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SYSTEMATIC REVIEW

Thrice-Weekly Insulin Degludec Versus Once-Daily Insulin Glargine in Insulin-Naïve Patients With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis

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Abstract

Aims/Background Data from randomized controlled trials (RCTs) comparing the efficacy and safety of thrice-weekly insulin degludec (IDeg 3TW) versus once-daily insulin glargine (IGlar OD) in patients with type 2 diabetes mellitus (T2DM) are scarce and not uniform. Moreover, no systematic review and meta-analysis (SRM) is available for such a comparison. This SRM aimed to compare the effectiveness and safety of IDeg 3TW versus IGlar OD in the available RCTs in T2DM.

Methods Electronic databases and registers, which include MEDLINE (via PubMed), Scopus, Cochrane Central Register, and ClinicalTrials.gov, were searched for RCTs conducted among T2DM subjects with IDeg 3TW as intervention and IGlar OD as control from inception to 30 July 2024. The primary outcome was glycated haemoglobin (HbA1c) reduction from baseline; secondary outcomes were the changes in other glycemic parameters and adverse events (AEs). RevMan web was used to conduct meta-analysis using random-effects models. Outcomes were presented as mean difference (MD), odds ratio (OR), or risk ratio (RR) with 95% confidence intervals (CIs).

Results Three RCTs (N = 1171) with study durations ranging from 16–26 weeks and minimal risk of bias were included. IDeg 3TW was less effective than IGlar OD in HbA1c reduction (MD 0.27%, 95% CI [0.14, 0.39], $p < 0.0001$), reduction in mean nine-point self-monitored capillary blood glucose profile (MD 0.45 mmol/L, 95% CI [0.22, 0.67], $p < 0.0001$), and HbA1c reduction <7% (OR 0.69, 95% [0.53, 0.89], $p = 0.005$). IDeg 3TW outperformed IGlar OD regarding the mean daily insulin dose (MD –0.07 U, 95% CI [–0.13, –0.01], $p = 0.02$). However, both groups achieved comparable fasting plasma glucose reduction (MD 0.37 mmol/L, 95% [–0.19, 0.93], $p = 0.19$), changes in body weight (MD 0.04 kg, 95% CI [–0.46, 0.55], $p = 0.86$), and overall physical (MD 0.21, 95% CI [–0.62, 1.04], $p = 0.62$) and mental health scores (MD –0.02, 95% CI [–1.05, 1.01], $p = 0.97$). The risks for confirmed hypoglycemia (RR 1.16, 95% CI [0.83, 1.62], $p = 0.38$), nocturnal hypoglycemia (RR 1.18, 95% CI [0.49, 2.84], $p = 0.71$), any AEs (RR 1.04, 95% CI [0.84, 1.30], $p = 0.71$), serious AEs (RR 1.43, 95% CI [0.77, 2.65], $p = 0.25$), and injection-site reactions (RR 1.29, 95% CI [0.56, 2.96], $p = 0.55$) were identical in the two groups.

Conclusion In short-term follow-up, IDeg 3TW was less effective than IGlar OD in glycaemic control; however, their safety profile was comparable. Larger multicenter RCTs comparing the overall benefit-risk ratio are necessary for appropriate clinical practice decisions.

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Key words: insulin degludec; insulin glargine; type 2 diabetes mellitus; glycemic control; HbA1c; hypoglycemia

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Introduction

Alongside its rising burden worldwide, the therapeutic options for type 2 diabetes mellitus (T2DM) have tremendously changed over time. Innovative drug classes have risen, and insulin preparations have considerably evolved. Basal insulin analogs with favorable pharmacokinetic (PK) and pharmacodynamic (PD) profiles are designed to overcome the unfulfilled need for stable metabolic control with reduced glucose fluctuations and fewer hypoglycemic episodes (Chadha et al, 2023). Despite significant advances in formulations, a reported adherence to daily insulin administration is still poor, from 30% to 86%, depending on the study population, which grossly impacts the achievement and maintenance of glycemic goals, thus increasing the risk of long-term diabetic complications (Guerci et al, 2019). Therefore, it is rational to expect that extending the period between basal insulin doses could facilitate the decision regarding treatment intensification with insulin among clinicians, increase patient adherence, and improve quality of life (QoL) and overall treatment outcomes. Eagerly anticipated ultra-long-acting weekly insulin analogs including insulin icodec and insulin efsitora alfa could provide a simplified dosage regimen and minimize obstacles to sustained glycemic control (Rosenstock et al, 2023; Wysham et al, 2024).

Insulin degludec (IDeg) is a basal insulin featuring a distinctive protraction mechanism driven by multi-hexamer chains acting as a soluble depot from which, as zinc gradually diffuses, insulin monomers are slowly released in the systemic circulation (Owens et al, 2019). According to its PK and PD properties, IDeg is a long-acting insulin with a glucose-lowering effect extending beyond 42 hours; thus, it might be applied in less frequent intervals than once-daily (OD), currently its approved dosage regimen (Wang et al, 2024). Insulin glargine (IGlar) is another widely used basal insulin introduced in 2000 and marked a significant breakthrough in the field of insulin therapy. For clinically relevant doses, IGlar has a half-life of 12–14 hours and a duration of glucose-lowering action of ~24 hours. Globally, IGlar is among the most extensively studied, commonly prescribed, and well-established medications for diabetes. It is considered a gold standard of basal insulin therapy and also a benchmark for newer basal insulin analogs (Hirose et al, 2019). IGlar OD and IDeg OD are similarly effective in glycemic control; IDeg OD is linked to a reduced rate of nocturnal hypoglycemia than IGlar OD (Liu et al, 2018).

Considering the long glucose-lowering action of IDeg beyond a day and the direct and indirect benefits of reduced injection burden from the patient's perspective, clinical trials have tested the feasibility of using IDeg three times a week (3TW) instead of its usual recommended frequency of OD against IGlar OD, the current gold-standard basal insulin (Zinman et al, 2011; Zinman et al, 2013). However, there are only a limited number of randomized controlled trials (RCTs), and considerable heterogeneities were observed in these RCTs regarding glycemic and safety outcomes. Moreover, to date, no systematic review and meta-analysis (SRM) has been published to address the issue. With this background, we conducted an SRM

to compare the effectiveness and safety of IDeg in a 3TW dosing regimen with IGlar administered OD.

