A Bayesian Network Meta-Analysis (NMA) for Evaluating the Relative Efficacy of Dual Therapy Combinations of Dapagliflozin and Metformin in Patients with Type 2 Diabetes Mellitus (T2DM)

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Introduction

Type 2 diabetes mellitus (T2DM) is a progressive disease and patients often need therapy escalation over time. Metformin is recommended as the initial oral antidiabetic drug for T2DM, when monotherapy or increasing the therapeutic dose of metformin cannot effectively control blood glucose, a dual therapy combination with other oral antidiabetic agents should be adopted. Dapagliflozin is the first sodium-glucose cotransporter 2(SGLT2) inhibitor which could reduce renal glucose reabsorption, leading to dose-dependent increases in urinary glucose. However, data from head-to-head studies comparing dapagliflozin with other SGLT2 inhibitors add to metformin are not available.

Objectives

This study aims to utilize Bayesian network meta-analysis (NMA) to assess the relative efficacy of dapagliflozin add-on to metformin as a dual therapeutic strategy for managing T2DM. The main emphasis is on comparing the outcomes of this dual therapy approach with both placebo and other SGLT2 inhibitors used in combination with metformin.

Methods

A literature search of Medline and Embase via Ovid databases was performed following the PICOS search framework (Table 1).

Table 1. Systematic Literature Review PICOS Framework

PICOS	Content
Population(P)	Adults (≥18 years) with T2DM
Intervention(I)	SGLT2 and metformin dual therapy regimens
Comparison(C)	Unlimited
Outcome(O)	Unlimited
Study design(S)	Phase III RCT

➢ **Inclusion criteria:**

(1) be published in English;

(2) only patients who showed inadequate response to stable metformin monotherapy at randomization;

(3) patients who received a total metformin dose of at least 1500 mg/d and an SGLT-2 dose of 10mg/d;

(4) reported outcomes of glycated hemoglobin A1c (HbA1c)

➢ **Exclusion criteria:**

(1) Non-phase III RCTs

(2) Trial of a mixed cohort of participants with diabetes (people with type 1 and type 2 DM)

(3) Without metformin in dual therapeutic regimens or fixed-dose combinations

(4) Intervention contains non-oral hypoglycemic agents

(5) Participants under 18 years of age in the trial

(6) Trials using more than two antidiabetic drugs

Data abstraction

Two investigators (Xin Peng and Wan Li) independently abstracted the following information from each trial: (1) citation information; (2) trial ID; (3) study design; (4) sample size; (5) duration of follow-up;(6) baseline characteristics; (7) drug, dose, and schedule used. Endpoints collected included mean change in HbA1c, systolic blood pressure (SBP), and body weight (BW).

Methods

Statistical analysis

A Bayesian NMA with a random effects model has been conducted using R (version 4.2.3) to estimate the mean difference for changes from baseline in HbA1c, BW, and SBP together with the corresponding 95% confidence intervals (CIs). Brooks-Gelman-Rubin diagnosis plot was used to check whether the model has converged. We also ranked the interventions according to their surface under the cumulative ranking (SUCRA), which ranged from 0 to 1.

Results

We included 7 trials[1-7] from 3 types of SGLT-2 inhibitors (dapagliflozin, empagliflozin, and henagliflozin) administered alongside metformin, all of which provided outcomes for a minimum duration of 16 weeks.

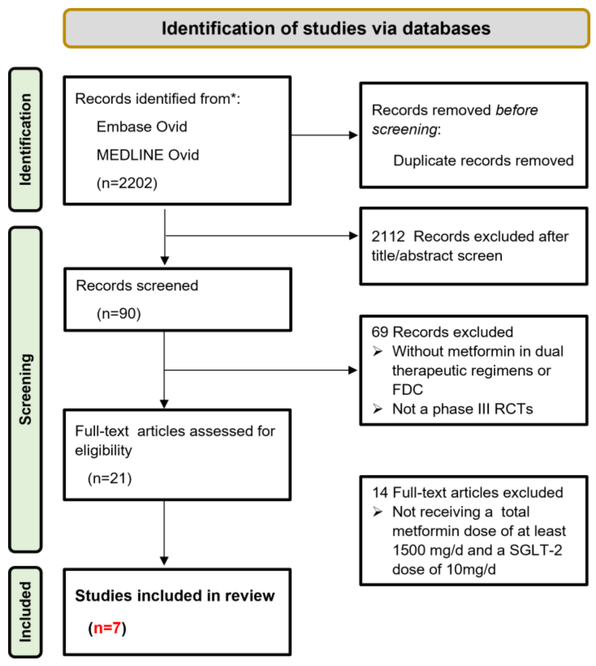

Fig 1. Results of the Literature Search

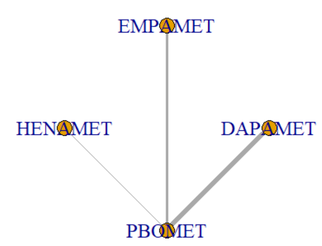

Fig 2. Network Diagram of Randomized Controlled Trials. PBOMET, placebo + metformin; DAPAMET, dapagliflozion + metformin; EMPAMET, empagliflozin + metformin; HENAMET, henagliflozin + metformin.

