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Original Article

Efficacy and Safety of Dulaglutide *versus* Semaglutide in Patients with Type 2 Diabetes and Cardiovascular Diseases: A Systemic Review and Meta-Analysis

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Abstract

Dulaglutide and semaglutide are both glucagon-like peptide-1 (GLP-1) receptor agonists that have been shown to be effective in reducing blood glucose levels in patients with type 2 diabetes. However, it is unclear whether there are any differences in their efficacy and safety in patients with type 2 diabetes and cardiovascular disease (CVD). This meta-analysis aimed to compare the efficacy and safety of dulaglutide and semaglutide in patients with type 2 diabetes and cardiovascular disease (CVD). This systematic review was conducted to identify randomized controlled trials (RCTs) comparing dulaglutide and semaglutide in patients with type 2 diabetes and CVD. We searched PubMed, virtual health library, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov for the last 5 years starting from 2018. Two authors independently screened the titles and abstracts of all identified studies, and full-text articles of eligible studies were retrieved. Data were extracted and analyzed using a random-effects model and quality assessed by ROB2 tool. The primary outcome measure was the reduction in HbA1c levels, while secondary outcomes included major adverse cardiovascular events (MACE) and adverse events. Statistical analysis was performed using standard difference in means (SDM) with 95% confidence intervals (CI). Three RCTs involving a total of 1691 patients were included in the meta-analysis. The analysis showed that both dulaglutide and semaglutide were effective in reducing blood glucose levels in patients with type 2 diabetes and CVD. However, the meta-analysis results indicated that semaglutide may be more effective than dulaglutide in controlling blood sugar levels, as measured by HbA1c. The SDM for HbA1c reduction favored semaglutide, with a pooled SDM of 0.383 (95% CI: 0.243-0.523, $p < 0.001$). In terms of MACE, both drugs were found to reduce the incidence of cardiovascular events, but there was no significant difference between the two treatments. The analysis of adverse events showed that the most common side effects for both drugs were mild to moderate gastrointestinal disturbances, such as nausea and diarrhea. This meta-analysis suggests that both dulaglutide and semaglutide are effective and welltolerated treatment options for patients with type 2 diabetes and CVD. However, semaglutide may provide better glycemic control, as indicated by a significant reduction in HbA1c levels compared to dulaglutide. Further research is needed to validate these findings and to evaluate the long-term cardiovascular and renal effects of these drugs. Clinicians should consider individual patient characteristics and preferences when selecting between dulaglutide and semaglutide for the management of type 2 diabetes and CVD, favoring therapies with high efficacy, tolerability, cost-effectiveness, low hypoglycemic risk, and increasingly, the benefit of CVD risk reduction.

Keywords. *Efficacy and Safety, Dulaglutide, Semaglutide, Type 2 Diabetes.*

Introduction

Several studies have compared the efficacy and safety of these two medications. A head-tohead clinical trial of dulaglutide versus semaglutide showed that semaglutide induced greater reductions in HbA1c and body weight compared to dulaglutide [1-6]. Furthermore, an indirect treatment comparison demonstrated significantly greater reductions in HbA1c with semaglutide versus dulaglutide and a significant reduction in body weight with semaglutide *versus* dulaglutide [1]. Additionally, a study evaluating the long-term cost-effectiveness of once-weekly semaglutide versus dulaglutide in the UK found that semaglutide was considered dominant versus dulaglutide, improving outcomes and reducing costs [7-9]. In terms of weight reduction, semaglutide consistently demonstrated superior outcomes compared to dulaglutide across various trials [1,2,5,6,10,11].

In regards to cardiovascular and renal effects of semaglutide and dulaglutide in patients with type 2 diabetes have been a subject of interest. Studies have shown that both semaglutide and dulaglutide have demonstrated cardiovascular safety and benefits in patients with type 2 diabetes [12,13].

