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REVIEW ARTICLE

The comparative analysis of efficacy and safety parameters of Insulin Degludec versus Insulin Glargine: A Narrative Review

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ABSTRACT

Background and aim: Insulin degludec and insuline glargine are the two long-acting insulins most commonly prescribed for the treatment of Diabetes Type 1 as well as Diabetes Type 2. Both insulins were generated to address a clinical need for the basal insulin which produces a more even and flat activity profile and reduces the number of hypoglycemia- a dangerous side effect of insulin therapy. Although glargine and degludec confirmed their superiority in terms of reduced rate of hypoglycemia, especially in comparison with first generations, several studies revealed that degludec is associated with less glycemic variability. Moreover, degludec is more effective in reaching better fasting plasma glucose levels without increasing a risk of nocturnal hypoglycemia. The aim of this study is to compare the five most essential efficacy and safety parameters of insulin degludec versus insulin glargine.

Methods: This study used a narrative synthesis of the research findings. The search for existing narrative and systematic reviews on the research topic was conducted through PubMed, Embase, and Google Scholar electronic databases. Reviews were selected according to a study design and methodological quality of the included studies. The reviews published within 2015-2023 period were included. The data on five safety and efficacy parameters (the reduction of fasting plasma glucose level, HbA1c levels, overall and nocturnal hypoglycemia episodes, body weight gain) were retrieved for the analysis.

Findings: The analysis of data retrieved out of 10 systematic reviews confirmed superiority of insulin degludec in comparison with insulin glargine in terms of four safety and efficacy parameters. The treatment with degludec was associated with fewer overall and nocturnal hypoglycemia episodes, a better reduction of fasting plasma glucose levels in both Diabetes Type 1 and Diabetes Type 2 groups (insulin naïve and experienced) patients, less weight gain in Diabetes Type 2 insulin experienced group and Diabetes Type 1 groups. Both insulins provided a similar reduction of HbA1c levels among patients with Diabetes Type 1 and Diabetes Type 2.

Conclusion: In conclusion, this narrative review revealed that insulin degludec is superior to insulin glargine in terms of four safety and efficacy parameters such as change in fasting plasma glucose, body weight gain, nocturnal and overall hypoglycemia episodes. Degludec and glargine produced similar changes in HbA1c levels. The most pronounced differences in almost all the examined reviews were detected in the variables indicating nocturnal and overall hypoglycemia. The treatment with degludec also resulted in less hypoglycemia, accompanied with a better reduction of fasting plasma glucose levels. This characteristic confirms that degludec produces less glycemic variability and a close to physiological activity profile.

1. Introduction

Degludec and glargine are the most novel basal, second-generation insulins widely used in a global clinical practice for the treatment of patients diagnosed with Diabetes Type 1(T1D) and insulin - dependent patients with Diabetes Type 2(T2D). Both types of diabetes are the most prevalent ones globally, and almost 90% of all cases constitute patients with Diabetes Type 2. The new cases of diabetes are increasing globally. According the World Health Organization, the number of people with diabetes reached 422 million in 2014. [1,2] Diabetes today has become a leading cause of disability and the ninth leading cause of death: from 2000 to 2019 deaths from diabetes increased by 70% worldwide. Diabetes is a primary cause of blindness, myocardial infarction, stroke, kidney failure and feet amputations; in order to prevent these complications an optimal glycemic control is needed. Therefore, the search for the insulin which maintains an optimal glycemic control and expresses less glycemic variability is essential. [3,4,5]

With regards to insulin therapy, about a half of patients with Diabetes Type 2 use basal insulins as an additional treatment to oral antidiabetic drugs or basal + bolus regimes alone. [2] Long- acting insulins ensures a non-stop mild hypoglycemic effect, and often are used as a standalone therapy for the treatment of Diabetes Type 2. However, along with multiple benefits insulin therapy has a main dangerous side-effect - hypoglycemia. Hypoglycaemia, especially severe ones can cause loss of consciousness, seizures, coma, an acute coronary syndrome. [6] The search for a basal insulin capable of ensuring stable hypoglycemic effect with a minimal risk of hypoglycemia is a priority in the treatment of insulin-dependent patients with diabetes today. [7] The quality of glycemic control worsens substantially in case of frequent hypoglycemia events. Hypoglycemia negatively impacts an individual's quality of life and productivity at work causing the fear and anxiety of developing hypoglycemia outside. Out of all other forms of hypoglycemia, nocturnal hypoglycemia can be considered as a worst form, because it happens during a sleep and can persist a long time leading to a severe decrease of a blood glucose lower than 3,1mmol/l. In addition to this, frequent nocturnal hypoglycemia impairs cognitive functions and worsens regulatory mechanisms which maintain blood glucose levels. 8 Several studies revealed that spontaneous nocturnal hypoglycemia in patients with Diabetes Type 1 changes cardiac repolarization and contributes to the risk of "dead in bed" syndrome. [9]

Second-generation insulins were invented to address a clinical need for the insulin whose activity profile would be close to a normal physiological pattern of insulin secretion. Insulin glargine(IGlar) manufactured by Sanofi Aventis company was approved by Food and Drug Administration USA in 2000 and has had a longer history of a clinical use compared to insulin degludec(IDeg). The newest basal insulin analogue degludec was generated later by Novo Nordisk company and obtained approval in 2012. Both insulins were invented as an improvement of a first-generation basal insulin NPH, which demonstrated a high risk of hypoglycemia, particularly nocturnal hypoglycemia. [10, 11]

Glargine and degludec showed a considerably lower rates of hypoglycemia, which resulted in a reduced rate of hospitalization for severe hypoglycemia and secondary health checks in real-world patients – 9,9% (p= 0,022) lower for glargine U100 compared to NPH. [1] However, the on-going need for the flat-profile insulin capable of reaching optimal fasting plasma glucose targets without increasing risk of nocturnal hypoglycemia remained, and degludec was consequently produced to address this need. [12] The other common side-effect of insulin therapy is weight gain; the issue of weight gain is particularly relevant in case of Diabetes Type 2. Therefore, the prescription of a basal insulin demonstrating less weight gain during a long -term use will be a preferable treatment option in patients with Diabetes Type 2.[4]

1. Methodology

2.1 STUDY DESIGN

This review follows a study design of a narrative review.

