ESC HEART FAILURE
ESC Heart Failure 2022; **9**: 1338–1350
Published online 29 January 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13822

ORIGINAL ARTICLE

Can glucose-lowering medications improve outcomes in non-diabetic heart failure patients? A Bayesian network meta-analysis

Trevor Yeong[1], Aaron Shengting Mai[1], Oliver Z.H. Lim[1], Cheng Han Ng[1]*, Yip Han Chin[1], Phoebe Tay[1], Chaoxing Lin[1], Mark Muthiah[1,2], Chin Meng Khoo[3], Mayank Dalakoti[4], Poay-Huan Loh[1,4], Mark Chan[1,4], Tiong-Cheng Yeo[1,4], Roger Foo[1,4], Raymond Wong[1,4], Nicholas W.S. Chew[4]* and Weiqin Lin[1,4]

[1]*Yong Loo Lin School of Medicine, National University of Singapore, 10 Medical Dr, 117597, Singapore;* [2]*Division of Gastroenterology and Hepatology, Department of Medicine, National University Hospital, Singapore;* [3]*Division of Endocrinology, Department of Medicine, National University Hospital, Singapore; and* [4]*Department of Cardiology, National University Heart Centre, Tower Block Level 9, 1E Kent Ridge Road, 119228, Singapore*

Abstract

Aims The cardioprotective effects of glucose-lowering medications in diabetic patients with heart failure (HF) are well known. Several large randomized controlled trials (RCTs) have recently suggested that the cardioprotective effects of glucose-lowering medications extend to HF patients regardless of diabetic status. The aim of this study was to conduct a Bayesian network meta-analysis to evaluate the impact of various glucose-lowering medications on the outcomes of non-diabetic HF patients.

Methods and results Medline and Embase were searched for RCTs investigating the use of glucose-lowering medications in non-diabetic HF patients in August 2021. Studies were included in accordance with the inclusion and exclusion criteria, and data were extracted with a pre-defined datasheet. Primary outcomes include serum N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels, left ventricular ejection fraction (LVEF), and maximal oxygen consumption (PVO_2). A Bayesian network meta-analysis was performed to compare the effectiveness of different classes of glucose-lowering medications in improving HF outcomes. Risk-of-bias was assessed using Cochrane Risk-of-Bias tool 2.0 for randomized trials (ROB2). Seven RCTs involving 2897 patients were included. Sodium-glucose transporter 2 inhibitor (SGLT2i) was the most favourable in lowering NT-proBNP, with the significant reduction in NT-proBNP when compared with glucagon-like peptide-1 receptor agonists (GLP1-RA) [mean differences (MD): −229.59 pg/mL, 95%-credible intervals (95%-CrI): −238.31 to −220.91], metformin (MD: −237.15 pg/mL, 95%-CrI: −256.19 to −218.14), and placebo (MD: −228.00 pg/mL, 95%-CrI: −233.99 to −221.99). SGLT2i was more effective in improving LVEF for HF with reduced ejection fraction patients relative to GLP1-RA (MD: 8.09%, 95%-CrI: 6.30 to 9.88) and placebo (MD: 6.10%, 95%-CrI: 4.37 to 7.84). SGLT2i and GLP1-RA were more favourable to placebo in improving PVO_2, with significant increase of PVO_2 at a MD of 1.60 mL/kg/min (95%-CrI: 0.63 to 2.57) and 0.86 mL/kg/min (95%-CrI: 0.66 to 1.06), respectively. All three drugs had comparable safety profiles when compared with placebo.

Conclusions This Bayesian network meta-analysis demonstrated that SGLT2i, when compared with GLP1-RA and metformin, was superior in improving LVEF in HF with reduced ejection fraction patients, as well as improving PVO_2 and NT-proBNP in non-diabetic HF patients. Further large-scale prospective studies are needed to confirm these preliminary findings.