Methods

Ethical Compliance

This SRM followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklists and the procedures described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al, 2023a; Page et al, 2021). The completed PRISMA checklist has been provided as a supplemental file (**Supplementary Material 1**). The SRM was registered with PROSPERO (CRD42024593493, https://www.crd.york.ac.uk/PROSPERO/view/CRD42024593493), and the protocol summary is available online.

Search Strategy

Several databases and registers were systematically searched, including MEDLINE (via PubMed), Scopus, Cochrane Central Register, and ClinicalTrials.gov. The search covered these sources from their commencement to 30 July 2024. The search terms were applied to titles and abstracts; the search technique followed a Boolean approach using the terms "insulin degludec" OR "NN1250" AND "thrice-weekly" OR "three times a week" AND "insulin glargine" AND "once-daily". All clinical studies in English, whether recently released or not yet published, were thoroughly and meticulously searched. This investigation entailed examining relevant publications and citations within the clinical studies incorporated in this study.

Study Selection

Population, Intervention, Comparison, Outcomes, and Study (PICOS) design was used as a methodology framework in formulating eligibility criteria for the clinical trials in this SRM. The patient population (P) consisted of insulin-naïve adults with uncontrolled T2DM; the intervention (I) was thrice-weekly insulin degludec (IDeg 3TW) subcutaneous injections; the comparison or control (C) included individuals receiving IGlar OD subcutaneous injections; the outcomes (O) included the difference in glycated haemoglobin (HbA1c) from baseline; and the randomized controlled trials (RCTs) were considered as the study type (S) for inclusion. This study comprised RCTs spanning a minimum duration of 12 weeks with study individuals aged at least 18. The trials had at least two treatment arms/groups, one receiving IDeg 3TW and the other receiving IGlar OD subcutaneous injections as an add-on to oral antidiabetic drugs (OADs). Nonrandomized trials, pooled analyses of clinical trials, retrospective studies, case reports, letters to the editor, conference abstracts, and articles missing data on relevant outcomes were excluded from consideration. Clinical trials involving animals or healthy humans and RCTs with less than 12 weeks were also excluded.

Outcomes Analyzed

The primary outcome of interest was the difference in HbA1c from baseline after the trials ended. Additional efficacy endpoints were fasting plasma glucose

(FPG) changes, required insulin dose, and nine-point self-monitored capillary blood glucose profiles. Safety outcomes were changes in body weight, adverse events, injection-site reactions, and hypoglycemic episodes.

Data Extraction and Handling of Missing Data

Using standardized forms, four review authors (ABMKH, SB, DD, LN) independently extracted data, with further details available elsewhere (Kamrul-Hasan et al, 2024). The same source also provides a detailed discussion on the handling of missing data (Kamrul-Hasan et al, 2024).

Risk of Bias Assessment

Four authors (ABMKH, SB, DD, LN) independently conducted the risk of bias (RoB) assessment utilizing version 2 of the Cochrane risk-of-bias instrument for randomized trials (RoB 2) within the Review Manager (RevMan) software (version 7.2.0, Cochrane Collaboration, London, UK) (Higgins et al, 2023b; RevMan, 2024). The domains encompassed by RoB 2 address all recognized biases that may influence the outcomes of RCTs, including biases stemming from the randomization procedure, deviations from the planned interventions, missing outcome data, inaccuracies in outcome measurement, and biases in the selection of reported results. The RoB judgment assigned one of three levels to each domain: low risk of bias, some concerns, or high risk of bias. The least favorable assessment across the domains of bias was considered the overall risk of bias for the result (Higgins et al, 2023b). The Risk-of-bias VISualization (robvis) web app was used to create risk-of-bias plots (McGuinness and Higgins, 2021).

Statistical Analysis

The outcomes were reported as mean differences (MDs) for continuous variables and as odds ratios (ORs) or risk ratios (RRs) for dichotomous variables, along with 95% confidence intervals (CIs). The RevMan-generated forest plots portrayed the MD, OR, or RR for the outcomes; the left side of the forest plot favoured tirzepatide, and the right side favoured the control group(s) (RevMan, 2024). Random effects models were selected for the analysis to address the anticipated heterogeneity resulting from population characteristics and trial length variations. The inverse variance method was applied in all cases. The meta-analysis included forest plots that synthesized data from a minimum of two trials. A significance level of $p < 0.05$ was established.

Assessment of Heterogeneity

The assessment of heterogeneity was initially conducted by studying forest plots. Subsequently, a Chi^2 test was performed using N-1 degrees of freedom and a significance level of 0.05 to determine the statistical significance. The I^2 test was also employed in the subsequent analysis (Song et al, 2000). The specifics of understanding I^2 values have already been explained in depth elsewhere (Kamrul-Hasan et al, 2024).

Results

Search Results

The steps of selecting studies are depicted in **Supplementary Fig. 1**. The initial search identified 46 articles; the number was narrowed to three after screening titles, abstracts, and subsequent full-text reviews. Finally, three RCTs with two published reports involving 1171 subjects meeting all the prespecified criteria were included in this SRM (Zinman et al, 2011; Zinman et al, 2013). The report by Zinman et al (2013) had two RCTs, BEGIN:EASY AM and BEGIN:EASY PM, both included in this SRM. One study was excluded as the trial duration was short and did not report the outcomes of interest (Nagai et al, 2016).

Characteristics of Included Studies

Of the three RCTs in this SRM, one was a phase 2 trial (Zinman et al, 2011) and the other two were phase 3 trials (Zinman et al, 2013). All three trials were randomized, open-label clinical trials. All the trials included insulin naïve adults with T2DM. The BEGIN:EASY trials had two arms; study subjects received either IDeg (200 U/mL) 3TW (on Monday, Wednesday, and Friday) or IGlar (100 U/mL) OD administered at any time during the day but consistently at the same time each day. IDeg was given in the AM trial at any time between waking up and the first meal of the day, but in the PM trial, it was administered with the main evening meal (Zinman et al, 2013). In the Zinman et al (2011) trial, participants were randomly allocated in a 1:1:1:1 ratio to receive IDeg (900 nmol/mL formulation) 3TW (dosed in the evening on Monday, Wednesday, and Friday), IDeg group A (600 nmol/mL formulation) OD, IDeg group B (900 nmol/mL formulation) OD or IGlar (600 nmol/mL formulation) OD. IDeg 3TW and IGlar OD arms were considered for meta-analysis (Zinman et al, 2011). In the BEGIN:EASY trials, the assignment of treatment groups was concealed from titration surveillance staff, safety committee members, and those responsible for defining analysis sets until the data were secured for statistical analysis (Zinman et al, 2013). Investigators were blinded to the data until the statistician released the database in the Zinman et al (2011) trial. The BEGIN:EASY trials were of 26 weeks duration; Zinman et al (2011) trial had a duration of 16 weeks. The baseline characteristics of the included RCTs were matched throughout the trial arms. The specifics of the included and excluded studies are shown in Table 1 and **Supplementary Table 1**, respectively.