2.2 SEARCH STRATEGY.

Initially, the PROSPERO databases and the Cochrane Database of Systematic Reviews (CDSR) were inspected for ongoing and existing reviews. The existing literature was searched according to Centre for Reviews and Dissemination (CRD) 2009. [13] PubMed, Embase, Google Scholar electronic databases were searched to identify systematic reviews with study results published within 2015-2023 period.

The following search terms were used: Embase: 56 articles identified, PubMed: "*insulin glargine*" OR "*insulin degludec*" AND "*Diabetes*"- 1831 articles, Google Scholar: advanced search (filter with the exact phrase) - keywords: "*insulin glargine*", "*insulin degludec*" - 76 articles identified.

The literature search was limited to meta-analyses, systematic and narrative reviews with the publication date not older than 2015 year, published on English language, full-free text peer-reviewed articles, reviews including studies with the design of a clinical or randomized controlled trial.

Data extraction

Data extraction includes strengths and limitations of the study, data on predetermined five safety and efficacy parameters such as:

1) Safety variables: Overall and nocturnal episodes of hypoglycaemia, body weight gain;

2) Efficacy variables: the level of HbA1c, changes in fasting plasma glucose (FPG).

Data analysis

A narrative synthesis of the retrieved research findings was used.

2. RESULTS

BODY WEIGHT GAIN

The research of Zhou,(2019) examining this variable is presented by a systematic review including 15 studies with 7075 patients in the insulin glargine group (control) and 9619 patients in the insulin degludec group (experimental). The review examined four main endpoints which included weight gain. The results did not identify a statistically significant difference in body weight gain between the degludec and glargine arms (WMD 0,12 [0,19 to 0,43] p = 0,46). [14]

Another review Liu et al, (2018) including 15 high-quality RCTs revealed similar changes in body weight gain - T1D (MD = −0.04, 95% CI = −0.35 to 0.26, , I^2 = 0%) and those with T2D (MD = 0.05, 95% CI = −0.11 to 0.22, , I^2 = 51%). MD= 0,03 [-0,11 to 0,18] p= 0,67. In both T1D and T2D IDeg vs IGlar groups results did not reach a statistical significance.[15]

The meta-analysis of Magomedova, (2023) using pooled results of 9 trials revealed that a treatment with IDeg is associated with less weight gain and the difference is statistically significant with MD -0,84kg [95% -1,50 to -0,18], Z=2,50 and p= 0,01. The subgroup analyses revealed that all subgroups (T2D,T1D, insulin experienced), except the insulin naïve group, showed a statistically significant reduction in weight gain associated with insulin degludec: T2D subgroup = -0,91(-1,73 to -0,08) p=0,03, Z= 2,16, I^2- 94%; T1D subgroup = -0,60(-1,08 to -0,12) p=0,01, Z=2,44, I^2= 0%; subgroup experienced- -1,19(-2,11 to -0,28) p= 0,01, Z=2,55, I^2– 93%. In subgroups the reduction ranges from -0,60 to -1,19kg. [16]

The findings of Madenidou, (2018) in contrast to those of Magomedova, (2023) revealed that weight loss was associated with basal insulin analogues detemir and glargine. [17.]

Episodes of overall and nocturnal hypoglycemia.

The findings of Zhou, (2019) based on the results of seven BEGIN 3a phase clinical trials (completed in the period 2011-2012) including both insulin-naïve and insulin experienced patients diagnosed with T2D (5 trials) and T1D (2 trials) demonstrated that end-of -trial rates of nocturnal hypoglycaemia were lower in groups treated with insulin degludec in both patient categories – T2D and T1D, however the rates were lower for T2D patients. The rate of overall, nocturnal and sever episodes of hypoglycaemia also favours groups treated with insulin degludec.[14]

The findings of Magomedova, (2023) showed that treatment with IDeg is associated with a considerable reduction in the overall episodes of hypoglycemia - RR- 0,61[95% 0,47 to 0,77] which can be interpreted as 39% lower risk of hypoglycemia. The result has a high statistical power Z= 4,20; p<0,0001 and a considerable heterogeneity (I^2- 85%). The subgroup analyses confirmed the consistency of the results favouring IDeg across all subgroups: subgroup insulin naïve- RR 0,58 [0,38 to 0,88] p= 0,01; subgroup insulin experienced- RR 0,64 [0,48 to 0,84] p= 0,001; subgroup T1D -RR 0,52 [0,33 to 0,72] p=0,001; subgroup T2D- RR 0,63 [0,49 to 0,82] p=0,0007. The subgroup analysis identified that T1D and insulin naïve groups showed the highest numbers for risk reduction 42% and 48%, respectively. [16]

In terms of hypoglycaemia events, treatment with IDeg was associated with lower nocturnal and overall hypoglycaemia in patients with T2D, according to the meta-analysis of Liu et al, (2018). [15]

