Efficacy of modern oral antidiabetic drugs:
A sistematc literature review & network meta-analysis

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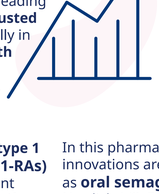
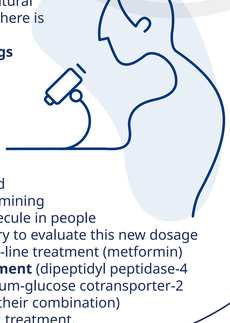
Context

Type 2 diabetes mellitus (DM2) is a **global growing challenge** in public health. This disease was the 17th leading cause of **mortality** and the 23rd leading cause of **Disability - adjusted life years (DALYs)** globally in 1990 ascending to the **9th and 7th** place respectively, by **2019** (1).



Considering DM2 epidemiology, natural history, and treatment objectives, there is a constant **pharmacological development of antidiabetic drugs** that **not only** seek to normalize **glycaemia**, but also to impact the disease **complications and risk factors** (16,17).



Glucagon-like peptide type 1 receptor agonists (GLP1-RAs) are one of the most recent groups of **new antidiabetic therapies** (18–22).

In this pharmacologic group innovations are arising, such as **oral semaglutide** (Novo Nordisk A/S, Bagsværd, Denmark), the first AR-GLP-1 for enteral administration (24).

Given the growing evidence of randomized clinical trials (RCTs) examining the efficacy of this molecule in people with DM2, it is necessary to evaluate this new dosage form **compared** to first-line treatment (metformin) and **second-line treatment** (dipeptidyl peptidase-4 [**DPP4i**] inhibitors, sodium-glucose cotransporter-2 [**SGLT2**] inhibitors and their combination) recommended for DM2 treatment.

Objective

This study aimed to perform a comparative analysis of the efficacy of oral semaglutide versus its comparators: DPP4i, SGLT2i, and their combination (DPP4i/SGLT2i) by means of a systematic review and a network meta-analysis.

Methods

1. Systematic literature review

Sources: MEDLINE, EMBASE and LILACS (Virtual Health Library - VHL)

PICOT strategy

P	Adults (≥ 18 years) with DM2 who had not initiated treatment or did not achieve adequate control (patients with HbA1c levels ≥ 7%) with metformin as monotherapycor combined with other oral antidiabetics (sulfonylureas, thiazolidinediones, DPP4i, SGLT2i, or DPP4i/SGLT2i combined).
I	Daily oral semaglutide
C	Metformin (flexible dose) with/without placebo, SGLT2i (Dapagliflozin, canagliflozin,cor empagliflozin), DPP4i (Vildagliptin, Sitagliptin, Linagliptin, or Saxagliptin), and the DPP4i/SGLT2i combination. Comparators DPP4i, SGLT2i, and the DPP4i/SGLT2i combination had background treatment with metformin.
0	o Proportion of patients achieving HbA1c <7%. o Change in HbA1c from baseline o Change in fasting glycaemia (mg/dL) from baseline o Change in body weight (kg) from baseline
T	Time of outcomes measuring was within the range of 48 to 56 weeks.

Exclusion Criteria

Observational, cross-sectional or longitudinal cohort studies, research protocols, post-hoc analyses, conference abstracts.

2. Network Meta-Analysis (NMA)

Bayesian approach

Was adopted, the inclusion of known parameters or priors with expected probability distribution and estimated plausibility function from a sample in order to estimate a joint or subsequent density function.(27–29).

Four efficacy outcomes

1. Percentage of patients achieving HbA1c <7%, 2. Change in HbA1c from baseline, 3. Change in fasting glycaemia (mg/dL) from baseline, 4. Change in body weight (kg) from baseline.

Markov chain Monte Carlo (MCCM) technique

was used with 20,000 iterations. The relative effect size is presented as the means differences with 95% credibility interval (95% CrI). (27,28,31).

