-300); LY2963016 (glargine biosimilar); neutral protamine lispro (NPL); and any other basal insulin analogue identified in our search. We excluded studies assessing insulin peglispro after its discontinuation due to safety concerns (9), studies assessing intermediate-acting NPH insulin or premixed insulin preparations, and studies in patients with type 1 or other diabetes. Glar-100 and Glar-300, as well as Deg-100, Deg-200, and Deg-3TW, were deemed separate treatments or nodes due to different concentrations or dosing schedules among individual regimens. Once- and twice-daily detemir were merged into 1 node based on current authorization and clinical practice, which support titration and modification of dosing regimens on the basis of the needs of individual patients (10).

Search results were imported into Covidence (11). After deduplication, each report was assessed for eligibility at the title and abstract level, and the full text of potentially eligible reports was examined by 2 of 3 independent reviewers (A.K., A.V.M., and P.P.). Conflicts were resolved by consensus or were arbitrated by a third reviewer (A.T.). We did not apply language restrictions during the screening process.

Data Extraction

Data extraction for each study was performed by 2 of 3 independent reviewers (A.K., A.V.M., and P.P.), and discrepancies were resolved by consensus. We used a predesigned data collection form to extract data on study characteristics, participants' baseline characteristics, and efficacy and safety outcomes. The primary outcome was change in hemoglobin A_{1c} (HbA_{1c}) level from baseline. Secondary outcomes included the percentage of patients with an HbA_{1c} level less than 7% at the end of the study; change in body weight from baseline; and the number of patients experiencing at least 1 event of any, severe, or nocturnal hypoglycemia. For outcomes related to hypoglycemia, we extracted data on the definition used in each study and the method used to assess hypoglycemia. To maximize the yield of available information, we collated information from different reports that referred to the same study, and for all outcomes, we used data from the report with the longest follow-up.

Risk-of-Bias Assessment

Risk of bias for each study was assessed separately for each outcome by 2 of 3 independent reviewers (A.K., A.V.M., and P.P.) using the Cochrane Collaboration revised tool to assess risk of bias in randomized trials (RoB 2.0) (12). Discrepancies were resolved by consensus. Trials were judged to have high risk of bias, low risk of bias, or some concerns about bias based on the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. Overall risk of bias was low when all domains were deemed to have low risk and high when at least 1 domain had high risk or at least 3 domains were deemed to have some concerns. In all other cases, studies were judged to have some concerns about bias. We assessed the presence of small-study effects for change in HbA_{1c} level, change in body weight, and nocturnal hypoglycemia by visual inspection of comparison-adjusted funnel plots (13).

Data Synthesis and Analysis

We performed frequentist random-effects network meta-analyses with a multivariate meta-analysis model using the mvmeta command and routines in Stata (14). Treatment effects were estimated as mean differences (MDs) (continuous outcomes) or odds ratios (ORs) (dichotomous outcomes) with 95% CIs. We constructed network plots for each outcome, with the node size proportional to the number of participants randomly assigned to each treatment and the thickness of lines between nodes corresponding to the number of studies assessing each comparison (13). We conducted a sensitivity analysis for the primary outcome that included only trials at low risk of bias and an additional sensitivity analysis that excluded trials with a crossover design.

We examined clinical heterogeneity by generating descriptive statistics for study and population characteristics across all eligible trials and assessed transitivity by considering the distributions of potential effect modifiers (baseline HbA_{1c} level and body weight) across pairwise comparisons. We investigated the extent of heterogeneity in every network by comparing the between-study variance (τ^2) estimated for the network of interest with an empirical distribution of heterogeneity variances specific to the type of outcome and treatments being compared (15, 16). Heterogeneity was considered low when the estimated τ^2 value was less than the suggested median τ^2 value for the specific outcome and treatments being compared. To check the assumptions of local and global consistency, we used the loop-specific approach and the design-by-treatment interaction model, respectively (17). All analyses were conducted using Stata, version 13 (StataCorp).

Evaluation of Confidence in the Evidence

We used the CINeMA (Confidence in Network Meta-analysis) Internet application (18) to determine the confidence in network estimates of change in HbA_{1c} level, change in body weight, and incidence of nocturnal hypoglycemia among treatments. We assessed study limitations (based on risk-of-bias assessment), indirectness, inconsistency (heterogeneity and incoherence), imprecision, and publication bias (based on presence of small-study effects) and summarized across these components to obtain the confidence in each comparison. Confidence was initially considered to be high and was maintained or downgraded to moderate, low, or very low according to the assessment of the quality of the evidence. Confidence in the evidence was based on consensus among all reviewers.

Role of the Funding Source

This study received no funding. All authors had full access to all data and share responsibility for the decision to submit the manuscript for publication.

