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Comparative efficacy and safety of weekly dulaglutide versus weekly insulin in type 2 diabetes: A network meta-analysis of randomized clinical trials

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ABSTRACT

Background: Advancements in type 2 diabetes mellitus (T2DM) therapy, notably with weekly agents like glucagon-like peptide-1 receptor agonists (GLP-RAs) such as dulaglutide, offer promising outcomes in clinical practice. The emergence of once-weekly insulin adds to this therapeutic arsenal. This research aims to explore and compare the efficacy and safety profiles of these agents in diabetes management, facilitating informed decision-making for optimizing their utilization in clinical practice.

Methods: A systematic search of PubMed, Scopus, Cochrane, and Web of Science databases was conducted. The research protocol was registered at OSF registries (https://osf.io/gd67x). The primary outcome of interest was the change in hemoglobin A1C (HbA1c), with secondary outcomes including the change in fasting plasma glucose, body weight, prevalence of hypoglycemia, and treatment discontinuation due to adverse events. The evaluation of bias risk was conducted utilizing the RoB2 tool developed by the Cochrane Collaboration. Statistical analysis was performed using RStudio version 4.3.2 with the meta package version 7.0–0 and the netmeta package version 2.9–0. Confidence in network meta-analysis estimates was evaluated using the CINeMA (Confidence In Network Meta-Analysis). Heterogeneity was assessed by comparing the magnitude of the common between-study variance (τ2) for each outcome with empirical distributions of heterogeneity variances.

Results: Dulaglutide 1.5 mg (mg) weekly demonstrated superior reduction in hemoglobin A1C (HbA1c) compared to insulin, with a mean difference (MD) of −0.35 (95 % CI: −0.51 to −0.19). Additionally, Dulaglutide 1.5 mg exhibited greater weight loss, with an MD of −3.12 (95 % CI: −3.55 to −2.68). However, it also showed a higher rate of adverse events, with an odds ratio (OR) of 1.40 (95 % CI: 1.12 to 1.75) compared to insulin. Both doses of Dulaglutide (1.5 mg and 0.75 mg) had lower prevalence of hypoglycemia compared to insulin, with ORs of 0.60 (95 % CI: 0.41 to 0.87) and 0.59 (95 % CI: 0.41 to 0.86), respectively. There was no significant difference in treatment discontinuation among the treatment groups.

Conclusion: Dulaglutide, particularly at higher doses, demonstrates superior efficacy in lowering hemoglobin A1C and reducing hypoglycemia risk compared to Icodec insulin in type 2 diabetes management. However, its use is also associated with a higher incidence of adverse events. Clinicians should carefully consider these factors when selecting optimal treatment strategies for patients with type 2 diabetes mellitus.

1. Introduction:

The landscape of type 2 diabetes mellitus (T2DM) management is driven by advancements in therapeutic options and a growing emphasis on personalized care [1,2]. Among the myriad treatment modalities available, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and basal insulin regimens have emerged as pivotal components, offering distinct mechanisms to address the complex pathophysiology of T2DM and achieve glycemic control [3]. Notably, the availability of once-weekly formulations of these agents, such as Dulaglutide and certain basal insulin analogs, such as Icodec represents a significant innovation in treatment delivery [1,2].

The once-weekly dosing regimen of these agents introduces a novel dimension to treatment adherence and patient convenience [4].

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Adherence to medication regimens is a critical determinant of therapeutic success in chronic conditions such as T2DM. Simplifying treatment regimens through less frequent dosing intervals, as offered by once-weekly formulations, has the potential to enhance patient adherence and persistence [5]. However, the relative impact of once-weekly Dulaglutide versus once-weekly basal insulin on treatment adherence, patient satisfaction, and long-term clinical outcomes remains to be elucidated. Understanding these factors is essential for optimizing treatment strategies and improving real-world effectiveness.

There are many clinical trials that compared once weekly insulin to daily basal insulin while other trials compared weekly Dulaglutide daily to basal insulin. No direct comparisons between weekly Dulaglutide and weekly insulin are available in the literature. Network meta-analysis is a novel analytical approach to bridge this knowledge gap.