The Risk of Bias in the Studies Included

Supplementary Fig. 2 illustrates the specific and overall RoB in the three RCTs. The overall RoB was low in all trials. Publication bias was not assessed due to the inadequate number of RCTs (at least 10) in forest plots (Debray et al, 2018).

Glycemic Outcomes

IDeg 3TW was less effective than IGlar OD in HbA1c reduction (MD 0.27%, 95% CI [0.14, 0.39], $I^2 = 22\%$, $p < 0.0001$) (Fig. 1A). More study subjects in the IGlar OD group achieved HbA1c <7% than those in the IDeg 3TW group (OR 0.69, 95% [0.53, 0.89], $I^2 = 0\%$, $p = 0.005$) (Fig. 1B). IDeg 3TW and IGlar OD

Table 1. Characteristics of the included clinical trials and participants.

	BEGIN:EASY AM	BEGIN:EASY PM	Zinman 2011
Authors, Year of publication [Reference no]	(Zinman et al, 2013)	(Zinman et al, 2013)	(Zinman et al, 2011)
Phase of the trials	Phase 3	Phase 3	Phase 2
Trial registration no.	NCT01068678	NCT01076647	NCT00611884
Place of the Trial	94 sites in seven countries	89 sites in seven countries	28 sites in four countries
Major inclusion criteria	- Adults with T2DM - Insulin naïve - Not taken GLP-1RAs or TZDs within 3 months of screening - HbA1c 7.0–10.0% - BMI $\leq$45 kg/m^2	- Adults with T2DM - Insulin naïve - Not taken GLP-1RAs or TZDs within 3 months of screening - HbA1c 7.0–10.0% - BMI $\leq$45 kg/m^2	- Adults (aged 18–75 years) with T2DM - Insulin naïve - Not taken TZDs, DPP-4is or other interventions that might affect glucose metabolism within 3 months of screening - HbA1c 7.0–11.0% - BMI 23–42 kg/m^2
Study arms (number of participants)	IDeg 3TW (229) IGlar OD (230)	IDeg 3TW (233) IGlar OD (234)	IDeg 3TW (62) IDeg OD- Group A* (60) IDeg OD- Group B** (61) IGlar OD (62)
Female	IDeg 3TW: 45.9% IGlar OD: 40.4%	IDeg 3TW: 43.3% IGlar OD: 42.3%	IDeg 3TW: 55% IDeg OD- Group A: 45% IDeg OD Group B: 36% IGlar OD: 40%
Age (years), mean (SD)	IDeg 3TW: 58.4 (9.9) IGlar OD: 57.9 (9.7)	IDeg 3TW: 57.3 (9.6) IGlar OD: 57.5 (10.7)	IDeg 3TW: 54.4 (8.8) IDeg OD- Group A: 55.3 (8.7) IDeg OD Group B: 53.9 (8.5) IGlar OD: 53.1 (10.2)

Table 1. Continued.

	BEGIN:EASY AM	BEGIN:EASY PM	Zinman 2011
Body weight (kg), mean (SD)	IDeg 3TW: 90.8 (18.6) IGlar OD: 95.7 (19)	IDeg 3TW: 92.3 (18.3) IGlar OD: 91.4 (18.7)	IDeg 3TW: 78.5 (20.8) IDeg OD- Group A: 78.5 (16.9) IDeg OD Group B: 81.7 (20.5) IGlar OD: 79.5 (18.5)
Duration of diabetes (years), mean (SD)	IDeg 3TW: 9.2 (6.4) IGlar OD: 8.5 (5.7)	IDeg 3TW: 8.4 (6.2) IGlar OD: 9.2 (6.0)	IDeg 3TW: 6.6 (5.4) IDeg OD- Group A: 7.3 (5.2) IDeg OD Group B: 7.2 (4.4) IGlar OD: 6.7 (5.0)
HbA1c (%), mean (SD)	IDeg 3TW: 8.2 (0.8) IGlar OD: 8.3 (0.9)	IDeg 3TW: 8.3 (0.8) IGlar OD: 8.3 (0.8)	IDeg 3TW: 8.8 (1.1) IDeg OD- Group A: 8.6 (1.2) IDeg OD Group B: 8.7 (1.1) IGlar OD: 8.7 (1.1)
Primary outcome	Non-inferiority of IDeg 3TW compared with IGlar OD, as measured by the HbA1c change	Non-inferiority of IDeg 3TW compared with IGlar OD, as measured by the HbA1c change	Change in HbA1C after trial end
Trial duration	26 weeks	26 weeks	16 weeks

BMI, body mass index; DPP-4i, Dipeptidyl-peptidase phosphate-4 inhibitor; GLP-1RAs, Glucagon-like peptide-1 receptor agonists; HbA1c, glycated haemoglobin; IDeg 3TW, thrice-weekly insulin degludec; IGlar OD, once-daily insulin glargine; T2DM, type 2 diabetes mellitus; TZDs, Thiazolidine-diones.

*Group A took 600 nmol/mL formulation of IDec.

**Group A took 900 nmol/mL formulation of IDec.

were similarly effective in FPG reduction (MD 0.37 mmol/L, 95% [–0.19, 0.93], I^2 = 67%, p = 0.19) (Fig. 1C). IDeg 3TW was less effective than IGlar OD in the reduction of overall mean self-monitored capillary blood glucose (SMBG) concentration of the 9-point profile (MD 0.45 mmol/L, 95% CI [0.22, 0.67], I^2 = 0%, p < 0.0001) (Fig. 1D).