Keywords Heart failure; Sodium-glucose cotransporter 2 inhibitors; Glucagon-like peptide 1 receptor agonists; Metformin

Received: 7 October 2021; Revised: 11 January 2022; Accepted: 16 January 2022
**Correspondence to: Nicholas Chew, Department of Cardiology, National University Heart Centre, Tower Block Level 9, 1E Kent Ridge Road, Singapore 119228. Email: nicholas_ws_chew@nuhs.edu.sg. Cheng Han Ng, Yong Loo Lin School of Medicine, 10 Medical Dr, Singapore 117597. Email: chenhanng@gmail.com*
Trevor Yeong and Aaron Shengting Mai contributed equally as first authors.
Nicholas W. S. Chew and Weiqin Lin supervised the work equally as senior authors.

Introduction

A myriad of evidence has surfaced regarding the potential cardioprotective effects of oral glucose-lowering agents in diabetic patients with heart failure (HF). Particularly, three recent trials have demonstrated the efficacy of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in reducing cardiovascular death and hospitalization in HF patients regardless of diabetic status.[1–3] There exists a multitude of other randomized controlled trials demonstrating the efficacy of SGLT2i in the management of HF in diabetic patients.[4–8] Furthermore, these trials suggested that SGLT2i might be beneficial in non-diabetic patients as well, especially because their cardioprotective effects appear to be independent of blood glucose levels.[4–8] On the other hand, glucagon-like peptide 1 receptor agonist (GLP1-RA) is yet another promising class of medication, with numerous trials supporting their use in lowering the risk of cardiovascular mortality.[9–13] As such, glucose-lowering medications have been shown to be efficacious for improving HF outcomes in diabetic patients, especially in diabetic patients with high risk or established cardiovascular disease.[14,15]

Furthermore, results from multiple meta-analyses have also showed the superiority of glucose-lowering medications over placebo in improving outcomes for diabetic HF patients. GLP1-RA and SGLT2i demonstrated significant cardiovascular benefits,[16,17] while SGLT2i were more superior for improving HF outcomes and reduce hospitalizations for HF.[17–19] The promising results from these meta-analyses, however, cannot be generalized to non-diabetic HF patients as their findings remain confounded by the inclusion of diabetic patients. Much of the focus has been directed towards clinical outcomes such as cardiovascular mortality, hospitalizations, and major adverse cardiac events in diabetic patients with HF.[16,18,19] Hence, this present study sought to evaluate the effects of glucose-lowering medications, namely SGLT2i, GLP1-RA, and metformin, on the HF outcomes of non-diabetic patients with HF.

Methods

Search strategy

This network meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[20] The Medline and Embase databases were accessed on 3 August 2021 and searched for relevant articles. The search strategy involved keywords and MeSH terms synonymous to 'heart failure', 'oral hypoglycemic agent', 'sodium-glucose cotransporter 2 inhibitor', 'glucagon-like peptide 1 receptor agonist', 'dipeptidyl peptidase IV inhibitor', 'sulfonylurea', 'biguanide derivative', 'insulin', 'alpha-glucosidase inhibitor', and 'meglitinide'. A randomized controlled trial filter was applied, and references of related reviews were screened to ensure a comprehensive search. A copy of the search strategy for Medline can be found in Supporting Information, *Table S1*.