RESULTS

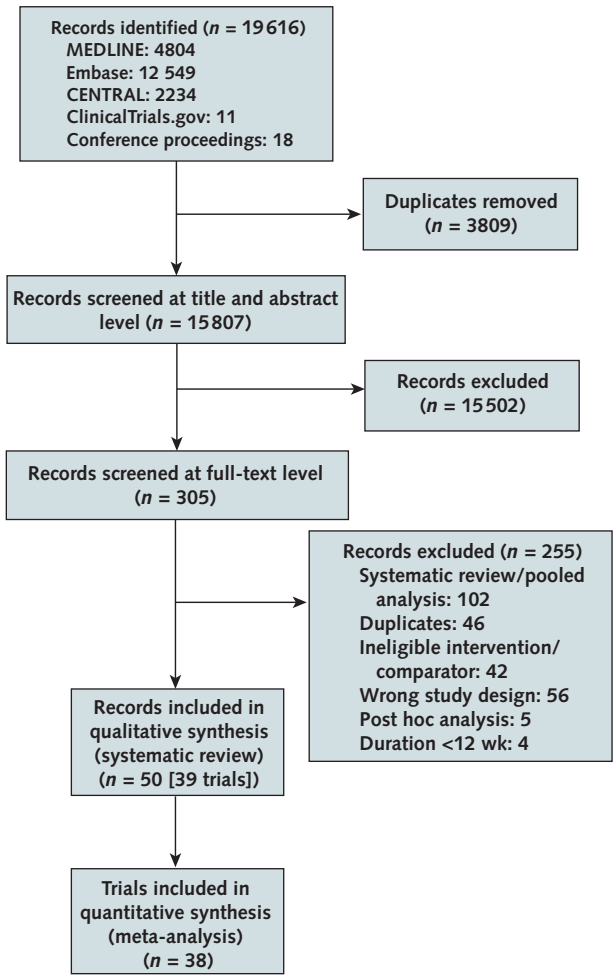
Overview of Trials

The study selection process is shown in Figure 1. Our searches yielded a total of 19 616 records. Of these, 50 records of 39 randomized controlled trials (n = 26 195 patients) were included in our systematic review (19–56). We identified 2 novel basal insulin analogues, MK-1293 and MYL-1501D (glargine biosimilars), which had not been included in our search strategy. We did not use 1 eligible study in the quantitative synthesis (meta-analysis) because it did not report data for our predefined outcomes (25).

Network plots of the main analysis for the primary outcome and for hypoglycemia-related outcomes are shown in Figure 2. Network plots for the remaining outcomes and sensitivity analyses for the primary outcome are presented in the Supplement Figure (available at Annals.org). In the network of the main analysis for the primary outcome, 25 121 patients were allocated to 10 interventions: Deg-100, Deg-200, Deg-3TW, detemir, Glar-100, Glar-300, LY2963016, MK-1293, MYL-1501D, and NPL (Figure 2, *A*). Among all comparisons, Glar-100 was the most commonly used treatment (37 trials [11 072 patients]), and only 3 comparisons assessed interventions other than Glar-100. The most common comparators against Glar-100 were detemir (10 trials) and Deg-100 (9 trials).

Baseline and key characteristics of included studies are presented in Supplement Tables 2 and 3 (available at Annals.org). We handled crossover trials (4 studies) similarly to parallel trials by extracting data from the first period only (57). Median study duration was 24 weeks (interquartile range [IQR], 24 to 26 weeks), and only 8 studies lasted more than 1 year (3 studies of Glar-300, 2 of detemir, and 3 of Deg-100). Patients in all studies were treated with at least 1 oral antidiabetic agent before randomization, and background antidiabetic therapy included insulin in 15 studies or an injectable glucagon-like peptide-1 receptor agonist in 4 studies. All but 4 trials were industry-funded, and the exact method of assessing hypoglycemia-related outcomes was described in 13 trials (Supplement Table 3). The median of the mean age of patients was 58.4 years (IQR, 56.7 to 60.2 years), and the median of the average duration of T2DM was 10.6 years (IQR, 9.1 to 12.7 years). The median of the mean HbA_{1c} level at baseline was 8.4% (IQR, 8.2% to 8.7%), and the median of the average body weight was 87.4 kg (IQR, 80.6 to 93.1 kg). Because we identified no variability in baseline HbA_{1c} level or body weight across included studies, we accepted the assumption of transitivity and concluded that a network meta-analysis was reasonable.

Figure 1. Evidence search and selection.