The comparison between once-weekly Dulaglutide and once-weekly basal insulin presents a compelling avenue to uncover practical differences between these treatments. Firstly, both agents operate on different physiological pathways to achieve glycemic control [1,2]. Dulaglutide stimulates insulin secretion and suppresses glucagon release both in a glucose-dependent manner, thereby reducing hyperglycemia. Gastrointestinal and neuronal effects also contribute to promoting weight loss [6]. Conversely, basal insulin provides a steady level of insulin throughout the day, mimicking endogenous insulin secretion and primarily regulating hepatic glucose production and muscle and adipose glucose uptake: largely targeting fasting hyperglycemia [2]. This fundamental distinction in the mechanism of action suggests the potential for differential effects on glycemic control, weight management, and other metabolic parameters, highlighting the importance of comparative analyses. Furthermore, understanding the comparative effects of agents with these different mechanisms on diabetes related outcomes offers important, real-word, practical insights into how these new medications might be deployed in an ever more complex landscape.

In light of these considerations, we conducted a comprehensive comparison between once-weekly Dulaglutide and once-weekly basal insulin through network meta-analysis (NMA) which represents a significant endeavor with pragmatic implications. By synthesizing evidence from a diverse array of randomized controlled trials (RCTs), NMA enables a robust evaluation of the relative efficacy, safety, and tolerability profiles of these agents. Such analyses can inform clinical decision-making, guideline development, and healthcare policy, ultimately facilitating the delivery of more personalized and effective care to individuals with T2DM.

2. Methods

The protocol for this network meta-analysis was registered in OSF registries (https://osf.io/7xtpy).

2.1. Data sources

We searched PubMed, Scopus, Cochrane, and Web of Science from inception to February 28th, 2024 (Supplement 1).

2.2. Study selection

We included RCTs with a follow-up duration ranging from a minimum of 16 weeks to a maximum of 78 weeks, published in English, enrolling individuals with type 2 diabetes treated with Dulaglutide or weekly insulin (e.g., Icodec) compared with an active comparator of once-daily insulin, reporting change from baseline in hemoglobin A1c (HbA1c). Dulaglutide doses included in the analysis were 0.75 mg once weekly and 1.5 mg once weekly. Extension studies, exploratory analysis, animal studies, and post hoc analysis were excluded. Trials conducted in non-diabetic individuals, or subjects with type 1 diabetes, prediabetes, or gestational diabetes were excluded.

The Primary outcome was the mean difference in HbA1c change from baseline. Secondary outcomes include the mean difference in change from baseline for fasting plasma glucose (FPG), mean difference in change from baseline in body weight (BW), the prevalence of treatment-emergent adverse events (TEAE), the prevalence of hypoglycemic events, and the proportion of patients who stopped treatment due to adverse events. The definition of a hypoglycemic event was heterogeneous across included studies; in the present analysis, we considered the prevalence of hypoglycemic events defined as blood glucose levels <70 mg/dL.

2.3. Data extraction

Mean change from baseline in HbA1c was extracted from each RCT as the primary outcome. Mean changes from baseline in FPG, BW, prevalence of TEAE, and hypoglycemic events were collected. Additionally, data regarding the proportion of participants who stopped treatment due to side effects were collected.

In our study, we estimated the standard error (SE) of the mean using the formula: $SE = (CI\_width)/(2 \times z\_value)$, where CI_width represents the width of the confidence interval and z_value corresponds to the z-score associated with the desired level of confidence. This method allowed us to approximate the SE when only the conference interval (CI) and mean of the data were available, facilitating further statistical analyses and interpretation of our findings [7].

2.4. Risk of bias assessment

The evaluation of bias risk was conducted utilizing the RoB2 tool developed by the Cochrane Collaboration evaluating the following domains: randomization process; deviations from intended intervention; missing outcome data; measurement of the outcome; selection of the reported result; overall bias with each domain was deemed low, with some concerns.