The review of Heller, (2015) reported that for T2D patients, the risk of nocturnal hypoglycaemia (timescale 00,01-5.59, plasma glucose ,3,1 mmol/l) was significantly lower with insulin degludec vs insulin glargine during all trial periods; for patients with T1D, nocturnal hypoglycaemia risk was similar or lower across different definitions, trial periods and timescales. Nocturnal documented symptomatic hypoglycaemia for T2D patients during entire trial period IGlar-100,5 /IDeg 73,8 (Episodes per 100PYE). [18]

The review of Madenidou, (2018) reported pooled results of 38 randomized controlled trials where several basal insulins were analyzed in terms of weight gain, hypoglycemia events and HbA1c. According to this review, IDeg-100 was associated with lower incidence of any hypoglycemia (confirmed, symptomatic, asymptomatic with blood glucose <3,9; 3,1) compared with Glar-100 (OR-0,64 [0,43 to 0,96]). The data for nocturnal hypoglycemia were reported altogether for IGlar 300 and IDeg 100, 200 showing less nocturnal hypoglycemia compared to insulin detemir, LY2963016 and NPL. [17]

The review of Woo,(2020) exploring this safety parameters reported that IDeg is associated with lower risk of overall and nocturnal hypoglycemia in both Diabetes Type 2(insulin-naïve and basal-bolus) and Type 1 patients with a risk reduction variating from 24% to 40% The review examined the results of different studies and trial phases (SWITCH trial- (RR 0,94, p = 0.002, DEVOTE trial, EDITION trials, CONFIRM trial - RR 0,70, p =0.05), BRIGHT trial) and meta-analyses. Also, the treatment with insulin degludec was associated with a significantly reduced risk (RR 0,60, p = 0,001) of developing severe hypoglycemia among patients with chronic kidney and cardiovascular disease (DEVOTE trial). [1]

The meta-analysis of Ratner, (2015) showed that among overall T2D population (Rate Ratio (RR) 0,83 and 0,68) and insulin-naive patients with T2D RR-0,83 and 0,64, groups that used IDeg experienced significantly lower rates of overall confirmed and nocturnal hypoglycemia than those using IGlar. In terms of T1D patients, during a maintenance period, a treatment with degludec was associated with the significantly lower rates of nocturnal confirmed hypoglycemia comparing to glargine (Rate Ratio 0,75). The results reached statistical significance. [19]

The review of Zhang, (2018) reported results favouring insulin degludec; IDeg was associated with a reduced risk for all confirmed hypoglycaemia. The results reached a statistical significance: ERR -0,81; 95% CI – 0,72-0,92; p-0,001), nocturnal hypoglycaemia (ERR-0,71, 95% CI – 0,63-0,80; p <0,001. [20]

The review of Russel-Jones,(2015) revealed a considerable difference in the number of nocturnal hypoglycemia – T2D pooled results of seven RCT trials - 0.62 [0,49 to 0,78], T1D – 0,75 [0,60 to 0,94], T1D=T2D pooled results- 0.68 [0,58 to 0,80] [21]

CHANGE IN HbA1C

In terms of HbA1c, according to the meta-analysis of Madenidou, (2018) based on 37 studies, no statistically significant difference was detected in comparisons between IGlar-300, IGlar-100 vs IDeg-100, IDeg-200. [17.]

The similar inferences were made in the review of Magomedova, (2023) - the pooled estimates of 19 studies showed numerically lower results for IDeg, but the overall difference lacked statistical significance (Z= 0,49; p = 0,62). In terms of percentage of patients with HbA1c level less than 7% pooled results of 26 studies revealed that more patients treated with Glar-100 achieved an HbA1c level less than 7% than those treated with Deg-3TW – Odds Ratio 1,45 [CI95% 1,06 to 1,96]. [16]

With regards to the review of Zhou,(2019), the sensitivity analysis performed in nine trials with 13072 participants in total, revealed that insulin glargine was associated with a greater mean overall reduction in HbA1c as compared to insulin degludec, but the results were not statistically significant - WMD 0,03 [0,01 to 0,07] p = 0,10. [14]

The review of Liu et al, (2018) reported that the proportions of patients who achieved HbA1c < 7% from the baseline level were similar in both groups (IDeg 46,1% vs IGlar -46,9%), the difference favouring IGlar was clinically insignificant (MD = 0,04% [0,01% to 0,07%]). [15]

The findings of Zhang, (2018) demonstrated that HbA1c concentration was higher in IDeg vs IGlar group, but the results were not clinically or statistically significant (estimated treatment difference (ETD - 0,03 [0,00 to 0,06%] p= 0,06. [20]

The review of Russel Jones, (2015) based on seven phase 3 clinical trials did not reveal a statistically significant difference in the level of HbA1c reduction between IDeg and IGlar groups, however due to the treat-to-target nature of the trials' design the difference was not expected. [21]

CHANGE IN FPG LEVELS.

The following authors reported the findings regarding changes in fasting plasma glucose from baseline to end-of -trial periods.