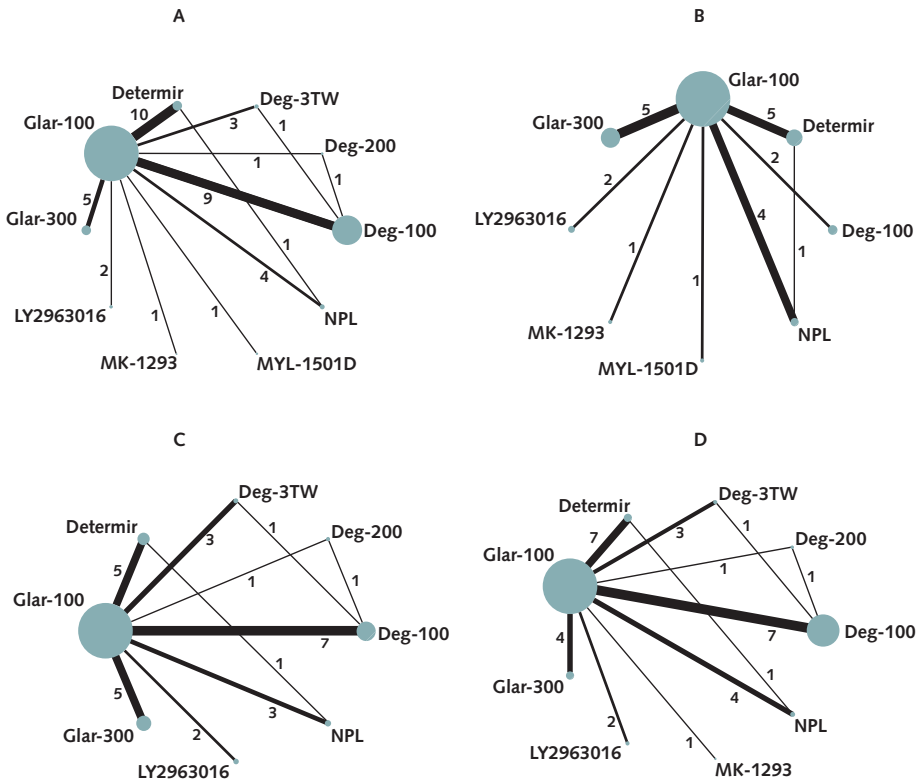


CENTRAL = Cochrane Central Register of Controlled Trials.

Change in HbA_{1c} Level

Estimates from network meta-analyses for change in HbA_{1c} level are presented in Figure 3 (*lower half*). The analyses were based on data from 37 studies (39 comparisons) assessing 10 insulin regimens (Figure 2, *A*). Deg-3TW was less effective at reducing HbA_{1c} level than Deg-100 (MD, 0.21% [95% CI, 0.03% to 0.38%]),

Figure 2. Network plots of treatment comparisons for change in HbA_{1c} level and incidence of any, nocturnal, or severe hypoglycemia.



Each node corresponds to a drug, and the node size is proportional to the number of participants assigned to that drug. Each line represents a direct comparison between drugs, and the width of the line is proportional to the number of randomized controlled trials providing data for the comparison, which is also shown next to each line. Deg-100 = degludec, 100 U/mL; Deg-200 = degludec, 200 U/mL; Deg-3TW = thrice-weekly degludec; Glar-100 = glargine, 100 U/mL; Glar-300 = glargine, 300 U/mL; HbA_{1c} = hemoglobin A_{1c}; NPL = neutral protamine lispro. **A.** Change in HbA_{1c} level from baseline. **B.** Incidence of any hypoglycemia. **C.** Incidence of nocturnal hypoglycemia. **D.** Incidence of severe hypoglycemia.

Deg-200 (MD, 0.28% [CI, 0.04% to 0.52%]), Glar-100 (MD, 0.26% [CI, 0.11% to 0.42%]), Glar-300 (MD, 0.32% [CI, 0.13% to 0.51%]), and LY2963016 (MD, 0.27% [CI, 0.05% to 0.48%]). Similarly, detemir was inferior to Glar-100 (MD, 0.15% [CI, 0.04% to 0.25%]) and Glar-300 (MD, 0.20% [CI, 0.05% to 0.35%]). We did not detect differences in any other comparisons (**Figure 3**).

Our confidence in estimates for change in HbA_{1c} level was generally low or very low due to study limitations, imprecision, and inconsistency (**Supplement Table 4**, available at Annals.org). Only about half of studies had low risk of bias (**Supplement Table 5**, available at Annals.org), and CIs were wide, extending into both clinically important and unimportant effects. We downgraded for inconsistency because we detected either heterogeneity or incoherence. We did not downgrade due to indirectness given that the transitivity assumption was valid. Evaluation of the funnel plot revealed no evidence of small-study effects, so we did not downgrade our confidence in estimates due to publication bias. Results were consistent in sensitivity analyses restricted to studies with low risk of bias (**Supplement Figure**, *A*, and **Supplement Table 6**, available at Annals.org) or parallel trials (**Supplement Figure**, *B*, and **Supplement Table 7**, available at Annals.org).