2.5. Statistical analysis

We performed frequentist random effects network meta-analysis [8], calculating mean differences (MDs) and 95 % confidence intervals (CIs) for change in HbA1c, FPG, BW, and odds ratios (ORs) and 95 % CIs for the risk of TEAE, hypoglycemic events, and treatment discontinuation due to adverse events.

Pairwise meta-analyses were conducted for direct comparisons. The transitivity assumption that a network meta-analysis approach could be appropriate was assessed by comparing the distribution of potential effect modifiers across treatment comparisons (sample size, study duration, BMI, duration of diabetes, age, baseline HbA1c). We assessed heterogeneity by comparing the magnitude of the common between-study variance ($\tau 2$) for each outcome with empirical distributions of heterogeneity variances [9]. We performed sensitivity analysis to evaluate the robustness of the results involving the trials with low risk of bias. An exploratory analysis of adverse events (serious adverse events, any adverse event, nausea, vomiting, diarrhea) was performed.

All analyses were performed using RStudio 4.3.2 (2023-10-31) and R packages meta version 7.0–0 and netmeta version 2.9–0. We assessed confidence in network meta-analysis estimates using the CINeMA (Confidence In Network Meta-Analysis) [10] framework and online application.

3. Results

3.1. Study characteristics

A total of 8 trials [11–18], were included in the systematic review and network meta-analysis (Fig. 1). Four studies evaluated the efficacy and safety of weekly Dulaglutide in comparison to once-daily basal insulin, four studies evaluated the efficacy and safety of once-weekly

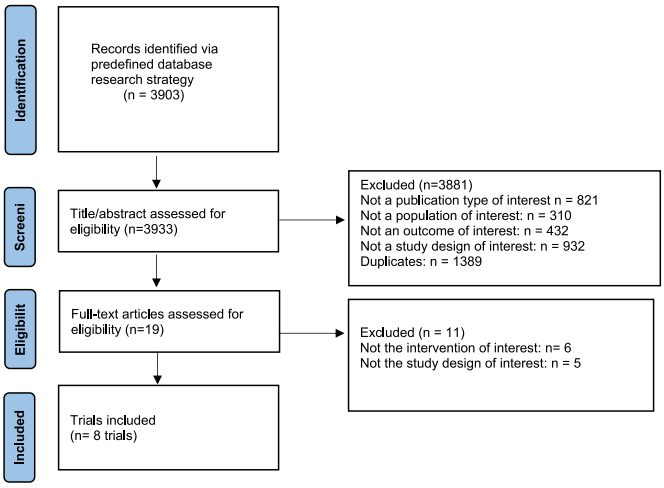

Fig. 1. PRISMA flowchart for study selection.

insulin vs once-daily insulin.

The network of trials used in the meta-analysis for evaluating HbA1c, FPG, BW, TEAE, and hypoglycemia is shown in Fig. 2. The characteristics of studies and patients' baseline features are presented in Supplement 2.

The mean age (standard deviation [SD]) in the included studies was 58.9 years (9.7), with 54.2 % male. The mean body mass index (BMI) (SD) was 30.6 kg/m^2 (5.2). The mean HbA1c level (SD) was 8.3 % (0.9). The mean duration of diabetes (SD) was 12.3 years (7.8).

A substantial amount of heterogeneity was detected for HbA1c, FPG, BW, and risk of hypoglycemia; low to moderate heterogeneity was found for risk of any adverse events and treatment discontinuation due to adverse events. Global inconsistency was generally low. Overall risk of bias for the main outcome was deemed low for 6 trials and of some concern for 2 trials (Supplement 3). Comparison-adjusted funnel plots did not suggest the presence of publication bias for HbA1c, hypoglycemia, TEAE, or treatment discontinuation due to adverse events but showed some degree of publication bias for FPG (Supplement 4). Evidence certainty was generally high for each of the main comparisons, with some having moderate certainty. All data from certainty analysis are included in (supplement 6).