A separate analysis of four trials with T2D patients in the review of Russel- Jones,(2015) showed that those who achieved FPG target <5 was higher in IDeg group (40,9%) vs IGlar (29,4%) Also, the proportion of patients who were likely to reach the FPG target without nocturnal confirmed

hypoglycaemia was considerably higher in IDeg group (34,9%) vs IGlar (23,8%). [21]

The analysis of Magomedova, (2023) based on 15 studies showed that IDeg is more effective in the reduction of fasting blood glucose levels as compared to IGlar (MD = -0,40[-0,47 to-0,34]). The results were generated with high statistical significance (Z=11,82; p< 0, 00001) and low heterogeneity- I^2– 39%. This result is consistent across all subgroups: T1D subgroup MD = -0,40[-0,46 to-0,35] p<0000,1, I^2 – 0%; T2D subgroup MD = -0,37[-0,50 to -0,24] p<0,00001, I^2 – 49%; subgroup experienced MD = -0,41[-0,45 to -0,35] p<0,00001, I^2- 0%; subgroup naïve MD = -0,32[-0,51 to -0,13] p<0,00001, I^2- 65%. [16]

The review of Zhang, (2018) based on eighteen trials with a total of 16791 participants reported that the FPG level was lower in the IDeg treatment groups vs IGlar ones (ETD -0,28 mmol/l [0,44 to -0,11] p= 0,001). [20]

Zhou,et al, (2019): the analysis revealed that insulin degludec produced better FPG levels as compared to insulin glargine (weighted mean difference − 5.20 mg/dL [− 7.34, − 3.07] p < 0.00001). [14]

The review of Hui, (2012) showed that the mean reductions in laboratory- reported FPGs were also similar between IDeg and IGlar treatment groups. [22]

The review of Liu, (2018) reported that treatment with IDeg was associated with a statistically significant reduction in FPG levels as compared to treatment with IGlar -MD = -0,41 [-0,54 to -0,28] p< 0,001, with low heterogeneity across studies- I^2- 27%. [15]

3. Discussion

All the included reviews used only primary research papers using quantitative research methods. The quality appraisal included the reliability and validity of research findings, studies' design, protocol violations, biases and methodological rigor. [23] The Critical Appraisal Skills Programme (CASP) Checklist for Randomized Controlled Trial(RCT) was used for the critical evaluation because virtually all studies followed a RCT design.[24] A majority of the selected reviews included trials consisting of patients with Diabetes Type 2, only 4 studies examined patients with Diabetes Type 1. The samples include adult 18+ patients with Diabetes Type 1 and Diabetes Type 2, insulin naïve and experienced groups. The trial's participants were mostly middle-aged patients with no severe diabetes complications, BMI lower than 30 and a long history of diabetes duration (9-23 years). Most reviews included studies with mixed samples (insulin experienced and insulin naïve participants), with only few pure insulin naïve groups. Drawing on consistent evidence the authors identified that insulin degludec demonstrated superiority in terms of glycemic variability, fasting plasma glucose level, overall and nocturnal hypoglycemia variables in both T1D and T2D (insulin-experienced and naïve patients) groups. The superiority of IDeg in body weight gain parameter was identified in one out of four reviews examining this variable. [16]

This article provides an extensive review of the literature on the researched topic. Concerning the validity and quality of the research findings, almost all review, except Woo,(2020) followed a study design of meta-analysis, which is ranked at the top the hierarchy of evidence - based medicine and produces the most valid quantitative evidence on the research topic. [25,26] Meta-analysis provides an opportunity to perform more objective, comprehensive and transparent evaluation of research evidence; to reveal associations that were not detected in the individual study. [27,28,29] In addition to this, the presence of the subgroup analyses facilitates identifying the patient groups who respond to the medical intervention better than others. [27,28] The authors conducted a thorough study selection process excluding those trials clearly demonstrating low quality of the research finding or high risk of bias. As this meta-analysis included randomized controlled trials, which are recognized as a "gold standard" for the experimental interventions, the research findings possess a high internal validity. [30,31,32]

In general, reviews including trials with a high methodological quality were selected for this analysis- baseline characteristics of study participants appeared to be quite similar; study samples were properly matched; withdrawal and incompletion rates were low, the number of study participants excluded during the trial in both experimental and control groups were similar; a sensitivity analysis was conducted in all included studies; in studies with a higher numbers of drop-outs the intention-to-treat analysis was implemented to minimize an attrition bias. [13,33] The average study duration time in most trials exceeded 12 weeks with extensions and prolonged follow-ups. Also, a wash-out periods were organized in studies with crossover designs in order to control the risk of a carryover effect. Concerning a publication bias, the Egger's regression test for a funnel plot asymmetry was performed by the authors which, except one review, did not detected any signs of a possible publication bias. [34,35,36]

However, the reviews included in this analysis possess several limitations. First, the research design of RCT implies a low external validity- the main drawback of the randomized controlled trial design. [32] As RCTs are usually implemented in artificial and ideal environments with high methodological rigor and homogenous samples, it is highly likely that the results may vary in a real-world practice with a more diversity of patients and a lack of supervision from trained specialists. Secondly, with regards to the participants selection, the exclusion criteria removed patients with severe and recurrent hypoglycemia in all reviews. Additionally, most samples included middle-aged participants (45-60 years), participant older than 75 years and younger than 45 years were underrepresented. These facts also restrict the application of the study results to certain patient groups and reduces their generalizability. [29]

Another limitation to consider is that in all reviews that were analyzed only few trials followed a double-blind study design, most reviews included trials with an open-label design and therefore the risk of observer/participant bias cannot be fully excluded. [32] Also, the different concentration of insulin glargine IGlar-300U/ml and IGlar100U/ml used in some trials may affect study results. Thus, other scientists examining the same topic noticed that IGlar 300U/ml demonstrated a significantly slower absorption as compared to insulin glargine 100U/ml concentration, and generally reflected a more even profile, similar to degludec 100U/ml with better glycemic control and longer duration of action. [37,38,39]