Percentage of Patients With HbA_{1c} Level Less Than 7%

Data on the percentage of patients with HbA_{1c} level less than 7% at the end of the study were available from 26 studies (**Supplement Figure**, *C*). Network meta-analysis showed that more patients treated with Glar-100 achieved an HbA_{1c} level less than 7% than those treated with Deg-3TW (OR, 1.45 [CI, 1.06 to 1.96]), detemir (OR, 1.28 [CI, 1.05 to 1.54]), or NPL (OR, 1.37 [CI, 1.04 to 1.79]). We observed no differences for other treatment comparisons (**Supplement Table 8**, available at Annals.org). Among included studies, 16 had low risk of bias and 10 had some concerns about bias (**Supplement Table 9**, available at Annals.org).

Change in Body Weight

Thirty-four studies (36 comparisons) contributed to the network meta-analysis for change in body weight (**Supplement Figure**, *D*). Detemir had a favorable weight profile versus all comparators, with weighted MDs ranging from −0.68 kg (vs. Glar-300) to −1.76 kg (vs. LY2963016) (**Supplement Table 10**, available at Annals.org). In addition, patients treated with Glar-300 had less weight gain than those treated with Deg-100 (MD, −0.75 kg [CI, −1.24 to −0.26 kg]), Deg-200 (MD,

−0.93 kg [CI, −1.70 to −0.16 kg]), Deg-3TW (MD, −0.74 kg [CI, −1.40 to −0.08 kg]), Glar-100 (MD, −0.70 kg [CI, −1.08 to −0.31 kg]), or LY2963016 (MD, −1.08 kg [CI, −1.76 to −0.40 kg]). Confidence in network estimates was generally high or moderate and was downgraded due to risk of bias or heterogeneity (**Supplement Tables 11** and **12**, available at Annals.org). Visual inspection of the funnel plot did not reveal evidence of small-study effects.

Any Hypoglycemia

Definitions of any hypoglycemia were not uniform among trials, ranging from incidence of symptoms typically associated with hypoglycemia with or without plasma glucose level of 3.9 mmol/L or less to confirmed blood glucose level of 3.9 mmol/L or less or 3.1 mmol/L or less. Based on results from 21 studies (**Figure 2**, *B*), there were no differences in incidence of any hypoglycemia among basal insulin regimens, except Deg-100, which was associated with lower incidence of any hypoglycemia compared with Glar-100 (OR, 0.64 [CI, 0.43 to 0.96]) (**Supplement Table 13**, available at Annals.org). Risk of bias for this outcome was deemed high for almost all studies (**Supplement Table 14**, available at Annals.org).

Nocturnal Hypoglycemia

Most studies defined nocturnal hypoglycemia as any hypoglycemic event occurring between bedtime and waking or between midnight and 6:00 a.m. Based on a network of 27 studies (29 comparisons) (**Figure 2**, *C*), Deg-100, Deg-200, and Glar-300 were associated with lower incidence of nocturnal hypoglycemia than detemir, Glar-100, LY2963016, and NPL (**Figure 3** [*upper half*]). In addition, NPL was associated with increased risk over all comparators except Deg-3TW (OR, 1.35 [CI, 0.79 to 2.30]). Our confidence in effect estimates for nocturnal hypoglycemia was low to very low (**Table**). All but 1 of the trials were deemed to have high risk of bias (**Supplement Table 15**, available at Annals.org), and CIs extended into both clinically important and unimportant effects. Evaluation of the funnel plot showed no evidence of small-study effects.

Severe Hypoglycemia

The definition of severe hypoglycemia (an episode requiring assistance) was consistent among studies. Incidence of severe hypoglycemia (30 studies [32 comparisons]) (**Figure 2**, *D*) did not differ among most insulin regimens, except NPL, which was associated with increased risk compared with Deg-100 (OR vs. NPL, 0.28 [CI, 0.09 to 0.86]), detemir (OR vs. NPL, 0.26 [CI, 0.09 to 0.74]), Glar-100 (OR vs. NPL, 0.32 [CI, 0.12 to 0.85]), and Glar-300 (OR vs. NPL, 0.29 [CI, 0.09 to 0.90]) (**Supplement Table 16**, available at Annals.org). Risk of bias was high for all but 1 of the trials evaluating severe hypoglycemia (**Supplement Table 17**, available at Annals.org).