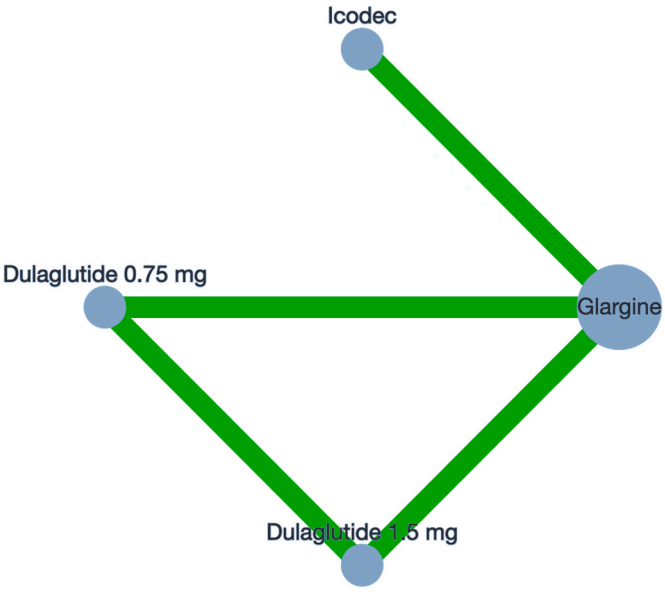

Fig. 2. Meta-analytic networks are utilized to illustrate alterations in HbA1c levels. Within this framework, each circle symbolizes a treatment node, with its size commensurate to the quantity of trials assessing said treatment. Connecting lines between nodes denote direct comparisons between treatments, and their thickness correlates with the number of trials directly comparing the connected treatments.

3.2. HbA1c

A total of 8 studies (4495 patients) were included in the main analysis evaluating the change from baseline in HbA1c. Pairwise meta-analysis results are presented in Table 1. Network meta-analysis results are presented in Fig. 3 a. Dulaglutide 1.5 mg weekly ranked first in terms of HA1c lowering efficacy (MD -0.35, 95 % CI [−0.51; −0.19]). No statistically significant difference was observed between Dulaglutide 0.75 mg (MD -0.14, 95 % CI [−0.29; 0.01]) and Icodec (MD -0.13, 95 % CI [−0.29; 0.02]) in HbA1c and both were not statistically different from active comparator Glargine.

3.3. FPG

Change in FPG was reported in 8 studies (4495 patients). Network meta-analysis results are presented in Fig. 3 b. Pairwise meta-analysis results are presented in Supplement 5. Icodec weekly (MD -0.11, 95 % CI [−0.47; 0.25]) ranked first in terms of FPG lowering efficacy. Both Dulaglutide 0.75 mg weekly (MD 1.12, 95 % CI [0.75; 1.48]) and 1.5 mg weekly (MD 0.71, 95 % CI [0.35; 1.07) showed higher mean FPG compared to Icodec and Glargine.

3.4. BW

A total of 8 studies (4495 patients) were included in the main analysis for change in BW. Network meta-analysis results are presented in Fig. 3 c. Pairwise meta-analysis results are presented in Supplement 5. Dulaglutide 1.5 mg weekly ranked first in terms of weight loss (MD -3.12, 95 % CI [−3.55; −2.68]) followed by Dulaglutide 0.75 mg weekly (MD -2.39, 95 % CI [−2.82; −1.96]). Icodec (MD 0.40, 95 % CI [−0.11; 0.92]) showed weight gain in comparison to Glargine but was not statistically significant.

3.5. Adverse events

3.5.1. Incidence of any adverse events

A total of 8 studies (4495 patients) were included in the main analysis for the prevalence of adverse events. Network meta-analysis results are presented in Fig. 4 a. Pairwise meta-analysis results are presented in Supplement 5. Dulaglutide 1.5 mg (OR 1.40, 95 % CI [1.12; 1.75] showed the highest prevalence of reported any adverse events followed by Dulaglutide 0.75 mg (OR 1.35, 95 % CI [1.08; 1.68]) and Icodec insulin (OR 1.09, 95 % CI [0.86; 1.37]) respectively.