Separate models were run

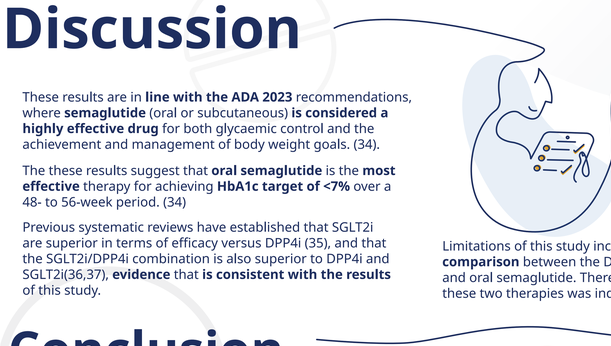
for each of the four outcomes. Estimation for relative effects between treatments was modelled depending on the nature of the type of outcome to be evaluated. (29,30).

SUCRA (Surface Under the Cumulative Ranking)

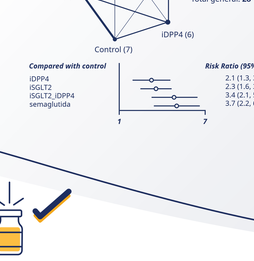
curves were used to assess which treatment of a network was likely to be the most effective. (29).

Results

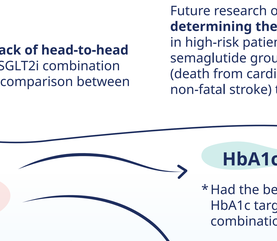
PRISMA diagram. Modified from: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews (32).



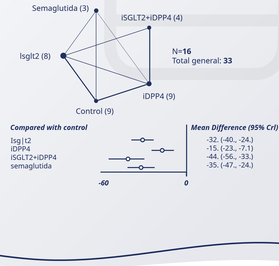
1. Achievement of HbA1c target of <7%.



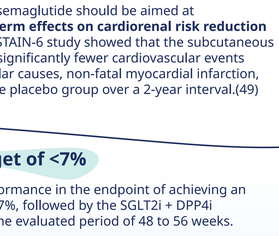
2. HbA1c % change from baseline



3. Change in fasting glycaemia from baseline



4. Change in body weight (kg) from baseline



Discussion

These results are in **line with the ADA 2023** recommendations, where **semaglutide** (oral or subcutaneous) **is considered a highly effective drug** for both glycaemic control and the achievement and management of body weight goals. (34).

The these results suggest that **oral semaglutide** is the **most effective** therapy for achieving **HbA1c target of <7%** over a 48- to 56-week period. (34)

Previous systematic reviews have established that SGLT2i are superior in terms of efficacy versus DPP4i (35), and that the SGLT2i/DPP4i combination is also superior to DPP4i and SGLT2i(36,37), **evidence** that **is consistent with the results** of this study.

Limitations of this study include **lack of head-to-head comparison** between the DPP4i/SGLT2i combination and oral semaglutide. Therefore, comparison between these two therapies was indirect

Future research on oral semaglutide should be aimed at **determining the long-term effects on cardiorenal risk reduction** in high-risk patients. SUSTAIN-6 study showed that the subcutaneous semaglutide group had significantly fewer cardiovascular events (death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke) than the placebo group over a 2-year interval.(49)

Conclusion

Our results suggest that oral semaglutide could be used as an alternative to the SGLT2i + DPP4i combination for the metabolic control of T2D patients. Additionally, oral semaglutide should be considered in overweight or obese T2D patients who require weight reduction.

Oral Semaglutide (14 mg once daily)

HbA1c target of <7%

* Had the best performance in the endpoint of achieving an HbA1c target of <7%, followed by the SGLT2i + DPP4i combination for the evaluated period of 48 to 56 weeks.

* Was superior to the other antidiabetic therapies in the endpoint of body weight reduction for the period evaluated from 48 to 56 weeks. DPP4i had no effect compared to the control group in this outcome.

* And the SGLT2i/DPP4i combination showed comparable efficacy results in the endpoints of change in HbA1c from baseline and change in fasting glucose levels, where SGLT2i/DPP4i combination was slightly superior for the 48- to 56-week period evaluated.

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