Assessment of Heterogeneity and Inconsistency

The estimated τ^2 value for each outcome (except change in body weight) was less than the suggested median τ^2 value from empirical distributions, suggesting that heterogeneity was low (**Supplement Table 18**, available at Annals.org) (15, 16). We found no evidence of local inconsistency, estimated as the difference between direct and indirect estimates, except for 1 of the 3 loops for change in HbA_{1c} level. In an evaluation of global consistency, the design-by-treatment interaction model suggested no inconsistency in the entire network (*P* values ranged from 0.096 to 0.84).

Figure 3. Network meta-analysis estimates for change in HbA_{1c} level and incidence of nocturnal hypoglycemia for each comparison of basal insulin analogues.

Deg-100	1.05 (0.71 to 1.55)	***0.58 (0.35 to 0.96)***	***0.67 (0.54 to 0.85)***	***0.70 (0.59 to 0.82)***	0.93 (0.75 to 1.16)	***0.62 (0.47 to 0.81)***	–	–	***0.43 (0.32 to 0.57)***
0.07 (−0.11 to 0.26)	**Deg-200**	0.55 (0.30 to 1.03)	***0.64 (0.42 to 0.99)***	***0.66 (0.44 to 0.99)***	0.89 (0.58 to 1.36)	***0.59 (0.37 to 0.93)***	–	–	***0.41 (0.26 to 0.65)***
−0.21 (−0.38 to −0.03)	***−0.28 (−0.52 to −0.04)***	**Deg-3TW**	1.16 (0.70 to 1.92)	1.20 (0.74 to 1.93)	1.60 (0.97 to 2.64)	1.06 (0.62 to 1.80)	–	–	0.74 (0.43 to 1.26)
−0.09 (−0.22 to 0.04)	−0.16 (−0.38 to 0.05)	0.12 (−0.08 to 0.31)	**Detemir**	1.03 (0.88 to 1.21)	***1.39 (1.12 to 1.71)***	0.91 (0.70 to 1.20)	–	–	***0.64 (0.50 to 0.82)***
0.06 (−0.02 to 0.14)	−0.02 (−0.20 to 0.17)	***0.26 (0.11 to 0.42)***	***0.15 (0.04 to 0.25)***	**Glar-100**	***1.34 (1.17 to 1.54)***	0.89 (0.71 to 1.11)	–	–	***0.62 (0.49 to 0.78)***
0.11 (−0.02 to 0.24)	0.04 (−0.17 to 0.25)	***0.32 (0.13 to 0.51)***	***0.20 (0.05 to 0.35)***	0.05 (−0.05 to 0.16)	**Glar-300**	***0.66 (0.51 to 0.86)***	–	–	***0.46 (0.35 to 0.61)***
0.06 (−0.10 to 0.22)	−0.01 (−0.24 to 0.22)	***0.27 (0.05 to 0.48)***	0.15 (−0.02 to 0.33)	0.00 (−0.14 to 0.14)	−0.05 (−0.23 to 0.12)	**LY2963016**	–	–	***0.70 (0.51 to 0.97)***
0.04 (−0.23 to 0.31)	−0.04 (−0.35 to 0.28)	0.24 (−0.06 to 0.55)	0.13 (−0.15 to 0.41)	−0.02 (−0.28 to 0.24)	−0.07 (−0.35 to 0.20)	−0.02 (−0.32 to 0.27)	**MK-1293**	–	–
−0.00 (−0.32 to 0.32)	−0.08 (−0.44 to 0.29)	0.20 (−0.15 to 0.56)	0.09 (−0.24 to 0.42)	−0.06 (−0.37 to 0.25)	−0.11 (−0.44 to 0.22)	−0.06 (−0.41 to 0.28)	−0.04 (−0.44 to 0.36)	**MYL-1501D**	–
−0.01 (−0.16 to 0.15)	−0.08 (−0.31 to 0.15)	0.20 (−0.01 to 0.41)	0.09 (−0.07 to 0.24)	−0.06 (−0.20 to 0.07)	−0.12 (−0.29 to 0.05)	−0.07 (−0.26 to 0.13)	−0.04 (−0.33 to 0.25)	0.00 (−0.34 to 0.34)	**NPL**

Drugs are listed alphabetically. The lower part of the figure (*light green shading*) shows column-to-row mean differences and 95% CIs for change in HbA_{1c} level from baseline; a mean difference <0.00 favors the column-defining treatment (i.e., the treatment in the column is associated with a greater reduction in HbA_{1c} level than the treatment in the row). The upper part of the figure (*no shading*) shows row-to-column odds ratios and 95% CIs for incidence of nocturnal hypoglycemia; an odds ratio <1.00 favors the row-defining treatment and means that the treatment in the row is associated with lower risk for nocturnal hypoglycemia than the treatment in the column. Statistically significant differences are italicized. Nocturnal hypoglycemia was not assessed in trials using MK-1293 or MYL-1501D, so no odds ratios could be calculated. Deg-100 = degludec, 100 U/mL; Deg-200 = degludec, 200 U/mL; Deg-3TW = thrice-weekly degludec; Glar-100 = glargine, 100 U/mL; Glar-300 = glargine, 300 U/mL; HbA_{1c} = hemoglobin A_{1c}; NPL = neutral protamine lispro.