3.5.2. Hypoglycemia

A total of 8 studies (4495 patients) were included in the main analysis for change in hypoglycemia. Network meta-analysis results are presented in Fig. 4 b. Pairwise meta-analysis results are presented in Supplement 5. Icodec showed the highest prevalence of hypoglycemia (OR 0.59, 95 % CI [0.40; 0.85]). Both Dulaglutide 0.75 mg (OR 0.59, 95 % CI [0.40; 0.85]) and Dulaglutide 1.5 mg weekly (OR 0.60, 95 % CI [0.41; 0.87]) had lower statistically significant hypoglycemia event in comparison to insulin (Glargine and Icodec). No statistically significant difference between Glargine and Icodec in the incidence of hypoglycemia.

3.5.3. Treatment discontinuation due to adverse events

A total of 8 studies (4495 patients) were included in the main analysis for the prevalence of treatment discontinuation due to adverse events. There was no statistically significant difference in treatment discontinuation among different treatment groups. Network meta-

Table 1
Change from baseline in HbA1c (mean difference with a 95 % confidence interval).

Dulaglutide 1.5 mg	**-0.22 (-0.30; -0.13)**	.	**-0.37 (-0.46; -0.29)**
-0.22 (-0.30; -0.13)	Dulaglutide 0.75 mg	.	**-0.16 (-0.24; -0.07)**
-0.26 (-0.38; -0.14)	-0.05 (-0.17; 0.07)	Icodec	**-0.11 (-0.20; -0.02)**
-0.37 (-0.46; -0.29)	**-0.16 (-0.24; -0.07)**	**-0.11 (-0.20; -0.02)**	Glargine

The network meta-analysis outcomes are detailed in the lower half, while the upper half displays pairwise meta-analysis results. Primary treatments are listed in order of efficacy ranking. Treatment estimates are articulated as mean differences along with their corresponding 95% confidence intervals, representing the change from baseline in HbA1c, with mean differences below zero indicating a preference for the column-defining treatment in network meta-analysis and the row-defining treatment in pairwise meta-analysis. Significant results are highlighted in bold.

