

Efficacy and Safety Among Second-Generation and Other Basal Insulins in Adult Patients with Type 1 Diabetes: A Systematic Review and Network Meta-Analysis

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Abstract

Aims: To assess the comparative efficacy and safety of second-generation basal insulins (glargine U300 and degludec U100) vs. neutral protamine Hagedorn (NPH) and first-generation basal insulins (glargine U100 and detemir) in type 1 diabetes (T1D) adults.

Methods: PubMed, the Cochrane Library, ClinicalTrials.gov, and Google Scholar (until January 2021) were systematically searched. Randomized controlled trials (RCTs) with ≥ 12 weeks of follow-up comparing efficacy (HbA_{1c}) or safety (hypoglycemia and weight gain) between second-generation basal insulins vs. other basal insulins in T1D adults were included. Bayesian network meta-analyses were used to estimate risk ratio, hazard ratio, and mean difference. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) was used to appraise evidence certainty.

Results: Eighteen RCTs (≥ 24 weeks of follow-up) involving 7,283 randomized participants were included for main analysis. Moderate to high certainty evidence suggested that second-generation basal insulins showed equivalent HbA_{1c} reduction compared with NPH and first-generation basal insulins. Compared with second-generation basal insulins, low to high certainty evidence suggested that NPH was associated with a higher risk of patients experiencing severe hypoglycemia; NPH and first-generation basal insulins were associated with a higher rate of nocturnal confirmed hypoglycemic events. For the weight gain, glargine U300 was comparable to detemir (low certainty), but degludec U100 was greater than detemir (moderate certainty).

Conclusions: In T1D adults, second-generation basal insulins maintained equivalent efficacy of glycemic control (moderate to high certainty), with differences in safety (low to high certainty) compared with NPH and first-generation basal insulins during ≥ 24 weeks of follow-up.

Introduction

Type 1 diabetes (T1D) is characterized by insulin deficiency and resultant hyperglycemia (DiMeglio et al. 2018). Patients with T1D require lifelong insulin administration, and basal insulin preparations are the most used and essential replacement to mimic pancreatic insulin secretion. Basal insulins, including human neutral protamine Hagedorn (NPH), first-generation analogs (i.e., glargine 100 U/mL [glargine U100] or detemir), and second-generation analogs (i.e., glargine 300 U/mL [glargine U300] or degludec), have been clinically used to control fasting glucose levels. However, since different preparations exhibit distinct pharmacokinetic and pharmacodynamics profiles, basal insulin preparations do not always provide the same efficacy and safety (Mathieu et al. 2017).

Systematical comparisons on the efficacy (glycemic controls) or safety (iatrogenic severe hypoglycemic events) between first-generation basal insulins vs. NPH have been discussed in an umbrella review (Laranjeira et al. 2018). Currently, there are no trials directly comparing the second-generation basal insulins with NPH or glargine U300 with detemir in T1D adults. The most recent updated network meta-analysis comparing NPH and detemir with the second-generation basal insulins in T1D adults indicated

similar reductions in HbA_{1c} and severe hypoglycemic events (Bain et al. 2020). However, their network meta-analysis on safety only concerned with severe hypoglycemia, defined as the most dangerous level (level one) by American Diabetes Association (ADA) (International Hypoglycaemia Study Group 2017). In contrast, the confirmed hypoglycemia (level two) was not evaluated. The confirmed hypoglycemia reduces patient quality of life and will develop to severe one if not properly treated (International Hypoglycaemia Study Group 2017). Especially, the confirmed hypoglycemia occurring at night is also dangerous and should also be aware. In their outcome of severe hypoglycemia, only the number of events per person-year was updated. The synthesized results based on the number of patients who experience hypoglycemia will provide a different aspect of information and is of clinical importance. On the other hand, insulin users often report body weight gains, limiting insulin intensification or basal-bolus therapy. Body weight gain caused by insulin-induced lipogenesis will increase cardiovascular risk (Purnell et al. 1998; Russell-Jones and Khan 2007). As one of the important adverse events, body weight gain was not included in their analysis. Furthermore, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) certainty of evidence was also unavailable in either efficacy or safety outcome. Thus, a more comprehensive analysis of the efficacy and safety of second-generation basal insulins is still necessary.

This study systematically evaluates the efficacy and safety of second-generation insulins analogs vs. NPH or first-generation basal insulins in T1D adults using the Bayesian network meta-analysis.

Methods

This systematic review and network meta-analysis was reported as per the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement (Table S1) and was performed according to the AMSTAR 2 critical appraisal tool (Moher et al. 2009; Hutton et al. 2015; Shea et al. 2017). In addition, the protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020175051).

Data sources and searches

Two investigators (M and YZ) systematically searched PubMed, the Cochrane Library, ClinicalTrials.gov, and Google Scholar from inception until 12 January 2021 (Table S2). The study selection process was recorded using a PRISMA-compliant flow chart (Moher et al. 2009). In addition, reference lists of relevant articles were reviewed for further study search.