Study selection and extraction

Eligibility assessment was carried out by two blinded authors (TY and ASM) independently. The authors screened the titles and abstracts before retrieving and reviewing the full texts. A third independent author (OZHL) was involved in the resolution of disputes. Only randomized controlled trials were considered for inclusion. Observational studies, case–control studies, reviews, meta-analyses, editorials, commentaries, conference abstracts, and non-English language articles were excluded. Studies were included if they (i) were randomized controlled trials that (ii) evaluated HF outcomes (iii) following the use of glucose-lowering medications (iv) in non-diabetic patients. We included studies that examined patients with HF with reduced ejection fraction (HFrEF) and excluded diabetic patients who were identified through patient history and either a positive response to an oral glucose tolerance test or had serum glycated haemoglobin (HbA1c) levels $\geq$ 6.5%. In trials with both diabetic and non-diabetic populations, the studies were included if the baseline characteristics and outcomes were reported separately for both groups of patients. Studies that examined preserved ejection fraction HF (HFpEF) were also included. HFrEF was defined as left ventricular ejection fraction (LVEF) $<$ 50%, and HFpEF was defined as LVEF $\geq$ 50%. The diagnostic criteria for HF for each of the included trials can be found in *Table S2*. The primary study outcomes were changes in serum N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels, LVEF, and maximal oxygen consumption (PVO_2). Changes in LVEF were only evaluated for patients with HFrEF in this study. Studies that evaluated BNP (instead of NT-proBNP) were also included. Data were extracted by two authors (TY and ASM) in an independent and blinded manner. The following variables were extracted: (i) baseline demographics—age, gender, body mass index, and HbA1c levels and (ii) reported HF parameters—changes in NT-proBNP, LVEF, and PVO_2.

Statistical analysis

All analyses were conducted in RStudio (Version 4.0.3). The Bayesian network meta-analysis was performed with the *BUGSnet* package with a fixed-effects model. The outcome measures included only continuous variables, hence mean differences (MD) and 95%-credible intervals (95%-CrI) were used. Treatment groups were defined according to the drug class of glucose-lowering medications used, namely

(i) SLGT2i, (ii) GLP1-RA, (iii) metformin, and (iv) placebo. Analyses were only performed when there were two or more trials available for the outcome studied. We then performed Markov Chain Monte Carlo simulations using vague priors[21] and a generalized linear model with Gaussian family distribution and an identity link function.[22] The analysis was conducted using 10 000 burn-ins, 100 000 iterations, and 1000 adaptations. The trace and density plots were used to assess for model convergence and consistency. The deviance information criterion and individual datapoint posterior mean deviance contribution were used to compare goodness-of-fit between the consistency and inconsistency models.[22] The deviance information criterion was also used to select between a fixed-effects or random-effects model.[22] The output of the network analysis was presented as a heat plot, in which a blue cell indicates a positive MD and a yellow cell indicates a negative MD. Publication bias with a funnel plot was not conducted as there were less than 10 studies included in the network analysis.[23]

Risk-of-bias assessment

The revised version of the Cochrane Risk-of-Bias tool for randomized trials (ROB2) was used to evaluate the potential for bias in our included studies.[24] The ROB2 evaluates bias across five dimensions: (i) the randomization process, (ii) deviations from intended interventions, (iii) missing outcome data, (iv) measurement of the outcome, and (v) selection of the reported result. Two independent and blinded authors (TY and ASM) assessed all included studies for risk-of-bias, and disagreements were resolved through discussion with a third independent author.

Results

Summary of included articles

A total of 3303 records were identified in the initial search, and 2841 records were screened following duplicate removal. A full-text review was conducted for 140 articles and 7 randomized controlled trials,[25–31] involving 2897 non-diabetic patients, were included in the final analysis (*Figure 1*). The included studies were conducted in the following countries: Denmark,[25–27] the United States of America,[28,29] Portugal,[30] and the United Kingdom.[31] All studies were placebo controlled. Two of the trials were with SGLT2i[29,31] (2689 subjects, duration from 4–6 months), three with GLP1-RA[25,26,28] (123 subjects, 2–168 days) and two with metformin[27,30] (85 subjects, 3–24 months). There were no SGLT1/2 inhibitors such as sotagliflozin in the analysis. A total of six studies included subjects with HFrEF: of which, three studies[25,28,31] defined HFrEF as LVEF $\leq$ 40%, two[26,27] defined as LVEF $\leq$ 45%, and one[29] defined as LVEF $<$ 50%. Only one study[30] examined the use of metformin in HFpEF patients, which defined HFpEF as LVEF $\geq$ 50%. Five trials each were included in the analysis for NT-proBNP,[25,27,28,30,31] LVEF,[25–29] and peak VO_2.[25,27–30] None of the trials had involved and/or separately reported data for pre-diabetic patients. Risk-of-bias assessment using Cochrane ROB2 is provided in *Figure 2*, and a summary of the included trials is provided in *Table S3*.