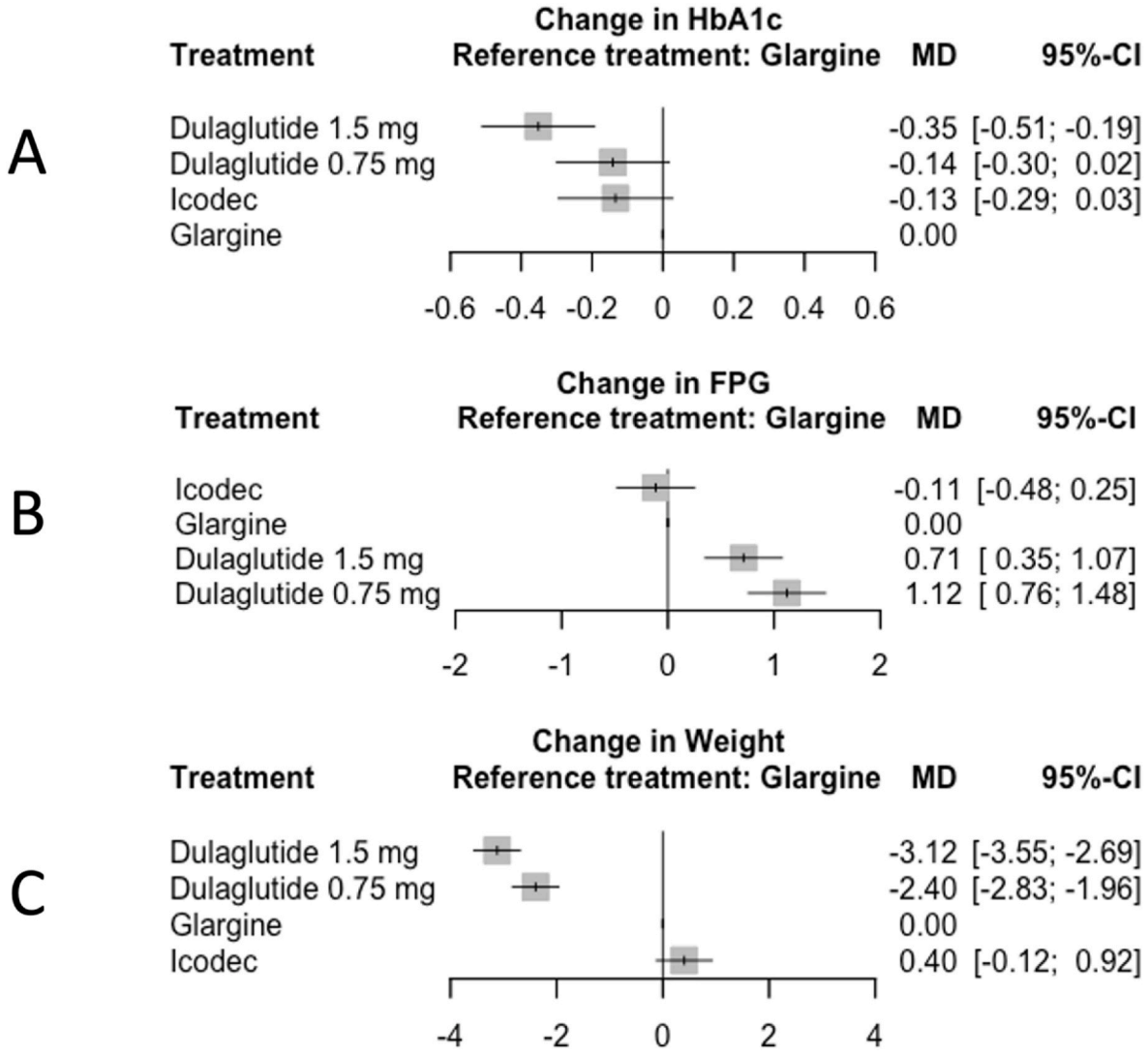

Fig. 3. Presented are the outcomes of a network meta-analysis assessing changes from baseline in HbA1c, FPG, and BW compared to glargine. The effect sizes, represented as mean differences (MD) along with their corresponding 95 % confidence intervals (CI), are arranged according to treatments' effect estimates relative to glargine.