Table. Summary of Confidence in Findings for Nocturnal Hypoglycemia

Comparison	Studies, *n*	OR (95% CI)*	Study Limitations	Imprecision	Inconsistency		Indirectness	Publication Bias	Confidence in Estimates
					Heterogeneity	Incoherence			
Mixed evidence									
NPL vs. detemir	1	**1.56 (1.22-2.00)**	Major concerns†	Some concerns‡	No concerns	No concerns	No concerns	Undetected	Very low
NPL vs. Glar-100	3	**1.61 (1.28-2.04)**	Major concerns†	No concerns	No concerns	No concerns	No concerns	Undetected	Low
Deg-100 vs. Deg-200	1	1.05 (0.71–1.55)	Major concerns†	Major concerns§	No concerns	No concerns	No concerns	Undetected	Very low
Deg-100 vs. Deg-3TW	1	**0.58 (0.35-0.96)**	Major concerns†	Some concerns‡	No concerns	No concerns	No concerns	Undetected	Very low
Deg-100 vs. Glar-100	7	**0.70 (0.59-0.82)**	Major concerns†	Some concerns‡	No concerns	No concerns	No concerns	Undetected	Very low
Deg-200 vs. Glar-100	1	**0.66 (0.44-0.99)**	Major concerns†	Some concerns‡	No concerns	No concerns	No concerns	Undetected	Very low
Deg-3TW vs. Glar-100	3	1.20 (0.74–1.93)	Major concerns†	Major concerns§	Some concerns‖	No concerns	No concerns	Undetected	Very low
Detemir vs. Glar-100	5	1.03 (0.88–1.21)	Major concerns†	No concerns	No concerns	No concerns	No concerns	Undetected	Low
Glar-100 vs. Glar-300	5	**1.34 (1.17-1.54)**	Major concerns†	Some concerns‡	No concerns	No concerns	No concerns	Undetected	Very low
Glar-100 vs. LY2963016	2	0.89 (0.71–1.11)	Major concerns†	Some concerns‡	No concerns	No concerns	No concerns	Undetected	Very low
Indirect evidence									
NPL vs. Deg-100	–	**2.33 (1.75-3.13)**	Major concerns†	No concerns	No concerns	No concerns	No concerns	Undetected	Low
NPL vs. Deg-200	–	**2.44 (1.54-3.85)**	Major concerns†	No concerns	No concerns	No concerns	No concerns	Undetected	Low
NPL vs. Deg-3TW	–	1.35 (0.79–2.33)	Major concerns†	Major concerns§	No concerns	No concerns	No concerns	Undetected	Very low
NPL vs. Glar-300	–	**2.17 (1.64-2.86)**	Major concerns†	No concerns	No concerns	No concerns	No concerns	Undetected	Low
NPL vs. LY2963016	–	**1.43 (1.03-1.96)**	Major concerns†	Some concerns‡	No concerns	No concerns	No concerns	Undetected	Very low
Deg-100 vs. detemir	–	**0.67 (0.54-0.85)**	Major concerns†	Some concerns‡	No concerns	No concerns	No concerns	Undetected	Very low
Deg-100 vs. Glar-300	–	**0.70 (0.59-0.82)**	Major concerns†	Some concerns‡	No concerns	No concerns	No concerns	Undetected	Very low
Deg-100 vs. LY2963016	–	**0.62 (0.47-0.81)**	Major concerns†	Some concerns‡	No concerns	No concerns	No concerns	Undetected	Very low
Deg-200 vs. Deg-3TW	–	0.55 (0.30–1.03)	Major concerns†	Some concerns‡	No concerns	No concerns	No concerns	Undetected	Very low
Deg-200 vs. detemir	–	**0.64 (0.42-0.99)**	Major concerns†	Some concerns‡	No concerns	No concerns	No concerns	Undetected	Very low
Deg-200 vs. Glar-300	–	0.89 (0.58–1.36)	Major concerns†	Major concerns§	No concerns	No concerns	No concerns	Undetected	Very low
Deg-200 vs. LY2963016	–	**0.59 (0.37-0.93)**	Major concerns†	Some concerns‡	No concerns	No concerns	No concerns	Undetected	Very low
Deg-3TW vs. detemir	–	1.16 (0.70–1.92)	Major concerns†	Major concerns§	No concerns	No concerns	No concerns	Undetected	Very low
Deg-3TW vs. Glar-300	–	1.60 (0.97–2.64)	Major concerns†	Some concerns‡	No concerns	No concerns	No concerns	Undetected	Very low
Deg-3TW vs. LY2963016	–	1.06 (0.62–1.80)	Major concerns†	Major concerns§	No concerns	No concerns	No concerns	Undetected	Very low
Detemir vs. Glar-300	–	**1.39 (1.12-1.71)**	Major concerns†	Some concerns‡	No concerns	No concerns	No concerns	Undetected	Very low
Detemir vs. LY2963016	–	0.91 (0.70–1.20)	Major concerns†	Some concerns‡	No concerns	No concerns	No concerns	Undetected	Very low
Glar-300 vs. LY2963016	–	**0.66 (0.51-0.86)**	Major concerns†	Some concerns‡	No concerns	No concerns	No concerns	Undetected	Very low