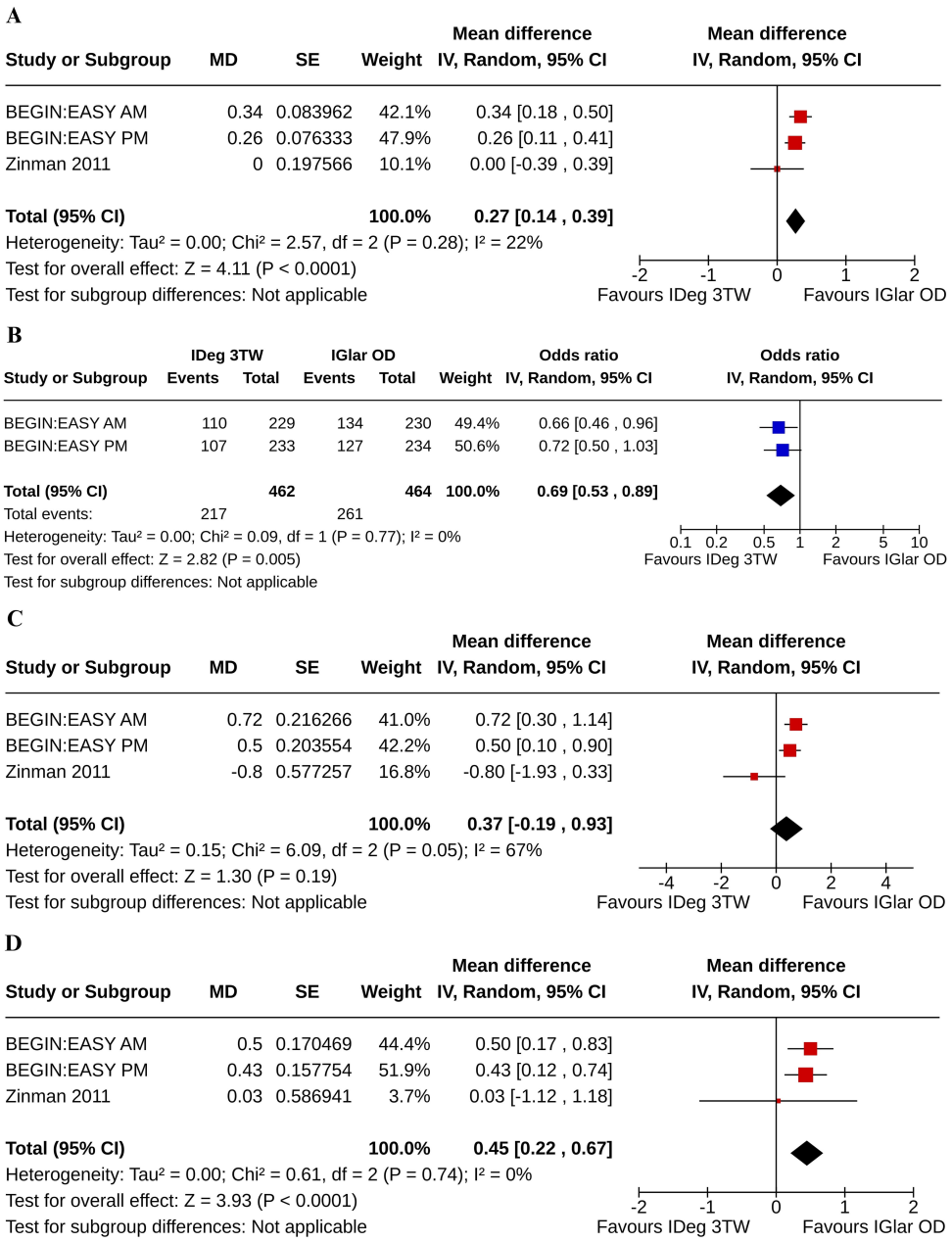

Fig. 1. Forest plot highlighting the comparison of IDeg 3TW vs. IGlar OD regarding (A) Changes from baseline in HbA1c, (B) Proportions of study subjects achieved HbA1c <7%, (C) Changes from baseline in FPG, and (D) Changes from baseline in overall mean SMBG concentration of the 9-point profile. CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; IDeg 3TW, thrice-weekly insulin degludec; IGlar OD, once-daily insulin glargine; IV, Inverse variance; MD, mean difference; SE, Standard error; SMBG, self-monitored capillary blood glucose.

Other Secondary Efficacy Parameters

The changes in body weight were identical in the IDeg 3TW and IGlar OD groups (MD 0.04 kg, 95% CI [–0.46, 0.55], I^2 = 29%, p = 0.86) (Fig. 2A). The mean calculated daily insulin dose was lower in the IDeg 3TW group than the IGlar OD group (MD –0.07 U, 95% CI [–0.13, –0.01], I^2 = 64%, p = 0.02) (Fig. 2B). The change from baseline in overall physical health score (MD 0.21, 95% CI [–0.62, 1.04], I^2 = 0%, p = 0.62) (Fig. 2C) and overall mental health score (MD –0.02, 95% CI [–1.05, 1.01], I^2 = 0%, p = 0.97) (Fig. 2D) of the Health-related quality of life (HRQoL) questionnaire (The 36-Item Short Form Survey (SF-36)) showed no significant difference between the IDeg 3TW and IGlar OD groups.

Adherence to the Study Drug

The risk of study drug discontinuation was identical in the IDeg 3TW and IGlar OD groups (RR 1.18, 95% CI [0.80, 1.76], I^2 = 15%, p = 0.40) (Fig. 3A). When the individual cause was considered, both groups had similar risks for study drug discontinuation due to non-compliance (RR 1.15, 95% CI [0.44, 3.00], I^2 = 18%, p = 0.78) (Fig. 3B), ineffective therapy (RR 1.06, 95% CI [0.22, 5.01], I^2 = 0%, p = 0.94) (Fig. 3C), adverse events (RR 1.53, 95% CI [0.14, 16.49], I^2 = 37%, p = 0.73) (Fig. 3D), meeting the withdrawal criteria of the trial (RR 1.64, 95% CI [0.68, 3.92], I^2 = 0%, p = 0.27) (Fig. 3E), and other causes (RR 1.05, 95% CI [0.63, 1.74], I^2 = 0%, p = 0.86) (Fig. 3F).

Safety Parameters

Adverse Events

The risks of any adverse events (AEs) (RR 1.04, 95% CI [0.84, 1.30], I^2 = 77%, p = 0.71) (Fig. 4A) and serious AEs (RR 1.43, 95% CI [0.77, 2.65], I^2 = 0%, p = 0.25) (Fig. 4B) were identical in the IDeg 3TW and IGlar OD groups. The two groups also had similar risk of injection-site reactions (RR 1.29, 95% CI [0.56, 2.96], I^2 = 65%, p = 0.55) (Fig. 4C).