Study selection

The eligible studies were limited to 1) randomized controlled trials (RCTs) (study design); 2) adults with T1D (aged ≥ 18 years) and ≥ 12 weeks of follow-up under basal and mealtime insulins (study population); 3) interventions and comparisons were second-generation basal insulins vs. NPH, glargine U100, or detemir; 4) studies reported at least one of the following outcomes: change in HbA_{1c} or body weight between baseline and endpoint, severe hypoglycemia, nocturnal severe hypoglycemia, confirmed

hypoglycemia, or nocturnal confirmed hypoglycemia; 5) in case of duplicate studies, we extracted data with the longest follow-up if retrievable. Severe hypoglycemia was defined as an event requiring assistance or as per the American Diabetes Association (ADA) categories (International Hypoglycaemia Study Group 2017). Confirmed hypoglycemia was defined as an event with plasma glucose concentration $< 3.0\text{--}3.1$ mmol/L ($< 54\text{--}56$ mg/dL) or severe hypoglycemia. Nocturnal hypoglycemia was defined as an event occurring during the night (23.00 to 06.00 hours or narrower duration). The exclusion criteria included participants with recurrent severe hypoglycemia, cross-over trials with < 12 weeks of follow-up for each period, and children, adolescents, pregnant or breastfeeding women.

Data extraction and quality assessment

Two investigators (M and YZ) independently extracted data from the eligible RCTs and evaluated the qualities of the eligible RCTs and the network evidence. A third investigator (YST) resolved disagreements. Extracted data were comprised of study characteristics and outcomes. Outcomes were comprised of the following: 1) changes in HbA_{1c} (%) and mean body weight (kg) between baseline and endpoint; 2) the number of patients experiencing severe hypoglycemia, nocturnal severe hypoglycemia, confirmed hypoglycemia, and nocturnal confirmed hypoglycemia (percentage of participants experiencing \geq one hypoglycemic event); and 3) the number of events on severe hypoglycemia, nocturnal severe hypoglycemia, confirmed hypoglycemia, and nocturnal confirmed hypoglycemia (hypoglycemic events per person-year). Person-year data were extracted either from the trial results or by multiplying the sample size by the follow-up years. If the SE or SD of the change was unable to be extracted, we imputed it according to the Cochrane guidelines (Higgins et al. 2019a) or using the average SD of the change reported from similar trials with the same interventions.

The risk of bias was assessed using the Cochrane risk of bias (RoB) 2.0 tool. Ratings of risk of bias within individual trials comprised the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result, and overall bias (Higgins et al. 2019b). Evidence certainty was appraised using the GRADE approach (Puhan et al. 2014) and the rules in Confidence in Network Meta-Analysis (CINeMA) (Nikolakopoulou et al. 2020). Evidence certainty ratings comprised within-study bias, across-studies bias, indirectness, imprecision, heterogeneity, and incoherence.

Data synthesis and statistical analysis

The main analysis was measured in ≥ 24 weeks of follow-up. Sensitivity analysis was measured in ≥ 12 weeks of follow-up to explore the robustness of effect sizes. The effect sizes were comprised of mean difference (MD) for assessing the changes in HbA_{1c} or body weight; risk ratio (RR) for assessing the risk on the number of patients experiencing hypoglycemia; and hazard ratio (HR) for assessing the number of hypoglycemic events per person-year. We assumed exchangeability between treatments (direct and indirect evidence concurs (van Valkenhoef et al. 2012)) and used a random-effects model to allow for inevitable heterogeneity (Higgins et al. 2012). The effect sizes were calculated using the Markov Chain Monte Carlo (MCMC) simulation in the Bayesian hierarchical model (BHM). We used the binomial

distribution with a log link function to calculate RR, the Poisson distribution with a log link function to calculate HR, and the normal distribution with an identity link function to calculate MD (Dias et al. 2013a). We set a uniform prior distribution model, discarded the first 50,000 iterations, and performed 100,000 MCMC simulations with a thinning of 20 (5,000 samples) for four chains.

Heterogeneity in the treatment comparators was assessed using per-comparison I^2 (van Valkenhoef 2014). Assessment of inconsistency between direct and indirect evidence was analyzed by node splitting method (Dias et al. 2013b). The risk of bias across trials (publication bias) was assessed using comparison-adjusted funnel plots (Chaimani and Salanti 2012). Funnel plot asymmetry was tested using Egger's regression (Egger et al. 1997). Statistical significance was defined as two-sided with $\alpha < 0.05$. The funnel plots and Egger's regression were performed using the "netmeta" (version 1.2-0) package. Network meta-analyses, with statistical significance defined as 95% credible interval (CrI) did not cross 0.00 (MD) or 1.00 (RR and HR), were performed using the "gemtc" (version 0.8-2) package implemented in R (version 4.0.2). The 2.5% and 97.5% quantiles of the CrI were derived from the Bayesian inference.

Results

Search results

The literature search yielded 4,965 citations (Fig. 1). Among them, we reviewed 50 full-text articles and finally included 31 eligible RCTs published between 2000 and 2019 in this network meta-analysis (Table S3).

Study selection and characteristics

The total of 31 RCTs included 10,229 randomized participants with follow-up durations ranging from 12 to 104 weeks. The detailed characteristics were summarized in Table S4. Eighteen trials (N = 7,283) with ≥ 24 weeks of follow-up were included for the main analysis. Network graphs of all outcomes for main analysis were shown in Fig. 2. The mean age across the RCTs ranged from 34 to 48.2 years. Most trials were multicenter and received financial aid.

Overall risk of bias within trials was that one trial (3%) had a low risk of bias, twenty (65%) had some concerns, and ten (32%) had a high risk of bias (Fig. S1). Table S5 shows the Cochrane risk of bias judgments. Table S6 shows the extracted data for each outcome.