τ^2 = between-study variance; Deg-100 = degludec, 100 U/mL; Deg-200 = degludec, 200 U/mL; Deg-3TW = thrice-weekly degludec; Glar-100 = glargine, 100 U/mL; Glar-300 = glargine, 300 U/mL; NPL = neutral protamine lispro; OR = odds ratio.
* Statistically significant results are in boldface.
† Most evidence comes from studies deemed to be at high risk of bias.
‡ CI extends into clinically important effects zone (0.80 to 1.25) in 1 direction.
§ CI extends into clinically important effects zone (0.80 to 1.25) in both directions.
‖ The estimated τ^2 value for the direct comparison is greater than the reference median τ^2 value (0.096).

DISCUSSION

On the basis of our findings, differences in glycemic efficacy among basal insulin analogues were minimal and probably lacked clinical significance (58). Detemir caused less weight gain than any other regimen, whereas Glar-300 had a favorable weight profile compared with Deg-100, Deg-200, Deg-3TW, Glar-100, and LY2963016. Fewer patients treated with Deg-100, Deg-200, and Glar-300 had nocturnal hypoglycemia than those treated with other basal insulin analogues. Incidence of severe hypoglycemia did not differ among interventions, except NPL, which was associated with higher hypoglycemic risk than any other insulin regimen. We observed no differences between glargine and glargine biosimilars (LY2963016, MK-1293, and MYL-1501D) in terms of reduction in HbA_{1c} level, effect on body weight, or incidence of hypoglycemia.

We performed a MEDLINE search for systematic reviews or meta-analyses up to April 2018 to identify pertinent analyses assessing the comparative efficacy and safety of basal insulin analogues for T2DM. Findings of previous pairwise meta-analyses that suggest a lower rate of nocturnal hypoglycemia with degludec (59–62) and less weight gain with detemir (63) compared with Glar-100 are consistent with our results. An earlier network meta-analysis did not detect differences in body weight and incidence of nocturnal hypoglycemia between Glar-300 and other basal insulin analogues (64). This was probably because its research question was restricted to comparing Glar-300 with detemir, Deg-100, NPH, and premixed insulin regimens rather than assessing the comparative effects of all basal insulin analogues. In contrast, we analyzed direct and indirect evidence for a broader range of basal insulin analogues and incorporated a larger number of studies of 10 regimens identified through a comprehensive literature search. We also evaluated individual-study quality and overall confidence in the evidence using robust methodological tools.

The optimal treatment choice among basal insulin analogues for T2DM should be based on effects of individual drugs on clinically relevant parameters that clinicians and patients consider important (1). Our findings suggest that newer basal insulin analogues do not seem to provide improved glycemic control compared with Glar-100 or detemir. In cases where minimizing weight gain is a priority, detemir or Glar-300 could be considered over other options. In patients for whom nocturnal hypoglycemia is the main concern, Deg-100, Deg-200, or Glar-300 could be preferred. On the other hand, the association of NPL with increased risk for both nocturnal and severe hypoglycemia, with no com-

parative beneficial effects on glycemic control or body weight, raises questions about its clinical utility. These implications should be placed in the context of findings of cardiovascular safety trials of select basal insulin analogues. In the ORIGIN (Outcome Reduction with Initial Glargine Intervention) and ORIGINALE (ORIGIN and Legacy Effects) trials, insulin glargine had a neutral effect on cardiovascular outcomes and incidence of several types of cancer compared with standard care (65, 66). Similarly, in DEVOTE (Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events), Deg-100 was noninferior to Glar-100 with regard to major cardiovascular outcomes in patients with T2DM who were at high cardiovascular risk (36). Finally, to achieve optimal allocation of health care resources, adoption of newer basal insulin regimens in clinical practice should be based on cost-effectiveness evidence in addition to data on clinical efficacy.