Comparison of SGLT2i, GLP1-RA, and metformin with placebo

Compared with placebo, SGLT2i had significantly greater reduction in serum NT-proBNP levels (MD: −228.00 pg/mL, 95%-CrI: −233.99 to −221.99) (*Figure 3*) and significant improvement in LVEF (MD: 6.10%, 95%-CrI: 4.37 to 7.84) (*Figure 4*). Furthermore, SGLT2i significantly increased PVO_2 (MD: 1.60 mL/kg/min, 95%-CrI: 0.63 to 2.57) relative to placebo (*Figure 5*).

GLP1-RA use improved PVO_2 significantly (MD: 0.86 mL/kg/min, 95%-CrI: 0.66 to 1.06) when compared with placebo. However, GLP1-RA and placebo had no significant differences regarding changes in serum NT-proBNP levels (MD: 1.60 pg/mL, 95%-CrI: −4.70 to 7.89). Unexpectedly, GLP1-RA demonstrated an unfavourable change in LVEF when compared with placebo (MD: −1.99%, 95%-CrI: −2.43 to −1.55).

There were no significant differences between metformin and placebo in all four outcomes: NT-proBNP (MD: 9.13 pg/mL, 95%-CrI: −8.94 to 27.22); LVEF (MD: 1.99%; 95%-CrI: −2.39 to 6.37); PVO_2 (MD: 0.95 mL/kg/min, 95%-CrI: −0.12 to 2.02).

Network analysis of SGLT2i, GLP1-RA, and metformin

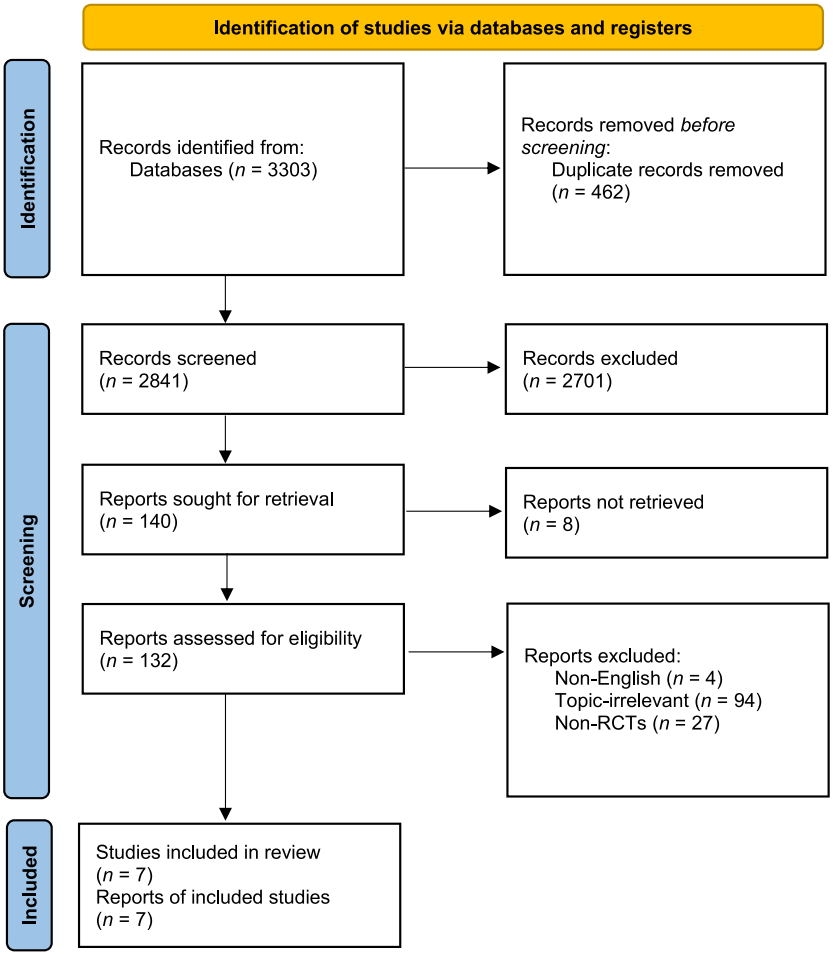
N-terminal prohormone of brain natriuretic peptide