Comparisons of outcomes

Efficacy outcome—change in HbA_{1c}

We conducted a network meta-analysis on change in HbA_{1c} that included 18 RCTs (Fig. 2a). The MD of HbA_{1c} from baseline to ≥ 24 weeks between the second-generation basal insulins vs. NPH or the first-generation basal insulins did not show significant differences (Fig. 3).

Safety outcome—number of patients experiencing hypoglycemia

Severe, confirmed, and nocturnal confirmed hypoglycemia were evaluated by three network meta-analyses, including 14, 8, and 8 RCTs on RR, respectively (Fig. 2c-2e). A significantly greater number of patients experiencing severe hypoglycemia were shown in the NPH group compared with the degludec U100 group (RR 1.88 [95% CrI 1.30 to 2.71]) and the glargine U300 group (RR 1.98 [95% CrI 1.08 to 3.68]) (Fig. 4). No other statistical differences existed in second and first-generation basal insulins for the number of patients experiencing severe hypoglycemia (Fig. 4). Furthermore, there was no significant difference among comparisons for the number of patients experiencing confirmed and nocturnal confirmed hypoglycaemic events (Fig. 4). Unfortunately, the RR of nocturnal severe hypoglycemia could not be determined due to the lack of data.

Safety outcome—number of hypoglycemic events per person-year

Four network meta-analyses on HR of severe, nocturnal severe, confirmed, and nocturnal confirmed hypoglycemic events were conducted, including 14, 9, 8, and 9 RCTs, respectively (Fig. 2f-2i). For severe, nocturnal severe, and confirmed hypoglycemia, NPH showed a greater number of hypoglycemic events per person-year than degludec U100 (HR 2.03 [95% CrI 0.98 to 4.07], HR 3.16 [95% CrI 0.58 to 14.90], HR 1.41 [95% CrI 0.99 to 1.98], respectively) (Fig. 5). However, no statistical significance was detected. There were also no significant differences for other comparisons between glargine U300 and NPH or the first-generation basal insulins (Fig. 5). For nocturnal confirmed hypoglycemic events, compared with the second-generation basal insulins, NPH and the first-generation basal insulins showed greater event numbers per person-year [NPH vs. degludec U100 (HR 2.84 [95% CrI 1.88 to 4.38]), glargine U100 vs. degludec U100 (1.35 [95% CrI 1.12 to 1.63]), detemir vs. degludec U100 (HR 1.55 [95% CrI 1.25 to 1.95]), NPH vs. glargine U300 (HR 2.78 [95% CrI 1.69 to 4.68]), glargine U100 vs. glargine U300 (HR 1.32 [95% CrI 1.03 to 1.74]), and detemir vs. glargine U300 (HR 1.52 [95% CrI 1.08 to 2.22])] (Fig. 5).

Safety outcome—weight gain

We conducted a network meta-analysis on the MD of change in body weight, including 14 RCTs (Fig. 2b). Compared with degludec U100, detemir resulted in less weight gain (MD 0.60 [95% CrI - 1.13 to - 0.01]) significantly. However, no other significant differences were found within comparisons (Fig. 6).

Quality of evidence network (GRADE), heterogeneity, and publication bias

The GRADE assessment rules of network estimates were presented in Table S7. The GRADE confidence ratings for each network were incorporated in Fig. 2–5. Among the GRADE domains, major and some concerns were mainly related to imprecision and within-study bias (Fig. S2). Incoherence analyses did not apply to some pairwise comparisons owing to the absence of either direct or indirect evidence (Fig. S2). A

comparison-adjusted funnel plot and Egger's regression test did not find asymmetry in all outcomes (Fig. S3). We observed heterogeneity on some pairwise comparisons (Fig. S4) but found no evidence of inconsistency from node splitting results (Table S8).

Sensitivity analysis

We conducted a sensitivity analysis to test the robustness of the effect sizes of all outcomes by adding thirteen ≥ 12 -week follow-up eligible trials (Table S6). Changes in HbA_{1c} and body weight outcomes showed robust results (Fig. S5a). Degludec U100 and glargine U300 showed the same effect sizes for the number of patients with severe hypoglycemia. The statistically significant difference between degludec U100 and NPH was robust. However, the statistically significant difference between glargine U300 and NPH was not maintained. Both degludec U100 and glargine U300 showed statistically lower numbers of patients on nocturnal confirmed hypoglycemia, which differed from the main analysis (Fig. S5b). For the HR of confirmed hypoglycemic events (Fig. S5c), degludec U100 vs. NPH showed a significant difference, while glargine U300 vs. NPH remained insignificant. The HR of the nocturnal confirmed hypoglycemic events produced larger effect sizes and robust significances (Fig. S5c).

Discussion

The present systematic review and network meta-analyses provide an evidence-based comparison of efficacy and safety between second-generation basal insulins vs. NPH or first-generation basal insulins for T1D adults. The efficacy evaluated in terms of the change in HbA_{1c} did not show significant differences between the second-generation basal insulins vs. NPH or first-generation basal insulins. In addition, sensitivity analysis showed this result is consistent in follow-up durations from either ≥ 24 weeks or ≥ 12 weeks.

This result of efficacy is consistent with Bain et al. (2020) that concluded no significant differences among insulin analogs in T1D adults (Bain et al. 2020). However, this result is inconsistent with another network meta-analysis (Tricco et al. 2021) that showed second-generation basal insulin degludec was superior to NPH in reducing HbA_{1c}. The inconsistent results between Tricco et al. (2021) and our study arose in the inclusion criteria. We only focused on RCTs for T1D adults (aged ≥ 18 years) with ≥ 24 or ≥ 12 weeks of follow-up, while Tricco et al. (2021) mixed observational studies, children, pregnant women with irrespective follow-up duration (8 days to 2 years).