Hypoglycemia

Both groups also had statistically indifferent risks for confirmed hypoglycemia (RR 1.16, 95% CI [0.83, 1.62], I^2 = 55%, p = 0.38) (Fig. 4D) and confirmed nocturnal hypoglycemia (RR 1.18, 95% CI [0.49, 2.84], I^2 = 58%, p = 0.71) (Fig. 4E).

Discussion

Main Findings From the Review

This SRM, including 3 RCTs with study durations ranging from 16 to 26 weeks, having low risk of bias, and involving 1171 participants, examined the efficiency and safety of IDeg 3TW versus IGlar OD. The results indicate that IDeg 3TW is less effective than IGlar OD in achieving HbA1c reduction, the proportion of participants achieving HbA1c <7%, and the reduction in mean SMBG concentration. However, both groups achieved almost identical FPG reduction. The mean daily insulin dose was lower in IDeg 3TW than in the IGlar OD group. The changes in body weight and overall physical and mental health scores were identical in the IDeg

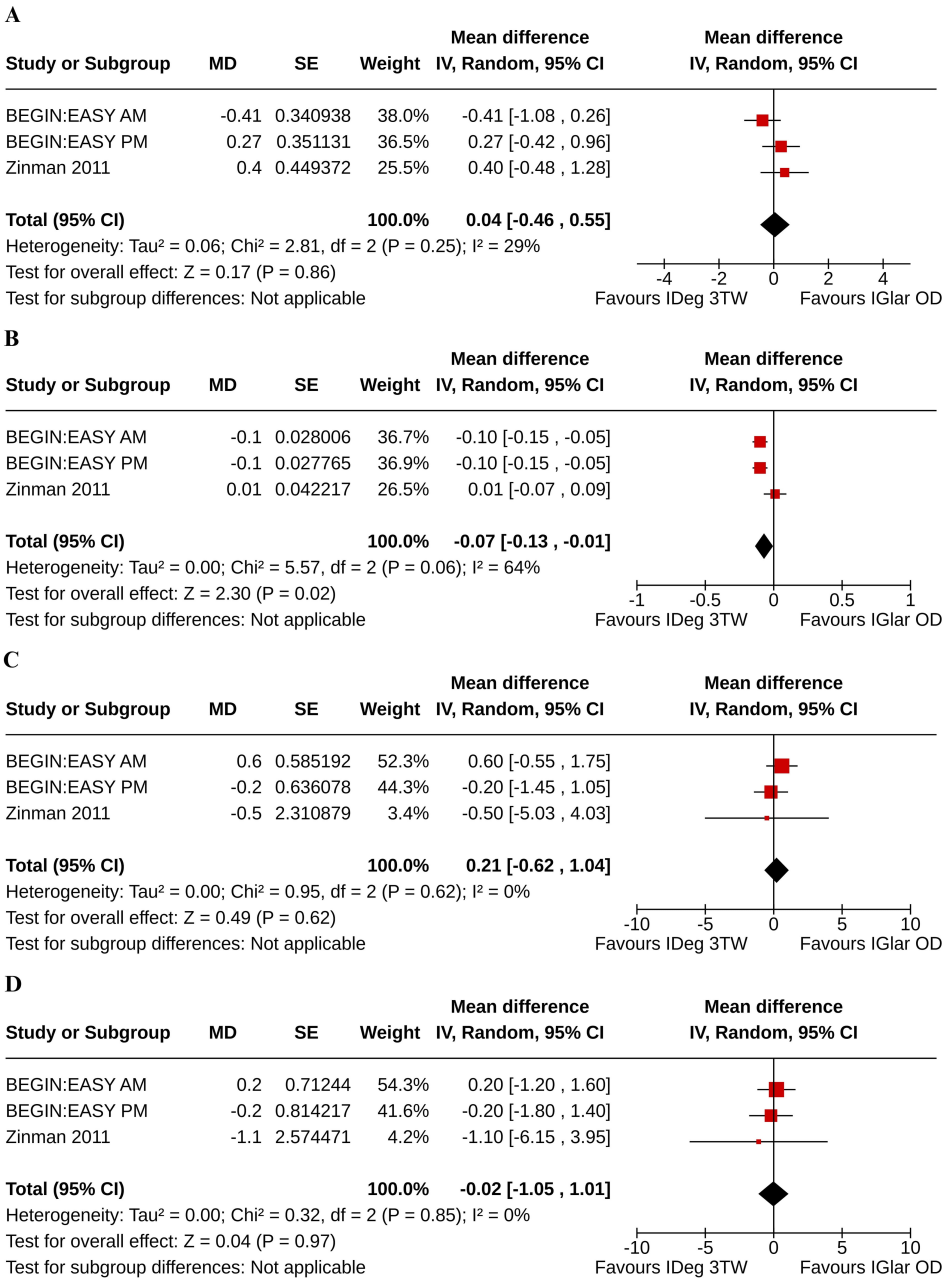

Fig. 2. Forest plot highlighting the comparison of IDeg 3TW vs. IGlar OD regarding the (A) Changes from baseline in body weight, (B) Mean calculated daily insulin dose, (C) Changes from baseline in overall physical health score of the HRQoL questionnaire (SF-36), and (D) Changes from baseline in overall mental health score of the HRQoL questionnaire (SF-36). CI, confidence interval; HRQoL, Health-related quality of life; IDeg 3TW, thrice-weekly insulin degludec; IGlar OD, once-daily insulin glargine; IV, Inverse variance; MD, mean difference; SE, Standard error; SF-36, The 36-Item Short Form Survey.

3TW and IGlar OD groups. Though the relative risks of confirmed hypoglycemia, confirmed nocturnal hypoglycemia, any AEs, serious AEs, and injection-site reactions were increased by 16%, 18%, 4%, 43%, and 29%, respectively, in the IDeg 3TW group than IGlar OD group, none of them was statistically significant.