Sodium-glucose transporter 2 inhibitor significantly outperformed the other three treatments groups in terms of lowering serum NT-proBNP levels. When compared with GLP1-RA, SGLT2i resulted in significantly lower serum NT-proBNP levels (MD: −229.59 pg/mL, 95%-CrI: −238.31 to −220.91). SGLT2i also outperformed metformin (MD: −237.15 pg/mL, 95%-CrI: −256.19 to −218.14) and placebo (MD: −228.00 pg/mL, 95%-CrI: −233.99 to −221.99) in lowering NT-proBNP levels. There were no significant differences in the improvement of NT-proBNP levels when comparing the other three treatment groups (*Figure 3*).

Left ventricular ejection fraction

Changes in LVEF were assessed for 243 HFrEF patients. SGLT2i demonstrated significantly improved LVEF in HFrEF patients when compared with GLP1-RA (MD: 8.09%,

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. RCTs, randomized controlled trials.



95%-CrI: 6.30 to 9.88) and placebo (MD: 6.10%, 95%-CrI: 4.37 to 7.84). GLP1-RA, on the other hand, resulted in a significantly lower LVEF when compared with placebo (MD: −1.99%, 95%-CrI: −2.43 to −1.55). No significant differences were found in the remaining pairwise comparisons (*Figure 4*).

PVO_2

When compared with placebo, administration of SGLT2i and GLP1-RA significantly improved PVO_2, with a MD of 1.60 mL/kg/min (95%-CrI: 0.63 to 2.57) and 0.86 mL/kg/min (95%-CrI: 0.66 to 1.06), respectively. We found no other significant differences in the remaining between-treatment comparisons (*Figure 5*).