Hypoglycemia has been considered to be the barrier to achieve stringent HbA_{1c} levels (Cryer 2008; Mathieu et al. 2017). In this study, we investigated level one and level two hypoglycemia (International Hypoglycaemia Study Group 2017), including nocturnal one, and analyzed safety in the number of patients experiencing hypoglycemia and in the number of hypoglycemic events per person-year to provide comprehensive safety information. This meta-analysis found that the second-generation basal insulins were associated with significantly fewer patients experiencing severe hypoglycemia than NPH, with certainty evidence from moderate to low. Furthermore, the number of nocturnal confirmed hypoglycemic events per person-year of the second-generation basal insulins was significantly lower than NPH and first-

generation basal insulins, with certainty evidence from moderate to high. For other hypoglycemia outcomes, no significant differences were detected in terms of neither RR nor HR. The inconsistent results from RR and HR were obtained here due to different measures of the event numbers and whether considering the time-dependent unit. Therefore, both RR and HR are suggested to be taken into consideration for assessing the safety of basal insulins.

Severe hypoglycemia has been well documented as a life-threatening event. Nocturnal confirmed hypoglycemia that is mainly affected by basal insulins can be considered less aware owing to the night. However, nocturnal confirmed hypoglycemia affects the patient quality of life and has a risk of escalating to a severe level (International Hypoglycaemia Study Group 2017). Therefore, the benefits of the second-generation basal insulins can be addressed. Stable pharmacodynamic profiles of the second-generation basal insulins may be a major factor (Heise et al. 2012; Becker et al. 2014). However, the evidence levels were not strong. Therefore, attention should be paid to these results.

The NICE network meta-analysis in T1D adults (NG17) (NICE (National Institute for Health and Care Excellence) 2015) and its update found no difference among basal insulins in the rate of severe hypoglycemic events (Dawoud et al. 2018; Bain et al. 2020). Our results are in line with these reports. However, based on the number of patients experiencing severe hypoglycemia, we found differences between second-generation basal insulins and NPH. Compared with Tricco et al. (2021), our result differed in detecting the statistical differences in the number of patients experiencing nocturnal hypoglycemia. Tricco et al. (2021) showed that degludec was statistically superior to NPH in the incidence of nocturnal hypoglycemia. However, we only detected differences in the rate of nocturnal confirmed hypoglycemia events. The differences may arise from the different inclusion criteria. Furthermore, we found that they included a study reported by Pieber et al. (Pieber et al. 2007), which was argued to have apparent inherent biases (Alcolado et al. 2008) and thus was excluded in this study. Compared to direct meta-analyses, we found a consistent difference that second-generation basal insulins had a lower rate of nocturnal hypoglycemic events than first-generation glargine U100 (Ratner et al. 2013; Vora et al. 2014; Liu et al. 2018; Díez-Fernández et al. 2019).

Basal insulin therapy can commonly cause weight gain in T1D. Weight gain negatively alters lipid levels and blood pressure, thereby increasing the risk of cardiovascular disease (Purnell et al. 1998; Russell-Jones and Khan 2007). Weight gain also affects the waist-to-hip ratio (Purnell et al. 1998), which may affect patients' self-perception, especially young people, leading to psychological insulin resistance (Brod et al. 2009). Our results showed no differences between second-generation basal insulins and NPH or first-generation basal insulins, except for the comparison between detemir and degludec U100. Detemir significantly resulted in less weight gain than degludec U100 with moderate certainty evidence. Therefore, when tailoring the treatment concerning weight gain, detemir and glargine U300 could be selected.

The strength of this study is the new insights into the harms concerning the second-generation basal insulins vs. other basal insulins in T1D adults by evaluating different categories of hypoglycemia in detail and changes in body weight. Meanwhile, we updated the results of the efficacy. The current network

meta-analysis applied the GRADE approach and used rigorous methodology by adhering to the AMSTAR 2.0 critical appraisal tool and the PRISMA and Cochrane's guidelines. In addition, we quantitatively evaluated the certainty evidence of each comparison. The information provided here may help select an appropriate basal insulin type for T1D adult patients under different backgrounds, which could be considered as a clinical imperative.

Several limitations should be considered when interpreting the results. First, the quality of RCTs in adults enhanced the information accuracy here; however, information may be limited. Second, due to the lack of information from RCT, we did not adjust the potential confounders, such as bolus (meal) insulin, frequency, injection device-dependent, and newly initiating effects on the efficacy and safety. Third, the trials involved in this network meta-analysis were limited in the number, varying from 8 to 14. Fourth, open-label design and sponsorship from pharmaceutical manufacturers in almost all included trials and differences in study design across trials. Finally, heterogeneity was observed for some comparisons, which may be accounted for different protocol designs. In the future, we expect more consolidated protocols and study designs in the RCTs and hopefully to update the present evidence.

In conclusion, based on the present eligible studies, second-generation basal insulins achieved similar HbA_{1c} levels compared with NPH and first-generation basal insulins with moderate to high certainty evidence. For hypoglycemia, second-generation basal insulins showed partial merits. For the weight gain, glargine U300 was comparable to detemir, while degludec U100 resulted in more weight gain than detemir. With the caution of the limitations of this study, the information can help tailor basal insulin for T1D adults via evidence-informed practice.