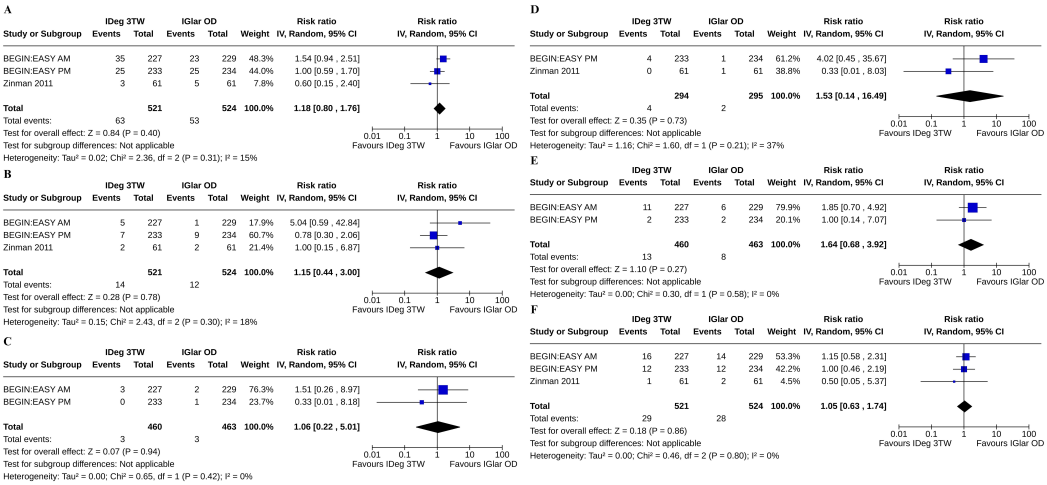

Fig. 3. Forest plot highlighting the comparison of IDeg 3TW vs. IGlar OD regarding the proportions of study subjects with (A) Study drug discontinuation due to any cause, (B) Study drug discontinuation due to non-compliance, (C) Study drug discontinuation due to ineffective therapy, (D) Study drug discontinuation due to adverse events, (E) Study drug discontinuation due to meeting the withdrawal criteria of the trial, and (F) Study drug discontinuation due to other causes. CI, confidence interval; IDeg 3TW, thrice-weekly insulin degludec; IGlar OD, once-daily insulin glargine; IV, Inverse variance; MD, mean difference; SE, Standard error.

Clinical Implications and Applicability of the Study Results

This SRM suggests that IDeg 3TW may be safe compared to the IGlar OD group, but it is inferior to the IGlar OD group in achieving glycaemic control. On the other hand, previous RCTs and meta-analyses comparing IDeg OD and IGlar OD observed that IDeg OD is non-inferior to IGlar OD for HbA1c reduction accompanied by a notably reduced risk of hypoglycemia, especially that of nocturnal hypoglycaemia (Garber et al, 2012; Heller et al, 2012; Ratner et al, 2013; Zinman et al, 2012). Hence, if glycemic outcomes are the main target of insulin therapy, IDeg may be better administered once daily, with improved flexibility regarding dosing time, that it can be administered with a minimum of eight and a maximum of forty hours between insulin injections (Woo, 2017).

All three RCTs discussed in the SRM used IDeg 200 units/mL for thrice-weekly administration. A review of the pharmacodynamic study comparing IDeg 200 units/mL and IGlar 300 units/mL showed that within-day variability was 37% lower and day-to-day variability was 4 times lower with IDeg 200 compared to IGlar 300, which would allow more flexibility in dosing with a lower hypoglycaemia risk (Heise et al, 2017). An RCT with a head-to-head comparison between IDeg 200 OD and IGlar 300 OD observed a statistically lower nocturnal symptomatic hypoglycaemia and severe hypoglycaemia favoring IDeg 200 (Philis-Tsimikas et al, 2020). Though there was no significant HbA1c reduction from baseline, lower total daily insulin dose at the study completion (66.6 ± 48.5 units vs. 73.0 ± 48.5 units) favored IDeg 200 daily.

We should be mindful about choosing insulin regimens in situations such as poor compliance, especially in young people, those with needle phobia, and patients with mental health issues who might occasionally refuse injections, and at times in