The mean difference in HbA1c between the three treatment regimens compared to placebo were -0.625% (-0.864, -0.396), -0.579% (-0.874, -0.294), and -0.801% (-1.187, -0.405). All three SGLT-2 inhibitors taken in combination with metformin significantly reduced HbA1c (mean reduction from 0.864 to 1.187), body weight (mean reduction from 1.219 to 2.027), and SBP (mean reduction from 4.217 to 6.498).

Table 2. Network Meta-Analysis Results

Outcome	MET+DAPA	MET+EMPA	MET+HENA
Efficacy outcomes: Mean difference (95% credible interval)			
HbA1c (%)	-0.625 (-0.864, -0.396)	-0.579 (-0.874, -0.294)	-0.801 (-1.187, -0.405)
SBP (mmHg)	-4.697 (-10.6543, -3.061)	-4.217 (-8.6105, -3.286)	-6.498 (-12.8335, -5.082)
Body weight (kg)	-2.027 (-2.516, -1.889)	-1.752 (-2.393, -1.583)	-1.219 (-2.092, -0.981)

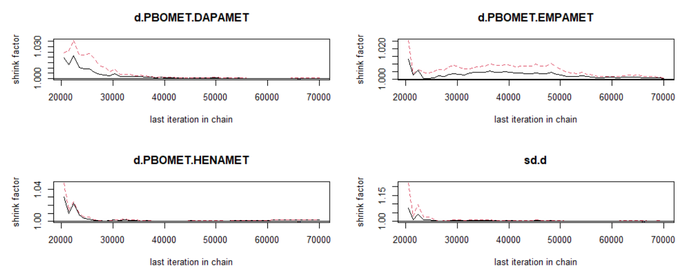

Fig 3. Brooks-Gelman-Rubin diagnosis plot

Results

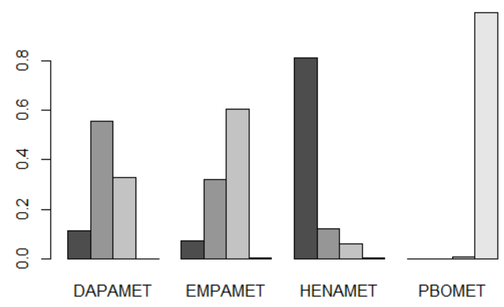

Fig 4. Surface under the cumulative ranking curve (SUCRA)

No statistically significant difference was observed in the efficacy endpoint of HbA1c reduction between dapagliflozin add-on to metformin compared to the other two SGLT-2 and metformin regimens.

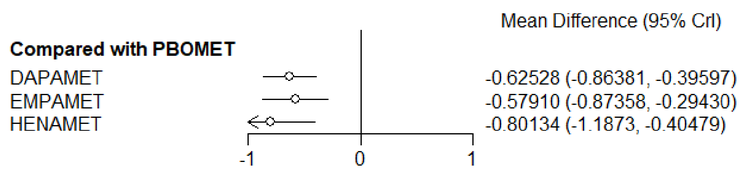

Fig 5. Forest Plot of the Effect of SGLT-2i Add-on to Metformin Compared with Metformin Monotherapy on Change in HbA1c From Baseline.

Conclusion

This study synthesized direct and indirect evidence to establish indirect comparisons of dual therapy combinations of different SGLT2 inhibitors and metformin. The result indicates that the therapeutic impact of dapagliflozin 10mg/d in conjunction with metformin at least 1500mg/d exhibited a considerable efficacy compared to metformin monotherapy; however, compared with empagliflozin and henagliflozin add-on to metformin regimens, the variance in effectiveness was similar.

Limitation

There are some limitations in this analysis that should be noted. First, the literature research was performed in April 2023, literature after this time was not included in the study. Second, only consider the studies published in English. Third, we set serious criteria for the medication's dosage (SGLT-2 at doses of 10mg/d and metformin at least 1500mg/d), the results of this study need to be interpreted with caution.

References

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