Abbreviations

ADA American Diabetes Association; BHM Bayesian hierarchical model; CINeMA Confidence in Network Meta-Analysis; CrI Credible interval; GRADE Grading of Recommendations, Assessment, Development and Evaluation; NICE National Institute for Health and Care Excellence; HR Hazard ratio; MCMC Markov Chain Monte Carlo; MD Mean difference; NPH neutral protamine Hagedorn; RR Risk ratio; T1D Type 1 diabetes

Declarations

Ethics approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Data availability

The datasets used in this research are published in Supplemental Material (Table S6) which can be found in this published article.

Author contributions

M conceived and conceptualized the study. M and YZ designed the methodology and contributed to data curation, data analysis, interpretation of the results, discussion, and drafted the manuscript. YST contributed to data analysis and discussion. YST and TT reviewed the manuscript. All authors revised and approved the final manuscript. The authors declare that all data were generated in-house and that no paper mill was used.

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Figures

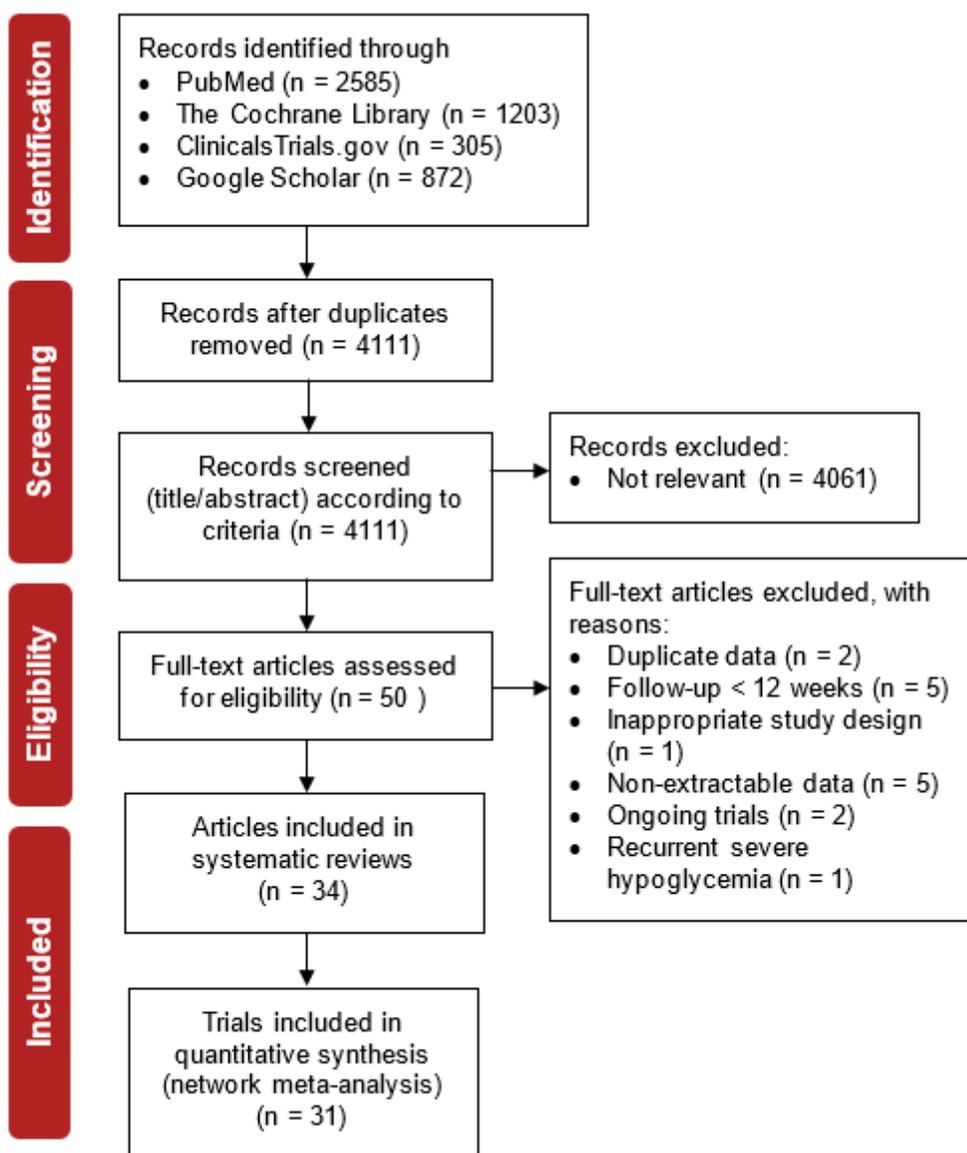


Figure 1

PRISMA flow diagram of the process for selecting studies with reasons

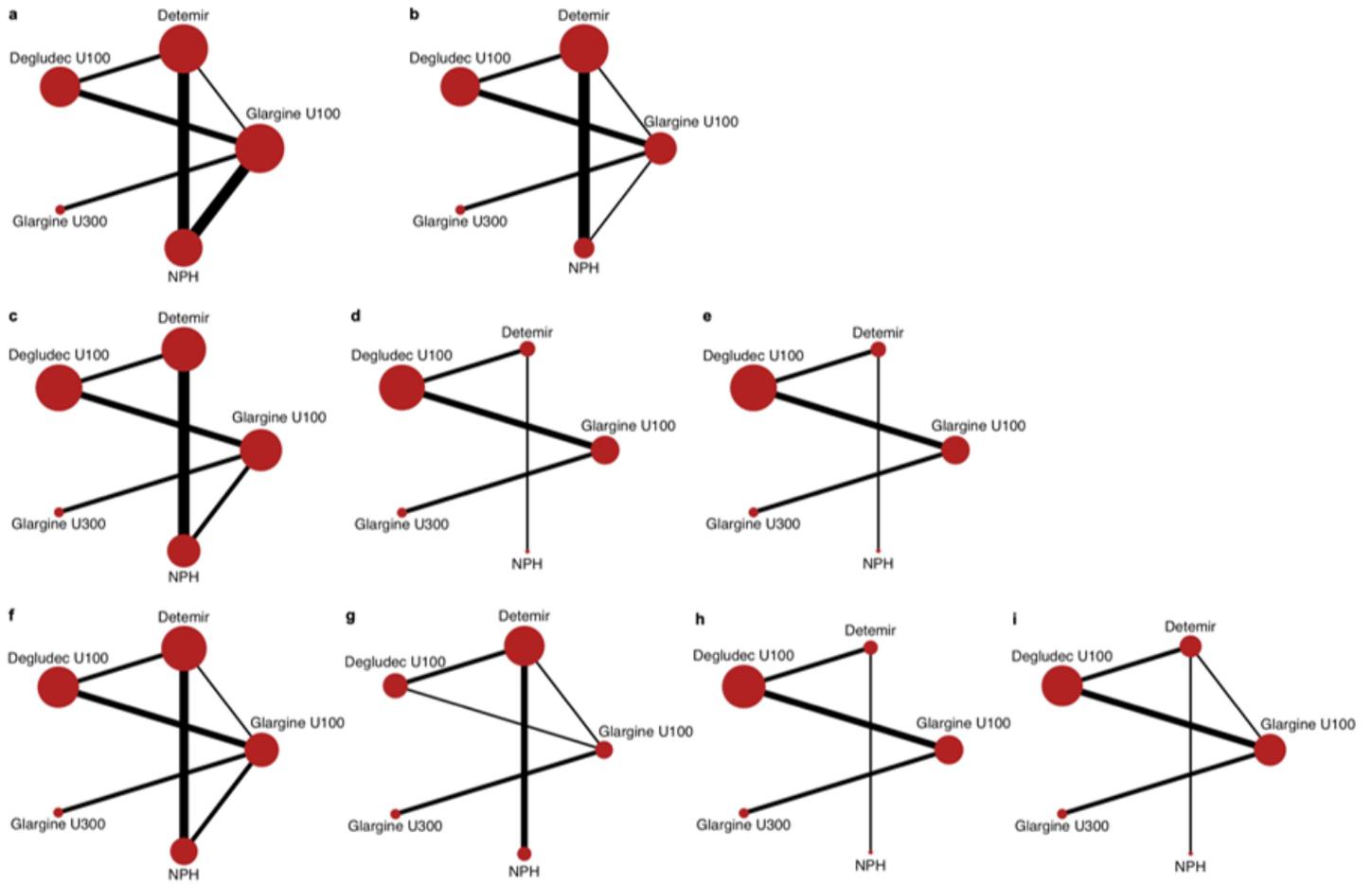


Figure 2

Network graphs of basal insulin treatments (main analysis): a change in HbA_{1c}, b change in body weight, c number of patients on severe hypoglycemia, d number of patients on confirmed hypoglycemia, e number of patients on nocturnal confirmed hypoglycemia, f number of events on severe hypoglycemia g number of events on nocturnal severe hypoglycemia, h number of events on confirmed hypoglycemia, and i number of events on nocturnal confirmed hypoglycemia. Each node represents different type of basal insulin and is proportional to the size of randomized participants. Width of lines is proportional to number of trials comparing respective nodes.

Change in HbA_{1c} (%)

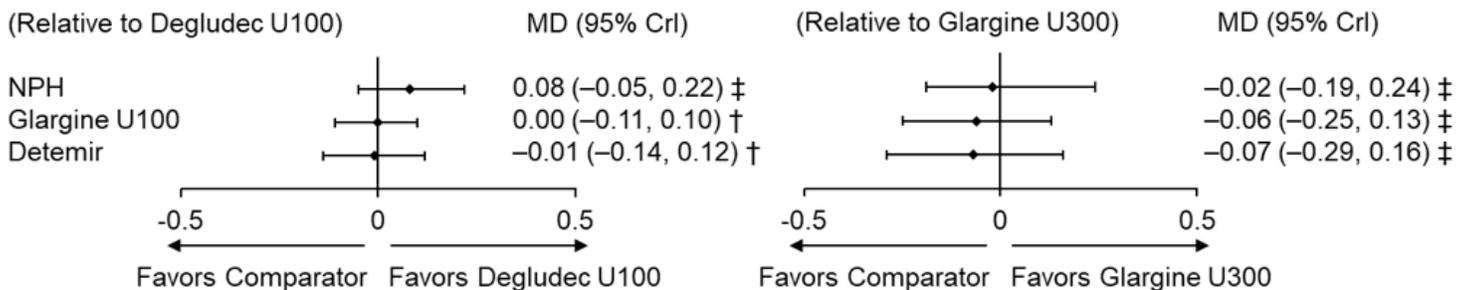
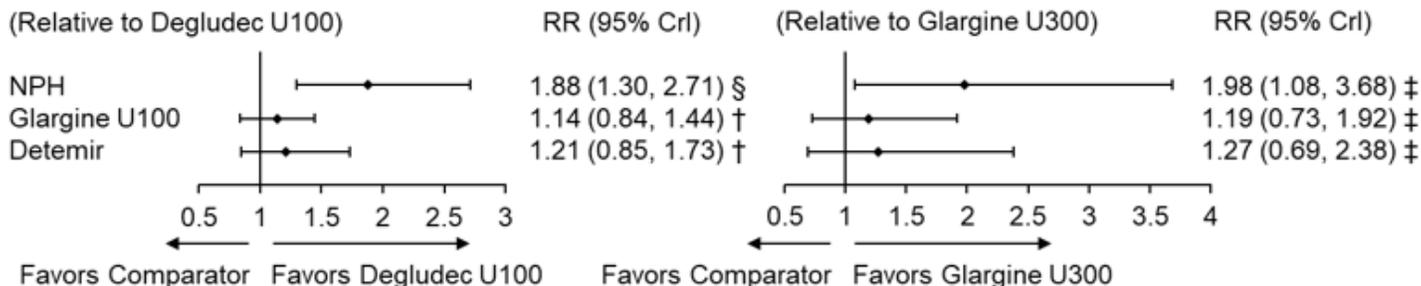