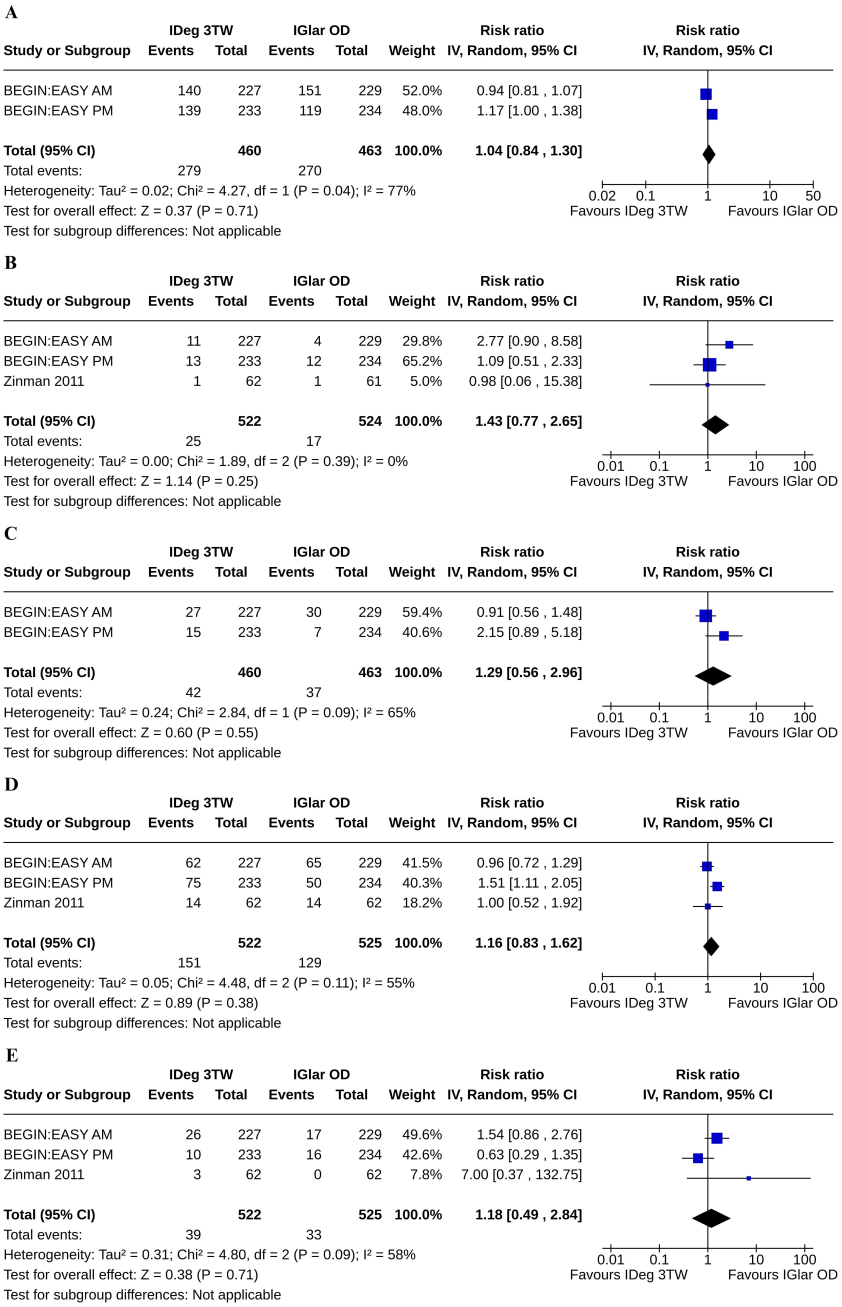

Fig. 4. Forest plot highlighting the comparison of IDeg 3TW vs. IGlar OD regarding the proportions of study subjects with (A) Any adverse events, (B) Serious adverse events, (C) Injection-site reactions, (D) Confirmed hypoglycemia, and (E) Confirmed nocturnal hypoglycemia. CI, confidence interval; IDeg 3TW, thrice-weekly insulin degludec; IGlar OD, oncedaily insulin glargine; IV, Inverse variance; MD, mean difference; SE, Standard error.

elderly people who get supervised insulin administration by healthcare workers, where lower injection burden may be an advantage as in IDeg 3TW regimen. Patients who cannot self-administer insulin injections due to various reasons (e.g., blindness) but need thrice-weekly healthcare support, such as during hemodialysis sessions, can also be candidates for IDeg 3TW (Oishi et al, 2015). Although IDeg 3TW was less effective in these patients for glycemic control compared to IGlar OD, reasonable safety profile and glycemic control in those who can't self-inject

were advantages. However, when available widely in the market, the newer weekly insulin molecules can address most of these issues more efficiently (Rosenstock et al, 2023; Wysham et al, 2024). The longer duration of action and reasonable efficacy in glycemic outcomes with less than once daily administration potential of degludec insulin also helps in making drug regimens as in the case of combining it with weekly antidiabetic agents like dulaglutide (Huang et al, 2023). Moreover, for economic reasons, IDeg 3TW could still be an option for resource-poor settings.

We acknowledge that this SRM has a small number of participants from only three RCTs and short follow-up durations of the RCTs included for such a common and lifelong disease as T2DM. The included RCTs were open-label; however, the overall RoB was low in all trials. Publication bias could not be assessed because only three studies were included. The potential benefits in special populations who can't self-administer daily insulin, as discussed above, were not addressed by the RCTs included. However, the strengths are the low RoB and the reasonable evidence generated by the RCTs for potential use in clinical practice.

Conclusion

This SRM suggests that IDeg 3TW is less effective than IGlar OD in glycemic control in patients with T2DM. However, the safety profile of either insulin regimen is comparable during the short-term follow-up period. IDeg 3TW may still be used in clinical settings, especially when compliance is an important issue. Therefore, large multicenter RCTs comparing the overall risk-benefit ratio are needed to make more appropriate clinical practice decisions.

Key Points

- IDeg 3TW is less effective than IGlar OD in achieving HbA1c reduction, the proportion of participants achieving HbA1c $<7\%$, and the reduction in mean SMBG concentration, though both molecules are equally effective in controlling FPG.
- Although there was a tendency for higher risks of confirmed hypoglycemia, confirmed nocturnal hypoglycemia, any AEs, serious AEs, and injection-site reactions with the use of IDeg 3TW than IGlar OD group, none of them was statistically significant in this study.
- IDeg should ideally be used once daily at a similar time each day when feasible. However, when this is not practical, the IDeg can be administered within 8 to 40 hours between the doses without compromising the glycaemic efficacy and safety.
- Patients with poor injection compliance, needle phobia, mental health issues, and those who cannot self-administer insulin injections due to various reasons (e.g., blindness) but need thrice-weekly healthcare support, such as during hemodialysis sessions, can be ideal candidates for IDeg 3TW.

Availability of Data and Materials

All data and materials included in this study are available upon request by contacting the corresponding author.

Author Contributions

ABMKH and LN contributed to the design, statistical analyses, performance of the research, implementation of the study, and the writing of the manuscript. CJF, SB, and JMP made substantial contributions to the conception and design, acquisition of data, and analysis and interpretation of data. DD contributed to the statistical analyses, research performance, and manuscript writing. LN, CJF, JMP and SB have been involved in critically drafting and revising the manuscript for important intellectual content. All authors have given final approval of the current version of the manuscript to be published. All authors agreed to be accountable for all aspects of the work to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2024.0716.

References

Chadha M, Jain SM, Chawla R, Dharmalingam M, Chaudhury T, Talwalkar PG, et al. Evolution of Guideline Recommendations on Insulin Therapy in Type 2 Diabetes Mellitus Over the Last Two Decades: A Narrative Review. Current Diabetes Reviews. 2023; 19: e160123212777. https://doi.org/10.2174/1573399819666230116150205

Debray TPA, Moons KGM, Riley RD. Detecting small-study effects and funnel plot asymmetry in meta-analysis of survival data: A comparison of new and existing tests. Research Synthesis Methods. 2018; 9: 41–50. https://doi.org/10.1002/jrsm.1266

Garber AJ, King AB, Del Prato S, Sreenan S, Balci MK, Muñoz-Torres M, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet (London, England). 2012; 379: 1498–1507. https://doi.org/10.1016/S0140-6736(12)60205-0

Guerci B, Chanan N, Kaur S, Jasso-Mosqueda JG, Lew E. Lack of Treatment Persistence and Treatment Nonadherence as Barriers to Glycaemic Control in Patients with Type 2 Diabetes. Diabetes Therapy: Research, Treatment and Education of Diabetes and Related Disorders. 2019; 10: 437–449. https://doi.org/10.1007/s13300-019-0590-x

Heise T, Nørskov M, Nosek L, Kaplan K, Famulla S, Haahr HL. Insulin degludec: Lower day-to-day and within-day variability in pharmacodynamic response compared with insulin glargine 300 U/mL in type 1 diabetes. Diabetes, Obesity & Metabolism. 2017; 19: 1032–1039. https://doi.org/10.1111/dom.12938

Heller S, Buse J, Fisher M, Garg S, Marre M, Merker L, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet (London, England). 2012; 379: 1489–1497. https://doi.org/10.1016/S0140-6736(12)60204-9

Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. In Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (eds.) Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane: London. 2023b. Available at: https://training.cochrane.org/handbook/archive/v6.4 (Assessed: 15 September 2024).