Finally, the results of the analysis for the body weight gain and episodes of overall and nocturnal hypoglycemia variables in some reviews including large number of studies showed high heterogeneity. [14,16] However, this heterogeneity can be explained by the difference in defining confirmed hypoglycemia- some studies set the level of 3,1 mmol/l for this measurement and others 3,9 mmol/l. Also, the measurement of blood glucose level differed- some trials used mmol/l and others mg/dL. Additionally, the variety in ethnicity, weight, baseline HbA1c, age group, absence or presence of comorbidities might lead to the heterogeneity of the results. [14,16]

The strengths and weaknesses of the included reviews are as follows:

Russel-Jones, (2015)

Strengths: trials consisted of large multi-national samples (329-1030 participants); all included studies are methodologically sound and followed a randomized controlled trial design which represents the evidence of high-quality according to the hierarchy of the evidence. [32]

Limitations: all seven studies excluded patients with severe, recurrent hypoglycemia and therefore, the rates of recorded hypoglycemia might be lower than in a real clinical practice; the open-label design of all clinical trials included in the review. As different devices were used for injection, masking in that case was not possible. [21]

Madenidou, (2018)

Strengths: the meta-analysis includes a large number of RCT trials (n=38), which increases a statistical power.

Limitations: the analysis of basal insulins' efficacy and safety parameters was limited because the conclusions were based on mostly indirect comparisons. Confidence in findings for glycemic efficacy and hypoglycemia was low due to imprecision, inconsistency and individual-study limitations. The studies with high risk of bias, especially for change in HbA1c and nocturnal hypoglacemia level were included, almost half of eligible studies had some concerns about bias; the definition of any hypoglycemia and dosing regimens varied among studies thus compromising the applicability of study results in clinical practice. [17]

Liu et al, (2018)

Strengths: the review included only high-quality studies following RCT design with a strong internal validity evaluated by the Jadad scale from 3 to five scores.

Limitations: self-reporting of hypoglycemic episodes; some studies followed an open-label design; different definitions of hypoglycemia across American Diabetes Association and European Medicines Agency; a publication bias was detected. [15]

Zhou et al, (2019)

Strengths: a robust methodology, the presence of sensitivity and subgroup analyses; a large number of RCTs and patients with T2D were included in this review.

Limitations: most studies were funded by the manufacturer of degludec - Novo Nordisk and has an open-label design. In addition to these, insulin concentrations (IDeg -100Units/ml, IDeg-200Units/ml, IGlar-100Units/ml, IGlar-300Units/ml), frequency of injections (once daily or three times a week) insulin preparations and intervals between insulin injections led to high between-study heterogeneity. [14]

Zhang et al, (2018)
Strengths: a large number of high-quality trials included (18 trials with a total of 16791 patients), which increases a statistical power; the data was adjusted for multiple baseline factors minimizing a risk of bias.

Limitations: an open-label design; most of the trials were funded by the manufacturers; the definition of hypoglycaemia varied across studies; considerable heterogeneity observed for several outcomes. [20]

Hui, (2012)
Strengths: The long duration of the included trials up to 52 weeks, robust methodology, low dropout rates, presence of intention-to-treat analysis in all trials.

Limitations: open-label design; different dose adjustments and injection timings for IDeg and IGlar; exclusion of patients with comorbidities and severe hypoglycaemia in anamnesis i.e. not close to a real-world clinical practice. [22]

Heller, (2015)
Strengths: extensive trial periods ranging from 26 weeks to 52 weeks; the analysis include all trial periods- maintenance period, core period and trial extension period; a high methodological quality of the included trials.
Limitations: different dose adjustments and administration times; sensitivity analysis was not performed; participants from Begin Flex T1 trial who were in the arm that used forced-flexible regimen were excluded from the core period analysis, some mild statistical flaws in the use of a regression model. [18]

Ratner et al, (2015)
Strengths: pre-planned design and the inclusion of all phase-3 trials comparing directly insulin degludec with insulin glargine. The presence of the sensitivity analyses which demonstrated that baseline characteristics of the population did not influence the estimated rate ratio- the findings can be applied to a wider population.

Limitations: the blinding of investigators and subjects was not possible due to the use of the different devices for the injection; absence of masking, a reporting bias can be suggested in this meta-analysis. [19]

Woo, (2020)
Strengths: data were retrieved from studies and meta-analyses of high quality; studies contain large samples with various types of patients (insulin-naïve, insulin experienced, wide age range; some studies include participants with comorbidities (cardiovascular, chronic kidney diseases), data for both types of diabetesT2D, T1D were analyzed.
Limitations: limitations mostly relate to individual-study limitations such as open-label design and variations in definition of hypoglycaemia across studies. [1]

Magomedova, (2023)
Strengths: high methodological quality of the included studies, high internal validity of the research findings, no publication bias.
Limitations: low external validity due to a RCT study design of the most included trials, risk of observer/participant bias due to absence of masking in most trials; high heterogeneity of the results. [16]