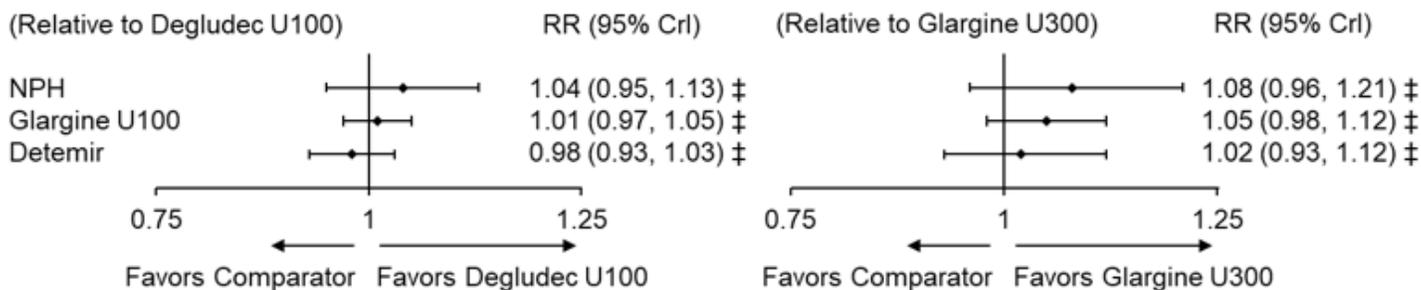
Figure 3

Forest plots of network meta-analysis for change in HbA1c. The GRADE confidence of evidence network was incorporated in this figure: † High certainty evidence and ‡ Moderate certainty evidence. CrI Credible interval; MD Mean difference.

Severe Hypoglycemia



Confirmed Hypoglycemia



Nocturnal Confirmed Hypoglycemia

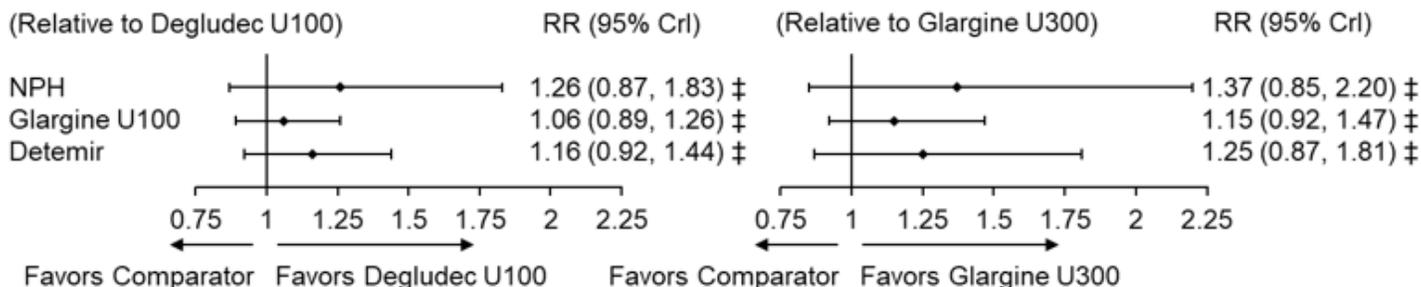
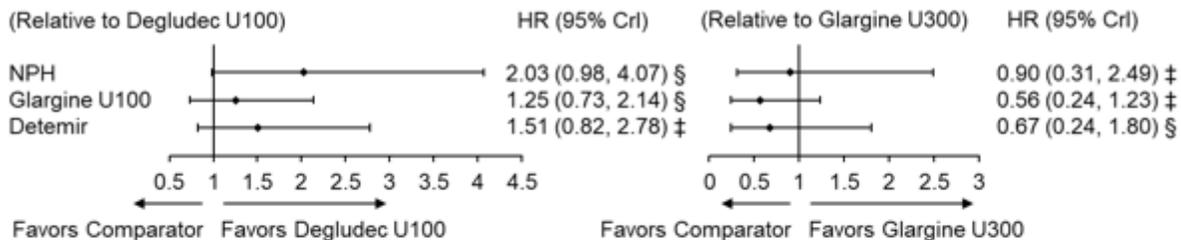