Additionally, a pilot study indicated an improvement in left ventricular global longitudinal strain after a 6-month therapy with both semaglutide and dulaglutide in patients with type 2 diabetes [14].
Furthermore, the effectiveness and tolerability of once-weekly GLP-1 receptor agonists, including (semaglutide and dulaglutide, have been assessed in clinical practice, indicating their potential cardiovascular and renal metabolic benefits A study specifically focusing on the cardiovascular and /or renal metabolic benefits of semaglutide in overweight and obese patients has also been conducted, shedding light on the potential positive effects of semaglutide in these aspects [15].
Further research and comparative studies are necessary to comprehensively evaluate and compare the specific cardiovascular and renal effects, the relative efficacy, safety, and cost-effectiveness of these two medications in the management of type 2 diabetes.

Methods
This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) group guidelines [16]. A systematic and comprehensive search was undertaken of MEDLINE, PubMed, google scholar Cochrane Library databases, searching for studies published since January 2018.
Databases were searched using the following search terms: Semaglutide vs dulaglutide. The full search strategy with all the included search terms is presented in Table 1. The study protocol has been registered in PROSPERO with the following registration number (CRD42023454778). Total included studies 44 for full text screening only 3 studies were chosen for this meta-analysis, the studies included were: Number 49→ Lijima et al / number 140→ PIONEER 10 / manual research→ SUSTAIN 7

Table 1. Searching strategy

Database	Search terms	Number of publication
Pubmed 1 27/11	Semaglutide and dulaglutide	13
Pubmed 2 28/11	Semaglutide vs dulaglutide	4
VHL 1 27/11	Semaglutide vs dulaglutide	15
VHL 2 27/11	Semaglutide and dulaglutide	73
Cochrane lib 1 28/11	Semaglutide and dulaglutide	77
Cochrane lib 2 28/11	Semaglutide vs dulaglutide	30
Google scholar Manual search across this database 28/11	dulaglutide vs semaglutide clinicaltrials	71
	Total pub before duplication removal	283
	Number of dupplicate	134
	Total pub after duplicate removal	149

Inclusion and exclusion criteria
Inclusion criteria
One reviewer reviewed comparative clinical trials that reported difference in the primary or the secondary outcomes comparing semaglutide and dulaglutide, the references list of relevant papers manually, with 44 articles included for initial screening. We included randomized clinical trials of adult patients with diabetes mellitus with or without cardiovascular disease, using PICO research strategy tool [22].
PICO: P or target population = Adult diabetic type 2 with or without cardiovascular disease. I or variables = age/gender/BMI/Blood pressure / cardiovascular disease / Hba1c. C= comparing the effectiveness and safety of dulaglutide vs semaglutide in diabetic patients with cardiovascular disease over the past five years. O= primary outcomes: Hba1c reduction and decrease in cardio renal mortality.
Secondary outcomes: weight reduction, risk of cancer or other side effects

Exclusion criteria:
1. Irrelevant topic 2. Duplicate 3. Case reports 4. Literature review or narrative review 7. Systemic review 8. Full paper not found 9. Abstracts 10. Clinical trials with No results yet has published 11. Observational study.

Data extraction
Mean baseline characteristics and demographic data collected included country of the paper, semaglutide and dulaglutide doses, duration of diabetes, age, HbA1c, body weight, side effects. In addition, (95% CI) changes from baseline to study endpoint for HbA1c, weight, and BP were extracted from each treatment arm but were not imputed if data were missing. Data entered into the statistical model were checked for accuracy against the original references by the 2 Authors.

Table 2. Baseline characteristic table

Name of 1st author	Study arms (drugs in the study)	Country of the study	Number of centers	Type of the study	Study interval duration	Total of patients had ended the study	Duration of followup	Total of pts. on sema.	Total of pts. On dula.
Lijima et al	switching from liraglutide to semaglutide or dulaglutide	Japan (Yokosuka Kyosai Hospital)	1 hospital	open-label, prospective, randomized, parallelgroup controlled trial	26 weeks	30 pts	At the 8th, 16th, and 26th week	15	15
SUSTAIN 7 Pratley et al	semaglutide 0·5 mg, dulaglutide 0·75 mg, semaglutide 1·0 mg, or dulaglutide 1·5 mg subcutaneously.	16 countries Bulgaria, Croatia, Finland, Germany, Greece, Hong Kong, India, Ireland, Latvia, Lithuania, Portugal, Romania, Slovakia, Spain, the UK, and the USA	194 hospitals	open-label, parallel-group, phase 3b trial	40 weeks	1201 Pts	5 weeks and 40 weeks follow up	601	598
PIONEER 10	Semaglutide Oral 14 mg Dulaglutide 0.75 mg SC	Japan	36 sites (clinics and hospitals)	open-label, randomised, active-controlled, phase 3a trial	52 weeks	458 pts	26 weeks and 52 weeks	130 pts	65 pts