4. Conclusion

In conclusion, a thorough analysis of the retrieved data confirmed superiority of insulin degludec versus insulin glargine in terms of four safety and efficacy variables such as overall and nocturnal hypoglycemia, change in fasting plasma glucose and body weight gain. A considerable difference detected in the number of overall and nocturnal hypoglycemia can bring benefits to the patient groups with severe and recurrent hypoglycemia and therefore a further expansion of research within these groups is recommended. Moreover, those patients who struggle with mild frequent hypoglycemia episodes can benefit from switching their treatment to insulin degludec. According to several reviews included in this study those participants who used basal-bolus regimes experienced more frequent hypoglycemia events as compared to others. The samples including naïve patients and T2D groups using only basal insulins reflected fewer nocturnal and overall episodes of hypoglycemia due to the absence of bolus insulin's effect. This inference is also true for T1D patients, who usually are prescribed with both short and long-acting insulins. [12] Therefore, the use of IDeg is particularly beneficial and relevant to the T1D patient groups and T2D groups using basal-bolus treatment regimes. Also, IDeg can be safely prescribed as an alternative treatment to those T1D and T2D patients switching from first and second-generation basal insulins. [40]

In addition to aforesaid, IDeg treatment produces less hypoglycemia which is accompanied with the reduced FPG levels. This association results in less glycemic variability and facilitates sustaining close to a physiological insulin production and overall reduction of emotional and physiological distress. [41,42]

In general, this article adds scientific value and knowledge for health practitioners and managers considering administration of a basal insulin to patients with T1D and T2D in favour of IDeg. As the cost of IDeg on the market is high, the robust evidence is needed to justify the administration of IDeg for a wider use. [7,11]. The findings of this article can be considered for a use in the real-world clinical practice, and inferences of this research can be applied to T1D and insulin- dependent T2D patients in order to provide a better option for the glycemic control and treatment of this groups. [5]

With regards to weight gain parameter, the prescription of insulin degludec for a diabetes treatment can be particularly relevant in obese and overweight patients with T2D. As insulin therapy is prescribed for a lifetime, and both insulins provoke weight gain, this difference might become larger and more influential. [43] However, further research is recommended including a larger number of studies in order to generate more precise numbers and inferences. Additionally, T1D and T2D insulin naïve patients starting insulin therapy in primary care can benefit from the treatment with IDeg.

To conclude, several suggestions can be made for future research such as:

1 further investigation is recommended in comparison of overall and nocturnal hypoglycemia events between insulin degludec and insulin glargine including direct comparison between IDeg-100U/ml and IGlar-300U/ml.
2 the division of samples with basal-bolus regimes and samples using isolated basal regimes, so that the hypoglycemic effect of bolus insulin would not interfere during the testing of basal insulins. [44] This is particularly relevant for T2D insulin naïve patient groups.
3 the inclusion of older than 65 years patients, people with neural and cardiovascular diabetes complications, patients with BMI more than 30 and those with severe hypoglycemia is recommended for the further investigations on the topic.

List of References

1. Woo V, Berard L, Roscoe R. Understanding the Clinical Profile of Insulin Degludec, the Latest Basal Insulin Approved for Use in Canada: a Narrative Review. 2020; Diabetes Ther, 11: 2539–2553. https://link.springer.com/content/pdf/10.1007/s13300-020-00915-w.pdf Accessed December 15, 2023.
2. World Health Organisation. Diabetes. 2020. Geneva: WHO Press. https://www.who.int/news-room/fact-sheets/detail/diabetes Accessed December 15, 2023.
3. World Health Organisation. WHO reveals leading causes of death and disability worldwide:2000-2019. 2020. Geneva: WHO Press. https://www.who.int/news/item/09-12-2020-who-reveals-leading-causes-of-death-and-disability-worldwide-2000-2019 Accessed December 15, 2023.
4. Syaifuddin M, Anbananthen MKS. Framework: Diabetes management system. *IMPACT-2013;* 2013:112-116. https://0-ieeexplore-ieee-org.serlib0.essex.ac.uk/document/6782099?arnumber=6782099 Accessed December 15, 2023.
5. CINAHL. Better diabetes management could prevent 1 million complications. *Pract. Nurse.* 2016. 46(2): 10-10. https://eds.s.ebscohost.com/eds/detail/detail?vid=23&sid=cfd1dcff-e11e-4527-bfb9-dda0077d3d1e%40redis&bdata=JnNpdGU9ZWRzLWxpdmU%3d#AN=113300202&db=ccm Accessed October 14, 2023.
6. Febo FC, Molinari C, Piatti PM. Hypoglycemia and insulin treatment. *Journal of Endocrinol Investig*. 2011; 34(9): 698-701. https://0-link-springer-com.serlib0.essex.ac.uk/content/pdf/10.1007/BF03345405.pdf Accessed December, 16, 2023.
7. Kalra S. Newer basal insulin analogues: Degludec, Detemir, Glargine. JPMA. 2013; *63(11): 1442-4.* https://jpma.org.pk/article-details/5202?article_id=5202 Accessed December 3, 2023.
8. Edelman SV, Blose JS. The Impact of Nocturnal Hypoglycemia on Clinical and Cost-Related Issues in Patients With Type 1 and Type 2 Diabetes. *The Diabetes Educ*.2014; 40(3):269-279. https://journals.sagepub.com/doi/abs/10.1177/0145721714529608?journalCode=tdea Accessed December 10, 2023
9. Koivikko ML. Changes in cardiac repolarisation during spontaneous nocturnal hypoglycaemia in subjects with type 1 diabetes: a preliminary report. *Acta Diabetol,*2017; *54*(3): 251–256. https://0-link-springer-com.serlib0.essex.ac.uk/article/10.1007/s00592-016-0941-2 Accessed December, 16 2023.
10. Pettus J, Cavaiola TS, Tamborlane WV. (2015) The past, present, and future of basal insulins. *Diab/Metabol Res and Rev*. 2015; 32(6): 478-479. https://onlinelibrary.wiley.com/doi/full/10.1002/dmrr.2763?saml_referrer Accessed October 04, 2023.
11. Standi E & Owen D. New Long-Acting Basal Insulins: Does Benefit Outweigh Cost? *Diabetes Care 2016* 39(2): S172- S179. https://care.diabetesjournals.org/content/39/Supplement_2/S172 Accessed November 24, 2023.
12. Lajara R, Cengiz E, Tanenberg RJ. The role of the new basal insulin analogs in addressing unmet clinical needs in people with type 1 and type 2 diabetes. *Curr Med Res Opin*. 2017; 33(6):1045-1055. https://pubmed.ncbi.nlm.nih.gov/28277867/ Accessed December 04, 2023.
13. Centre for Reviews and Dissemination (CRD) Systematic Reviews. CRD's guidance for undertaking reviews in health care. York: University of York.2009. Available from: https://www.york.ac.uk/crd/guidance/ Accessed December 3, 2023.
14. Zhou W, Tao J, Zhou X et al. Insulin Degludec, a Novel Ultra-Long-Acting Basal Insulin versus Insulin Glargine for the Management of Type 2 Diabetes: A Systematic Review and Meta-Analysis. *Diabetes Ther*. 2011; 10: 835–852. https://link.springer.com/article/10.1007/s13300-019-0624-4#citeas Accessed December 07, 2023.
15. 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. 2018. *Int J Endocrinol*. 2018. https://www.hindawi.com/journals/ije/2018/8726046/ Accessed November 23, 2023.
16. Magomedova A. & Wallymahmed A. The Comparative Analysis of Efficacy and Safety Parameters of Insulin Degludec Versus Insulin Glargine: A Systematic Review and Meta-Analysis (2023) *LJP* 23(12): 1-55. https://journalspress.com/LJMHR_Volume23/The-Comparative-Analysis-of-Efficacy-and-Safety-Parameters-of-Insulin-Degludec-Versus-Insulin-Glargine-A-Systematic-Review-and-