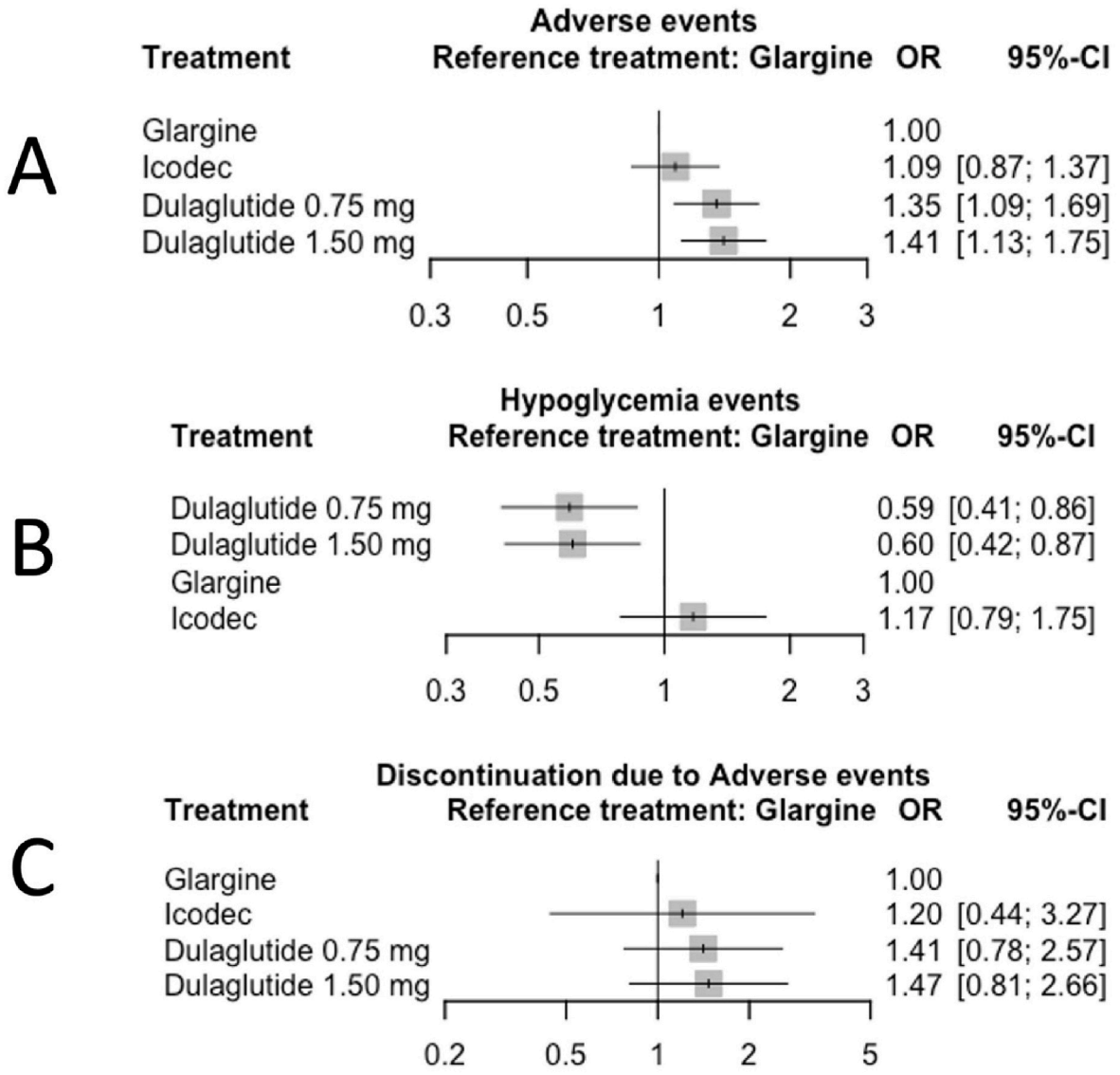

Fig. 4. The network meta-analysis findings for TEAE, hypoglycemia, and treatment discontinuation due to adverse events in comparison to glargine are outlined. Treatments are categorized based on their effect estimates relative to glargine. Effect sizes are presented as odds ratios (OR) alongside their respective 95 % confidence intervals (CI).

analysis results are presented in Fig. 4 c. Pairwise meta-analysis results are presented in Supplement 5.

3.6. Subgroup and sensitivity analyses

Sensitivity analyses including only trials at low risk of bias yielded similar results to those of the main analysis for all prespecified outcomes. The ranking of the analysis for change in HbA1c, FPG, BW, and TEAE, hypoglycemia, and treatment discontinuation was confirmed regardless of baseline BMI and HbA1c.

4. Discussion:

Dulaglutide, a GLP-1 agonist administered weekly, has emerged as a promising treatment option for type 2 diabetes mellitus (T2DM) due to its established cardiovascular benefits and wide availability. Its favorable characteristics, including weight loss promotion and positive effects on cardiometabolic parameters, make it an attractive choice among treatment options [19]. Conversely, weekly insulin, a newcomer to the market, has shown promising efficacy and safety profiles [20].

Our network meta-analysis aims to provide clinicians with comparative insights into the safety and efficacy profiles of these therapeutic modalities, aiding clinical decision-making. This is particularly relevant because this analysis provides a pragmatic insight into the clinical utility of therapeutics with disparate mechanisms of action. Our findings revealed that Dulaglutide 1.5 mg weekly led to significant reductions in HbA1c compared to weekly and daily insulin (Icodec and Glargine). This is true despite observing lower fasting glucose levels in the insulin group, likely due to titration algorithms used in the trials; Dulaglutide's fixed dosing regimen still resulted in notable reductions in HbA1c.

Furthermore, Dulaglutide demonstrated a dose-dependent effect on weight loss, with higher doses associated with more pronounced reductions. However, no statistically significant difference in body weight was observed between Glargine and Icodec.

Regarding adverse events, both weekly insulin Icodec and Glargine exhibited higher incidences of hypoglycemia compared to Dulaglutide, an observation consistent with known mechanisms of action. However, the Dulaglutide cohort demonstrated a higher overall incidence of adverse events, similarly expected given known mechanisms of action in the gastrointestinal tract.