Assessment of study quality

Two researchers independently appraised the methodological quality and standard of outcome reporting of the included studies, with any discrepancies resolved through discussion amongst themselves or in consultation with the senior researchers. The reviewers assessed the quality of the randomized clinical trials using The Risk of Bias for randomized clinical trials of exposures ROB2 (17)

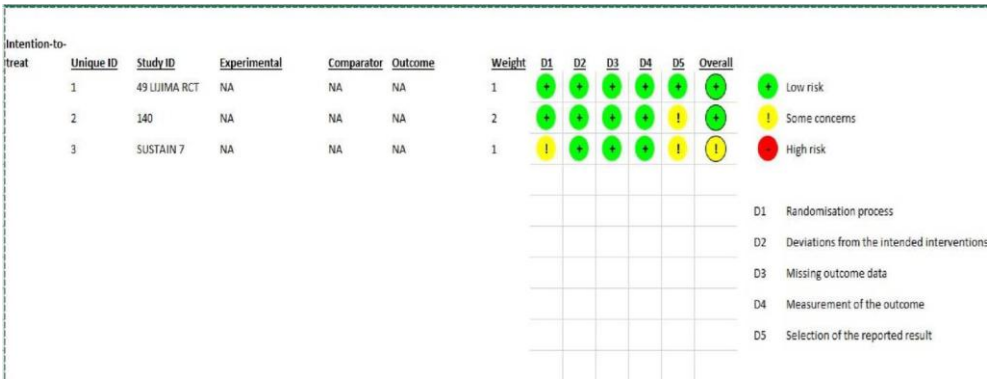

Figure 1. Risk of bias

Statistical analysis

This systematic review and network meta-analysis was conducted in accordance with the recommendations of the Cochrane Library and PRISMA guidelines (18) (19) Data analysis was undertaken Using Statistical software to produce a random-effects meta-analysis for each outcome, providing pooled odds ratios (OR) with 95% confidence intervals (95% CI). The I^2 test was used to evaluate statistical heterogeneity of the included studies, with levels of heterogeneity defined as not important (I^2 = 0% TO 40%), moderate (I^2 = 30% TO 60%), substantial (I = 50% TO 90%), or considerable (I^2 = 75% TO 100%). The X^2 test was used for the same purpose, with a statistical significance level of $p < 0.05$, indicating presence of statistical heterogeneity.