Meta-Analysis-2023.pdf Accessed December 08, 2023.

17. Madenidou AV, Paschos P, Karagiannis T. Comparative Benefits and Harms of Basal Insulin Analogues for Type 2 Diabetes: A Systematic Review and Network Meta-analysis. *Ann Intern Med*. 2018. 7; 169(3): 165-174. https://pubmed.ncbi.nlm.nih.gov/29987326/ Accessed November 27, 2023.
18. Heller S, Mathieu C, Kapur R. A meta-analysis of rate ratios for nocturnal confirmed hypoglycaemia with insulin degludec vs. insulin glargine using different definitions for hypoglycaemia. Diabet Med. 2016; 33(4): 478-87. https://pubmed.ncbi.nlm.nih.gov/26484727/ Accessed December 05, 2023.
19. Ratner RE, Gough SC, Mathieu C, 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 Obes Metab. 2013 ;15(2):175-84. https://pubmed.ncbi.nlm.nih.gov/23130654/ Accessed November 29, 2023.
20. Zhang XW, Zhang XL, Xu B. Comparative safety and efficacy of insulin degludec with insulin glargine in type 2 and type 1 diabetes: a meta-analysis of randomized controlled trials. Acta Diabetol. 2018; 55(5): 429-441. https://link.springer.com/article/10.1007/s00592-018-1107-1 Accessed December 1, 2023.
21. Russel-Jones D, Gall MA, Niemeyer M, et al. Insulin degludec results in lower rates of nocturnal hypoglycaemia and fasting plasma glucose vs. insulin glargine: A meta-analysis of seven clinical trials. *Nutrition, Metabolism and Cardiovascular diseases*. 2015. 25(10): 898-905. https://www.nmcd-journal.com/article/S0939-4753(15)00151-9/fulltext Accessed November 26, 2023.
22. Hui E, Lam SL. In search of the ideal basal insulin: Does the new-generation ultra-long-acting insulin, degludec, provide the answer? *Journal of Diabetes Investigation*.2013; 4(1) :9-41. https://onlinelibrary.wiley.com/doi/10.1111/j.2040-1124.2012.00243.x Accessed December 16, 2023.
23. Ajetunmobi O. *Making Sense of Critical Appraisal. 1st edition*. London: CRC Press. 2002. https://0-www-taylorfrancis-com.serlib0.essex.ac.uk/books/mono/10.1201/9780367807160/making-sense-critical-appraisal-ajetunmobi Accessed November 30, 2023.
24. Critical Appraisal Skills Programme. CASP Randomized Controlled Trial Standard Checklist. 2019. https://casp-uk.net/casp-tools-checklists/ Accessed November 10, 2023.
25. Bruce NG, Pope D. *Quantitative Methods for Health Research: A Practical Interactive Guide to Epidemiology and Statistics, 2nd edition*. John Wiley & Sons Ltd: Chichester. 2017. https://onlinelibrary.wiley.com/doi/book/10.1002/9781118665374 Accessed December 4, 2022.
26. Haig BD. *The Philosophy of Quantitative Methods: Understanding Statistics*. Oxford University Press. 2018. https://0-oxford-universitypressscholarship-com.serlib0.essex.ac.uk/view/10.1093/oso/9780190222055.001.0001/oso-9780190222055 Accessed November 11, 2022.
27. Egger M, Smith JD, Altman DG. *Systematic Reviews In Health Care: Meta-Analysis In Context. 2nd edition*. London: BMJ Publishing Group. 2001. https://onlinelibrary.wiley.com/doi/pdf/10.1002/9780470693926.ch1 Accessed November,15 2023.
28. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997; 315 (7109): 629-34. https://pubmed.ncbi.nlm.nih.gov/9310563/ Accessed December 7, 2023.
29. Littell J, Corcoran J, Pillai V. *Systematic reviews and meta-analysis*. New York: Oxford University Press. 2008. https://0-oxford-universitypressscholarship-com.serlib0.essex.ac.uk/view/10.1093/acprof:oso/9780195326543.001.0001/acprof-9780195326543-chapter-1 Accessed 15 February 2022.
30. Lim CY & In J. Randomization in clinical studies. *Korean J Anesthesiol*. 2019. 72(3): 221-232. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6547231/ Accessed November 26, 2023.
31. Ingham- Bromfield RJP. A nurses' guide to the hierarchy of research designs and evidence. *Australian Journal of Advanced Nursing*. 2016; 33(3): 38-43. https://www.ajan.com.au/archive/Vol33/Issue3/5Broomfield.pdf Accessed November 02, 2023.
32. Saks M. & Allsop J. *Researching Health. 3rd edition*. London: SAGE. 2019. Available from: https://online.vitalsource.com/#/books/9781526471857?context_token=fcac4e60-7306-