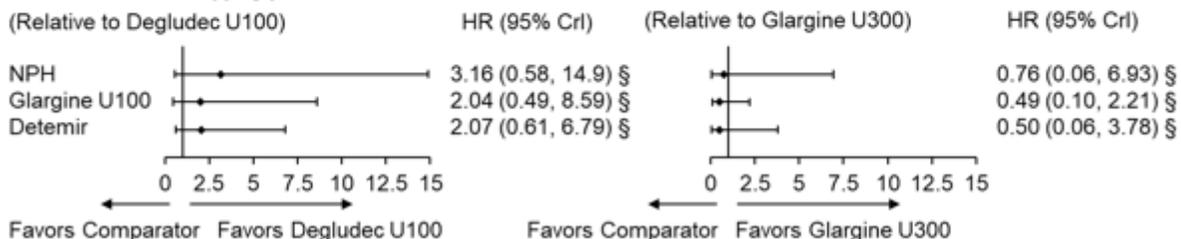
Figure 4

Forest plots of network meta-analysis for number of patients on hypoglycemia. The GRADE confidence of evidence network was incorporated in this figure: † High certainty evidence, ‡ Moderate certainty evidence, and § Low certainty evidence. CrI Credible interval; RR Risk ratio.

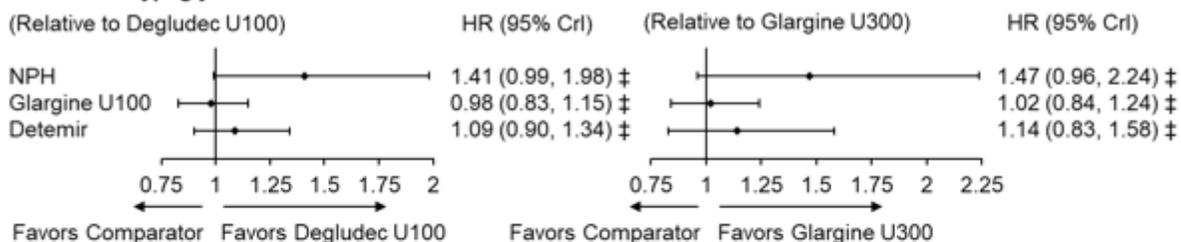
Severe Hypoglycemia



Nocturnal Severe Hypoglycemia



Confirmed Hypoglycemia



Nocturnal Confirmed Hypoglycemia

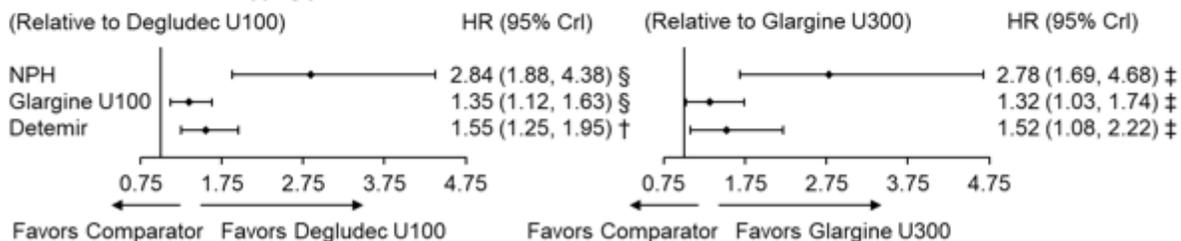


Figure 5

Forest plots of network meta-analysis for number of events on hypoglycemia. The GRADE confidence of evidence network was incorporated in this figure: † High certainty evidence, ‡ Moderate certainty evidence, and § Low certainty evidence. CrI Credible interval; HR Hazard ratio.

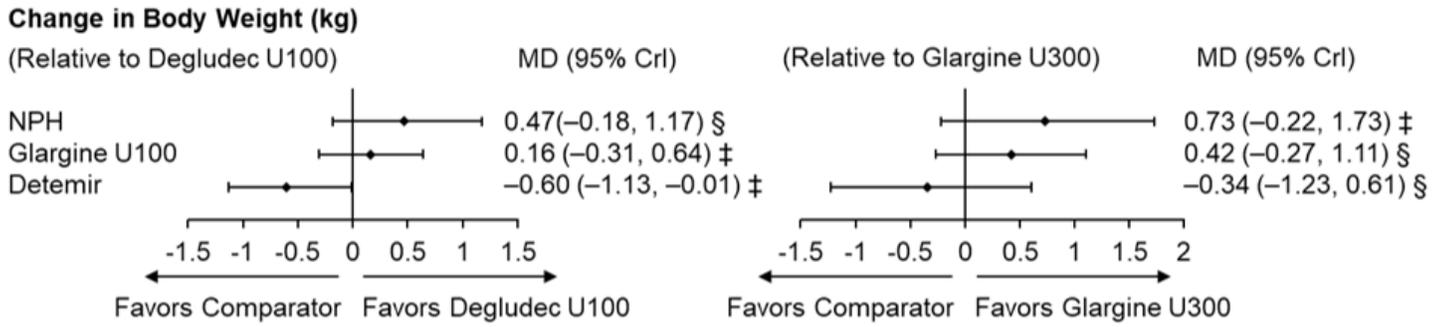


Figure 6

Forest plots of network meta-analysis for changes in body weight. The GRADE confidence of evidence network was incorporated in this figure: ‡ Moderate certainty evidence and § Low certainty evidence. CrI Credible interval; MD Mean difference.

Supplementary Files

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- [SupplementalMaterialNSAP.pdf](#)