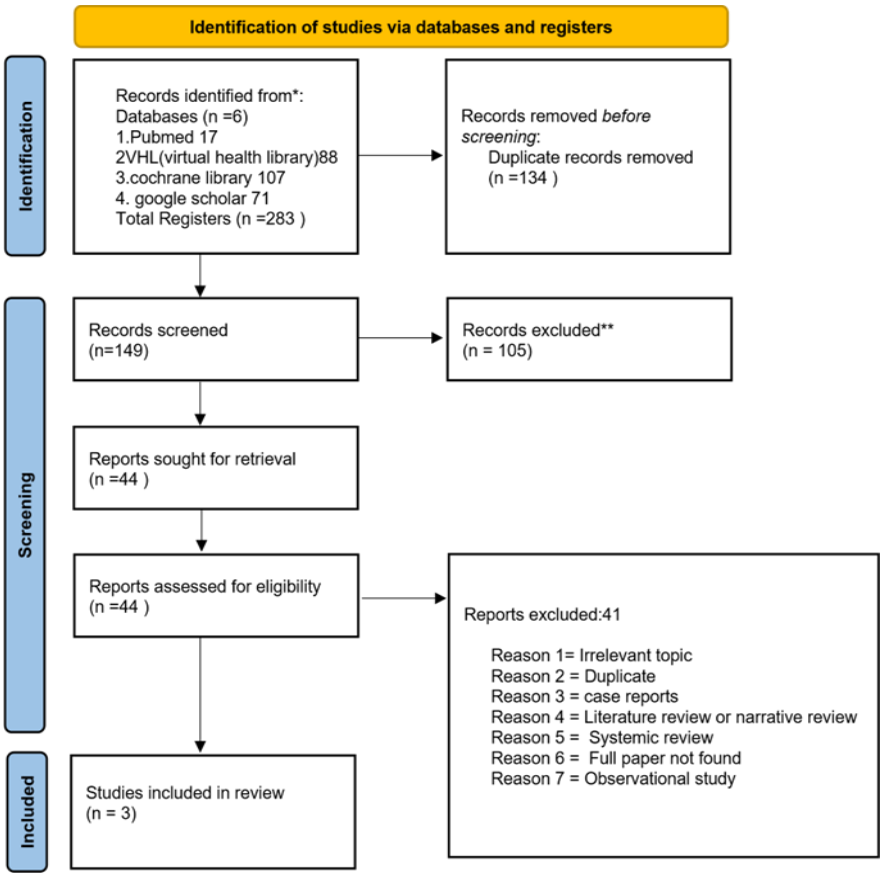

Figure 2. PRISMA 2020 flow diagram.

Results

After the initial database search, 149 potentially relevant publications were identified, of which 44 publications were screened for initial consideration. Of these, only 3 met full eligibility criteria and 1691 patients (Figure 1) (21). The analysis of those available RCTs, irrespective of their principal endpoint, confirms that both semaglutide and dulaglutide reduce the incidence of major cardiovascular events, with dulaglutide, the effect of the drug on MACE in patients without prior events was similar to that observed in those with previous cardiovascular events. in addition, it will reduce cardiovascular events with primary prevention (20). The drug doses included in the current meta-analysis included dulaglutide (0.75mg SC, 1.5mg SC) and semaglutide (0.5mg SC, 1mg SC, 14 mg oral). The meta-analysis focused on the standard difference in means for HbA1c (a measure of blood sugar control) between the two drugs. Here are the results:

Lijima et al: The standard difference in means was 0.800 with a standard error of 0.367. The 95% confidence interval was between 0.080 and 1.520. The Z-value was 2.177 with a p-value of 0.029, indicating a statistically significant difference favoring Semaglutide.
PIONEER 10: The standard difference in means was 0.000 with a standard error of 0.152. The 95% confidence interval was between -0.298 and 0.298. The Z-value was 0.000 with a p-value of 1.000, indicating no statistically significant difference between the two drugs.
SUSTAIN 7: The standard difference in means was 0.476 with a standard error of 0.083. The 95% confidence interval was between 0.314 and 0.639. The Z-value was 5.746 with a p-value of 0.000, indicating a statistically significant difference favoring Semaglutide.
The overall standard difference in means was 0.383 with a standard error of 0.071. The 95% confidence interval was between 0.243 and 0.523. The Z-value was 5.371 with a p-value of 0.000, indicating a statistically significant difference favoring Semaglutide.
In conclusion, the meta-analysis suggests that Semaglutide may be more effective than Dulaglutide in controlling blood sugar levels in type 2 diabetes patients with cardiovascular disease. However, more studies may be needed to confirm these findings.