0139-47ee-36d50b605d09 Accessed September 28, 2023.

33. Wysham C, Bhargava A, Chaykin L et al. Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 2 Diabetes: The SWITCH 2 Randomized Clinical Trial. JAMA. 2017; 318(1): 45-56. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5817473/ Accessed November 30, 2023
34. Mikolajewicz N. & Komarova S. Meta-Analytic methodology for Basic Research: A Practical Guide. *Front Physiol*. 2019. 10: 203. https://www.frontiersin.org/articles/10.3389/fphys.2019.00203/full Accessed November 11, 2023.
35. Laake P., Benestad H.B. *Research in Medical and Biological Sciences. From Planning and Preparation to Grant Application and Publication.2nd edition*. Academic Press: New York. 2015. https://www.sciencedirect.com/topics/medicine-and-dentistry/funnel-plot Accessed December 20, 2022.
36. Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomized controlled trials. *BMJ*. 2011, 343: d4002. https://www.bmj.com/content/343/bmj.d4002 Accessed December 3, 2023.
37. Velojic-Golubovic, M., Ciric, V., Dimitrijevic, M. *et al*. Clinical Benefit of Insulin Glargine 300 U/mL Among Patients with Type 2 Diabetes Mellitus Previously Uncontrolled on Basal or Premixed Insulin in Serbia: A Prospective, Observational, Single-Arm, Multicenter, Real-World Study. *Diabetes Ther*. 2021,12: 2049–2058. https://link.springer.com/article/10.1007%2Fs13300-021-01074-2#Sec11 Accessed November 29, 2023
38. Rosenstock J, Cheng A, Ritzel R, et al. More Similarities Than Differences Testing Insulin Glargine 300 Units/mL Versus Insulin Degludec 100 Units/mL in Insulin-Naive Type 2 Diabetes: The Randomized Head-to-Head BRIGHT Trial. *Diabetes Care*. 2018; 41(10):2147-2154. https://pubmed.ncbi.nlm.nih.gov/30104294/ Accessed November 8, 2023.
39. Kawaguchi Y, Sawa J, Sakuma N. Efficacy and safety of insulin glargine 300 U/mL vs insulin degludec in patients with type 2 diabetes: A randomized, open-label, cross-over study using continuous glucose monitoring profiles. *J Diab Investig*. 2018; 10(2): 343-351. https://onlinelibrary.wiley.com/doi/full/10.1111/jdi.12884 Accessed November 10, 2023.
40. Robinson, J.D., Neumiller, J.J. & Campbell, R.K. Can a New Ultra-Long-Acting Insulin Analogue Improve Patient Care? Investigating the Potential Role of Insulin Degludec. *Drugs*. 2012. (72): 2319–2325. https://pubmed.ncbi.nlm.nih.gov/23145524/ Accessed December 04, 2023.
41. Gelhorn H, Balantac Z, Shinde S. The Burden of Type 2 Diabetes and the Value of Achieving Near Normoglycemia from the Patient Perspective. *Diabetes Ther*. 2021; 12: 1821–1837. https://link.springer.com/article/10.1007%2Fs13300-021-01054-6#citeas Accessed December 2, 2023.
42. Jansen HJ, Vervoort GMM, de Haan AFJ. Diabetes-Related Distress, Insulin Dose, and Age Contribute to Insulin-Associated Weight Gain in Patients With Type 2 Diabetes: Results of a Prospective Study. *Diabetes Care*. 2014; 37(10): 2710–2717. https://diabetesjournals.org/care/article/37/10/2710/30776/Diabetes-Related-Distress-Insulin-Dose-and-Age Accessed November 24, 2023.
43. Aas AM. Insulin-induced weight gain and cardiovascular events in patients with type 2 diabetes. A report from the DIGAMI 2 study. *Diab Obes & Metabol*. 2009; 11(4): 323-329. https://dom-pubs.onlinelibrary.wiley.com/doi/full/10.1111/j.1463-1326.2008.00964.x Accessed November 25, 2023.
44. Kumar S, Jang HC, Demirağ NG. Efficacy and safety of once-daily insulin degludec/insulin aspart compared with once-daily insulin glargine in participants with Type 2 diabetes: a randomized, treat-to-target study. *Diab Med*. 2017; 34(2): 180-188. https://onlinelibrary.wiley.com/doi/full/10.1111/dme.13125 [Accessed November 29, 2023.