Our study underscores the advantageous glucose-lowering and weight-reducing effects of Dulaglutide, coupled with a favorable safety profile characterized by fewer hypoglycemic events. Although we observed a trend towards increased medication discontinuation in the Dulaglutide group, it did not reach statistical significance compared to weekly and daily insulin regimens.

The advantageous characteristics of Dulaglutide in reducing glucose levels and body weight underscore its significance in the management of diabetes. Nevertheless, the elevated incidence of adverse events and the propensity for treatment discontinuation necessitate a careful evaluation in light of its favorable profile. Literature reports indicate that GLP-RAs are linked with adverse effects, notably during dose escalation [21]. Analyses such as this raise intriguing new therapeutic opportunities, such as a synergistic strategy involving co-administration of once-weekly insulin in order to minimize the need for higher Dulaglutide doses, maximize efficacy and safety, and thereby improve adherence and tolerability of the medication [22]. This approach warrants deeper exploration in subsequent research endeavors.

However, while our study provides valuable insights into the comparative efficacy, safety, and tolerability profiles of once-weekly Dulaglutide and once-weekly basal insulin in the management of type 2 diabetes mellitus (T2DM), it is important to acknowledge certain limitations. Firstly, given that the treatment strategies under investigation have been recently introduced, a comparatively limited number of studies were eligible for inclusion in this analysis, likely contributing to the observed high levels of heterogeneity. Secondly, the duration of treatment and long-term outcomes should be considered. While our analysis provides insights into the short-term effects of Dulaglutide and weekly insulin, longitudinal studies are needed to assess their impact on disease progression, complications, and overall quality of life for individuals with T2DM. Additionally, the included trials varied in terms of study duration, patient demographics, and baseline characteristics, which may introduce heterogeneity and affect the generalizability of our findings. Furthermore, while network meta-analysis allows for indirect comparisons between interventions, it is subject to assumptions such as transitivity and consistency, which may influence the robustness of our results. Moreover, the definition and reporting of adverse events across trials were heterogeneous, which could impact the accuracy of our estimates. Finally, as with any meta-analysis, our study is limited by the quality and availability of the included trials, and the potential for publication bias cannot be entirely ruled out.

5. Conclusion:

In conclusion, our network meta-analysis provides valuable insights into the safety and efficacy profiles of Dulaglutide and weekly insulin as treatment modalities for T2DM. Dulaglutide demonstrates significant reductions in HbA1c and weight loss promotion, alongside a favorable safety profile characterized by fewer hypoglycemic events. However, careful consideration is required due to the observed higher incidence of adverse events and a potential trend towards treatment discontinuation. The exploration of collaborative strategies, such as combining once-weekly insulin with Dulaglutide, holds promise for optimizing treatment outcomes and improving medication adherence and tolerability. Nonetheless, further longitudinal studies are necessary to elucidate the long-term impacts of these therapies on disease progression, complications, and overall quality of life in individuals with T2DM.

Funding

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Ethics approval

Analyses were conducted using data extracted from previously published papers. Patient consent for publication was unnecessary.

Informed consent

Not applicable.

Availability of data and materials

The study contains the original findings, which are detailed in the article/supplementary material. For further details, please reach out to the corresponding author.

CRediT authorship contribution statement

Hazem Ayesh: Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Sajida Suhail:** Writing – review & editing, Software, Formal analysis, Data curation. **Suhail Ayesh:** Writing – review & editing, Writing – original draft, Validation, Conceptualization. **Kevin Niswender:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors of this article declare that they have no competing interests to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metop.2024.100284.

Abbreviations

GLP-RAs	Glucagon-like peptide-1 receptor agonists
T2DM	Type 2 diabetes mellitus
HbA1c	Hemoglobin A1c
BW	Body weight
MD	Mean difference
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and MetaAnalysis
NMA	Network meta-analysis
RCTs	Randomized controlled trials

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CINeMA	Confidence In Network Meta-Analysis
TEAE	Treatment-emergent adverse events
IQR	Interquartile range
SE	Standard error
CI	Confidence interval
SD	Standard deviation

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