Limitations at the review and study levels should be considered in the interpretation of our results. The external validity of our meta-analysis is limited by our decision to include only studies that assessed a basal insulin analogue in both the intervention and comparator groups; therefore, we cannot make inferences about the comparative efficacy of basal insulin analogues against NPH or premixed insulin regimens. We assessed heterogeneity by comparing τ^2 estimates with median values provided from predictive distributions (15, 16) rather than formally implementing a hierarchical Bayesian model to reestimate τ^2 values. Confidence in our findings for glycemic efficacy and hypoglycemia was low due to imprecision, inconsistency, and individual-study limitations. For change in HbA_{1c} level, approximately half of eligible studies had some concerns about bias or high risk of bias, and for nocturnal hypoglycemia almost all trials had high risk of bias. Moreover, our conclusions about the comparative effects of newer basal insulin analogues are based mostly on indirect comparisons. Therefore, any inferences about the favorable effect of Deg-100, Deg-200, and Glar-300 should be interpreted with caution given that direct comparisons for these regimens were mostly against Glar-100. Two trials assessing Glar-300 versus Deg-100 and Deg-200 are expected to provide valuable insights (25, 67). Similarly, we could not detect differences between Deg-100 and Deg-200, so it is unclear which one is preferred in clinical practice (22). Ongoing studies are assessing the safety and efficacy of glargine biosimilars (68–70) and inpatient introduction of basal insulin analogues (71, 72), and a pragmatic randomized controlled trial aims to compare Glar-300 with Glar-100 and detemir in a real-world setting (73). Finally, the definition of any hypoglycemia varied among eligible studies, which further attenuates the applicability of our findings in clinical practice. Future trials should focus on head-to-head comparisons among newer basal insulin analogues, with a double-blind design and uniform, consistent definitions for hypoglycemia-related outcomes.

In conclusion, low-quality, indirect evidence suggests that available basal insulin analogues for T2DM do not substantially differ in their glucose-lowering effects. Certain regimens may be associated with lower risk for nocturnal hypoglycemia (Deg-100, Deg-200, and Glar-300) or less weight gain (detemir and Glar-300). In addition to short-term efficacy and safety, effects of individual drugs on long-term cardiovascular outcomes and cost-effectiveness data should be considered for optimal therapeutic decision making.

From Aristotle University of Thessaloniki, Thessaloniki, Greece (A.M., P.P., T.K., A.K., E.A., K.K., E.B.); University of Oxford, Oxford, United Kingdom (D.R.M.); and Aristotle University of Thessaloniki, Thessaloniki, Greece, and University of Oxford, Oxford, United Kingdom (A.T.).

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Corresponding Author: Apostolos Tsapas, MD, PhD, MSc, Clinical Research and Evidence-Based Medicine Unit, Aristotle University of Thessaloniki, Konstantinupoleos 49, 54642 Thessaloniki, Greece; e-mail, atsapas@auth.gr.

Current author addresses and author contributions are available at Annals.org.

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Current Author Addresses: Drs. Madenidou, Paschos, Karagiannis, Katsoula, Kitsios, Bekiari, and Tsapas and Ms. Athanasiadou: Clinical Research and Evidence-Based Medicine Unit, Aristotle University of Thessaloniki, Konstantinupoleos 49, 54642, Thessaloniki, Greece.
Dr. Matthews: Harris Manchester College, University of Oxford, Mansfield Road, Oxford OX1 3TD, United Kingdom.

Author Contributions: Conception and design: A.V. Madenidou, P. Paschos, A. Tsapas.
Analysis and interpretation of the data: A.V. Madenidou, P. Paschos, T. Karagiannis, K. Kitsios, E. Bekiari, D.R. Matthews, A. Tsapas.
Drafting of the article: A.V. Madenidou, T. Karagiannis, A. Katsoula, K. Kitsios, E. Bekiari, A. Tsapas.
Critical revision of the article for important intellectual content: A.V. Madenidou, P. Paschos, T. Karagiannis, D.R. Matthews, A. Tsapas.
Final approval of the article: A.V. Madenidou, P. Paschos, T. Karagiannis, A. Katsoula, E. Athanasiadou, K. Kitsios, E. Bekiari, D.R. Matthews, A. Tsapas.
Statistical expertise: A.V. Madenidou, P. Paschos, E. Bekiari, A. Tsapas.
Administrative, technical, or logistic support: E. Athanasiadou.
Collection and assembly of data: A.V. Madenidou, A. Katsoula, E. Athanasiadou.