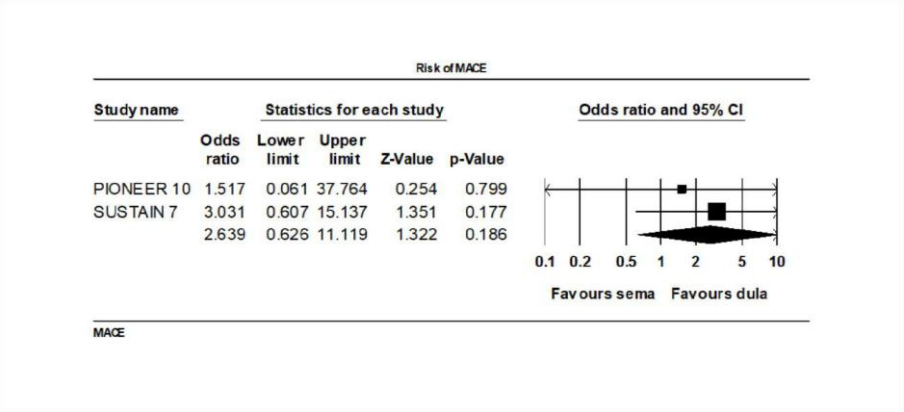

Figure 3. MACE forest plot

The image is showing a statistical forest plot comparing the risk of MACE (Major Adverse Cardiac Events) between two studies, PIONEER 10 and SUSTAIN 7. The plot includes odds ratios and their 95% confidence intervals, as well as p-values for each study.
From the data presented, we can conclude that there isn't a significant difference in the risk of MACE between the two treatments compared (sema and dula). This is indicated by the p-values for both studies being above the typical threshold for significance of 0.05 (PIONEER 10 has a pvalue of 0.799 and SUSTAIN 7 has a p-value of 0.177). The confidence intervals also overlap, which further suggests that the difference is not statistically significant.

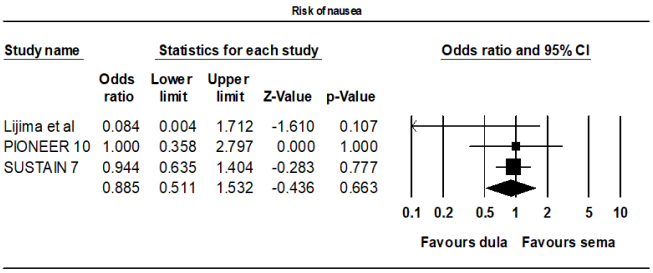

Figure 4. GFR reduction forest plot

The image is showing a statistical forest plot that compares the risk of nausea between two treatments, "dula" and "sema," across three different studies. The plot includes odds ratios and their 95% confidence intervals, as well as p-values for each study.
From the data presented, we can conclude that there is no significant difference in the risk of nausea between the two treatments. This is indicated by the p-values for all three studies being greater than 0.05, which is the conventional threshold for statistical significance. Additionally, the confidence intervals for each study overlap zero, further suggesting that the differences observed are not statistically significant.

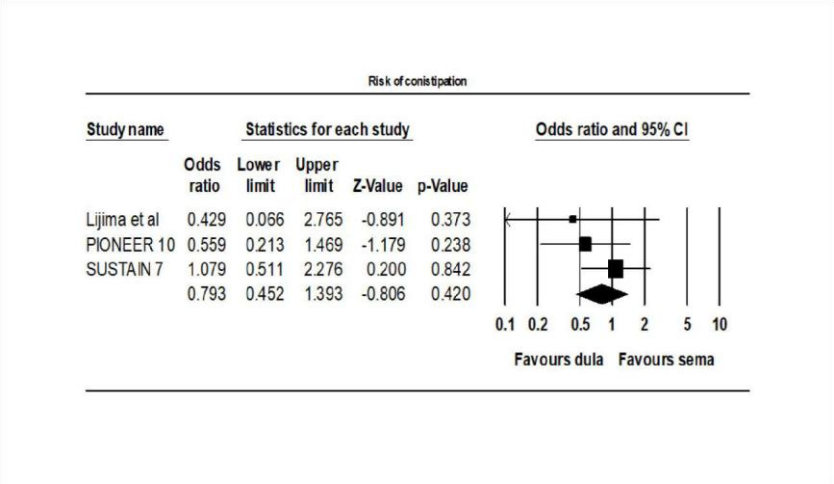

Figure 5. Risk of cancer

The image is showing a statistical forest plot that compares the risk of constipation between two treatments, "dula" and "sema," across three different studies. The plot includes odds ratios and their 95% confidence intervals, as well as p-values for each study.
From the data presented, we can conclude that there is no significant difference in the risk of constipation between the two treatments. This is indicated by the p-values for all three studies being greater than 0.05, which is the conventional threshold for statistical significance. Additionally, the confidence intervals for each study overlap zero, further suggesting that the differences observed are not statistically significant.