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. (eds.) Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane: London. 2023a. Available at: www.training.cochrane.org/handbook (Assessed: 15 September 2024).

Hirose T, Chen CC, Ahn KJ, Kiljański J. Use of Insulin Glargine 100 U/mL for the Treatment of Type 2 Diabetes Mellitus in East Asians: A Review. Diabetes Therapy: Research, Treatment and Education of Diabetes and Related Disorders. 2019; 10: 805–833. https://doi.org/10.1007/s13300-019-0613-7

Huang J, Hua F, Jiang X, Zhang X, Yang M, Wang L, et al. Effects of dulaglutide combined with insulin degludec on glucose fluctuations and appetite in type 2 diabetes. Frontiers in Endocrinology. 2023; 14: 1130470. https://doi.org/10.3389/fendo.2023.1130470

Kamrul-Hasan ABM, Alam MS, Talukder SK, Dutta D, Selim S. Efficacy and Safety of Omarigliptin, a Novel Once-Weekly Dipeptidyl Peptidase-4 Inhibitor, in Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. Endocrinology and Metabolism (Seoul, Korea). 2024; 39: 109–126. https://doi.org/10.3803/EnM.2023.1839

Liu W, Yang X, Huang J. Efficacy and Safety of Insulin Degludec versus Insulin Glargine: A Systematic Review and Meta-Analysis of Fifteen Clinical Trials. International Journal of Endocrinology. 2018; 2018: 8726046. https://doi.org/10.1155/2018/8726046

McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Research Synthesis Methods. 2021; 12: 55–61. https://doi.org/10.1002/jrsm.1411

Nagai Y, Murakami M, Igarashi K, Nakamura Y, Tsukiyama H, Matsubara F, et al. Efficacy and safety of thrice-weekly insulin degludec in elderly patients with type 2 diabetes assessed by continuous glucose monitoring. Endocrine Journal. 2016; 63: 1099–1106. https://doi.org/10.1507/endocrj.EJ16-0252

Oishi A, Makita N, Manaka K, Mitani K, Tomita H, Iiri T. Successful glycemic control with three times a week degludec injection by medical staff for an elderly hemodialysis patient with type 2 diabetes. Diabetology International. 2015; 7: 95–99. https://doi.org/10.1007/s13340-015-0220-4

Owens DR, S Bailey T, Fanelli CG, Yale JF, Bolli GB. Clinical relevance of pharmacokinetic and pharmacodynamic profiles of insulin degludec (100, 200 U/mL) and insulin glargine (100, 300 U/mL) - a review of evidence and clinical interpretation. Diabetes & Metabolism. 2019; 45: 330–340. https://doi.org/10.1016/j.diabet.2018.11.004

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ (Clinical Research Ed.). 2021; 372: n71. https://doi.org/10.1136/bmj.n71

Philis-Tsimikas A, Klonoff DC, Khunti K, Bajaj HS, Leiter LA, Hansen MV, et al. Risk of hypoglycaemia with insulin degludec versus insulin glargine U300 in insulin-treated patients with type 2 diabetes: the randomised, head-to-head CONCLUDE trial. Diabetologia. 2020; 63: 698–710. https://doi.org/10.1007/s00125-019-05080-9

Ratner RE, Gough SCL, Mathieu C, Del Prato S, Bode B, Mersebach H, et al. Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials. Diabetes, Obesity & Metabolism. 2013; 15: 175–184. https://doi.org/10.1111/dom.12032

Review Manager (RevMan) [Computer program]. Version 7.2.0. The Cochrane Collaboration. 2024. Available at: revman.cochrane.org (Assessed: 15 September 2024).

Rosenstock J, Bain SC, Gowda A, Jódar E, Liang B, Lingvay I, et al. Weekly Icodec versus Daily Glargine U100 in Type 2 Diabetes without Previous Insulin. The New England Journal of Medicine. 2023; 389: 297–308. https://doi.org/10.1056/NEJMoa2303208

Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ. Publication and related biases. Health Technology Assessment (Winchester, England). 2000; 4: 1–115.

Wang W, Chang X, Lehrskov LL, Li L, Nordentoft M, Quan J, et al. Insulin Degludec in People with Type 2 Diabetes in China: A Non-interventional, Retrospective Chart Review Study (CN-TREAT). Diabetes Therapy: Research, Treatment and Education of Diabetes and Related Disorders. 2024; 15: 725–739. https://doi.org/10.1007/s13300-024-01533-6

Woo VC. A Review of the Clinical Efficacy and Safety of Insulin Degludec and Glargine 300 U/mL in the Treatment of Diabetes Mellitus. Clinical Therapeutics. 2017; 39: S12–S33. https://doi.org/10.1016/j.clinthera.2017.01.007

Wysham C, Bajaj HS, Del Prato S, Franco DR, Kiyosue A, Dahl D, et al. Insulin Efsitora versus Degludec in Type 2 Diabetes without Previous Insulin Treatment. The New England Journal of Medicine. 2024; 391: 2201–2211. https://doi.org/10.1056/NEJMoa2403953

Zinman B, DeVries JH, Bode B, Russell-Jones D, Leiter LA, Moses A, et al. Efficacy and safety of insulin degludec three times a week versus insulin glargine once a day in insulin-naive patients with type 2 diabetes: results of two phase 3, 26 week, randomised, open-label, treat-to-target, non-inferiority trials. The Lancet. Diabetes & Endocrinology. 2013; 1: 123–131. https://doi.org/10.1016/S2213-8587(13)70013-5

Zinman B, Fulcher G, Rao PV, Thomas N, Endahl LA, Johansen T, et al. Insulin degludec, an ultra-long-acting basal insulin, once a day or three times a week versus insulin glargine once a day in patients with type 2 diabetes: a 16-week, randomised, open-label, phase 2 trial. Lancet (London, England). 2011; 377: 924–931. https://doi.org/10.1016/S0140-6736(10)62305-7

Zinman B, Philis-Tsimikas A, Cariou B, Handelsman Y, Rodbard HW, Johansen T, et al. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). Diabetes Care. 2012; 35: 2464–2471. https://doi.org/10.2337/dc12-1205