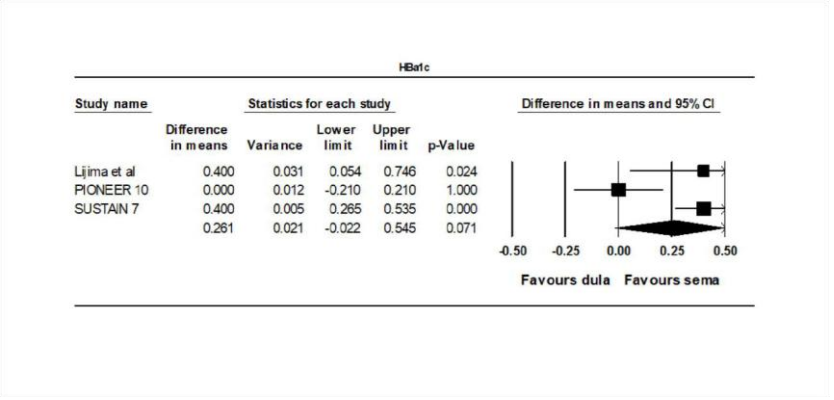

Figure 6. Risk of nausea forest plot

The image is showing a statistical forest plot for a study on HbA1c levels, comparing the effects of two treatments, dula and sema. The plot includes data from three different studies: Lijima et al., PIONEER 10, and SUSTAIN 7. It shows the difference in means, variance, lower and upper limits, and p-values for each study.
From the plot, we can conclude that there is no significant difference between the two treatments as the confidence intervals overlap zero. This suggests that neither treatment is superior to the other in terms of their effect on HbA1c levels based on the data provided. However, it's important to consider the context of the studies, such as the sample sizes and study designs, before making a definitive conclusion.

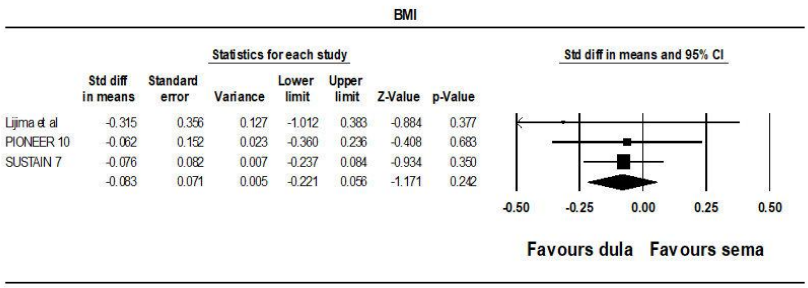

Figure 7. Risk of constipation forest plot

The image is showing a statistical forest plot related to BMI (Body Mass Index). It compares the effects of two variables, dula and sema, across three different studies. The plot shows that all confidence intervals intersect with zero, which suggests that there is no significant difference in BMI between the two variables. This conclusion is based on the standard difference in means values provided for each study, which do not show a consistent trend favoring one variable over the other. It's important to note that statistical significance can be influenced by the sample size and study design,

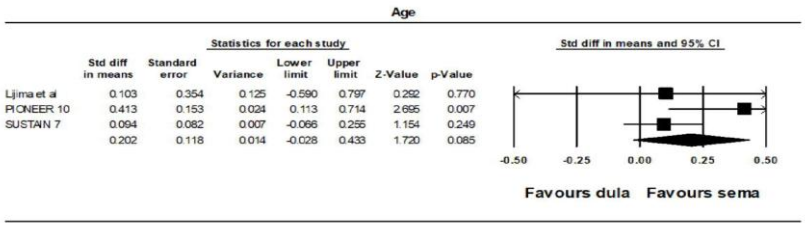

Figure 8. HBA1c forest plot

The image is showing a statistical forest plot comparing the effects of two treatments, dula and sema, on age. It includes a table with statistics for each study (Lijima et al., PIONEER 10, and SUSTAIN 7) and a graph showing the standard difference in means with 95% confidence intervals. The plot ranges from 0.50 to 0.50, with "Favours dula" on one side and "Favours sema" on the other. Each study has a square marker representing its standard difference in means value, with horizontal lines indicating the 95% confidence interval The conclusion drawn from the forest plot image you provided would be that the treatment "dula" seems to have a slight advantage over "sema" for the age group studied. This is indicated by the standard difference in means values leaning towards the "Favours dula" side of the plot. However, the confidence intervals for the studies overlap with zero, suggesting that the differences might not be statistically significant.

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