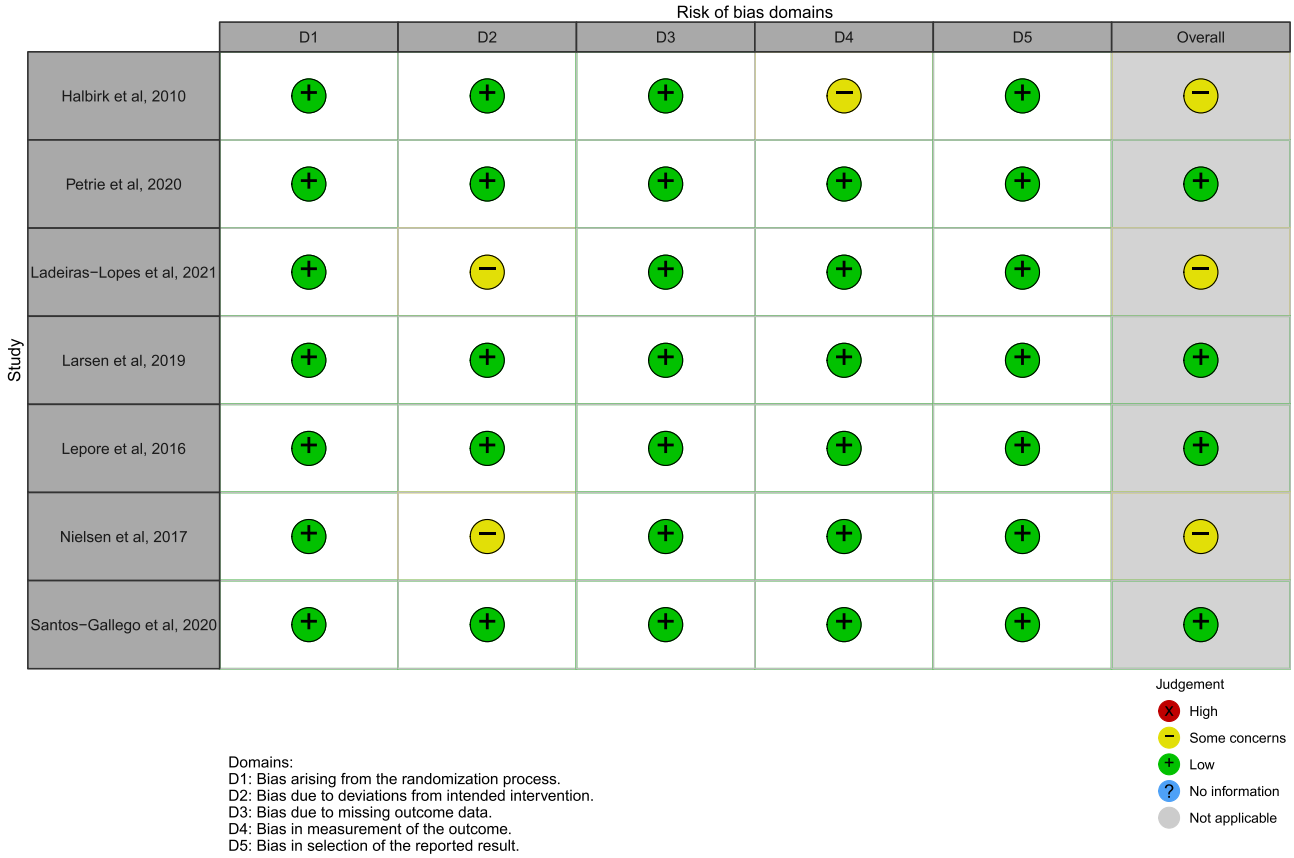
More detailed information such as baseline, follow-up, change in values for each endpoint, and a comparisons summary can be found in *Tables S4–S5* and *Figures S1–S3*.

Safety profile of glucose-lowering medications in non-diabetic patients

Sodium-glucose transporter 2 inhibitor

With the use of SGLT2i in non-diabetic patients, Petrie *et al.*[31] reported no significant differences between the dapagliflozin and placebo groups for volume depletion (7.3% vs. 6.1%, P = 0.40), doubling of serum creatinine (1.7% vs. 2.8%, P = 0.08), kidney adverse events (4.8% vs. 6.0%, P = 0.36), or fractures (2.1% vs. 1.9%, P = 0.58). The same study defined kidney adverse events in a similar fashion to the DAPA-HF trials,[1,32] as a composite outcome comprising of a sustained (i.e. ≥28 days) estimated glomerular filtration rate decline of ≥50%, kidney failure, or all-cause or kidney-related mortality. On the other hand, Santos-Gallego *et al.*[29] observed no hypoglycaemia, urinary or genital infections, or amputations in both the empagliflozin and the placebo groups.

Figure 2 Traffic light plot for the risk-of-bias assessment of included trials.



Glucagon-like peptide 1 receptor agonist

Halbirk *et al.*[25] reported nine episodes of hypoglycaemia across eight patients after the administration of GLP1-RA, with none occurring in the placebo arm. Furthermore, the study reported one patient suffering from severe nausea and two others with mild nausea. On the other hand, Lepore *et al.*[28] reported gastrointestinal side effects, such as nausea and vomiting, to be the most common.

Metformin

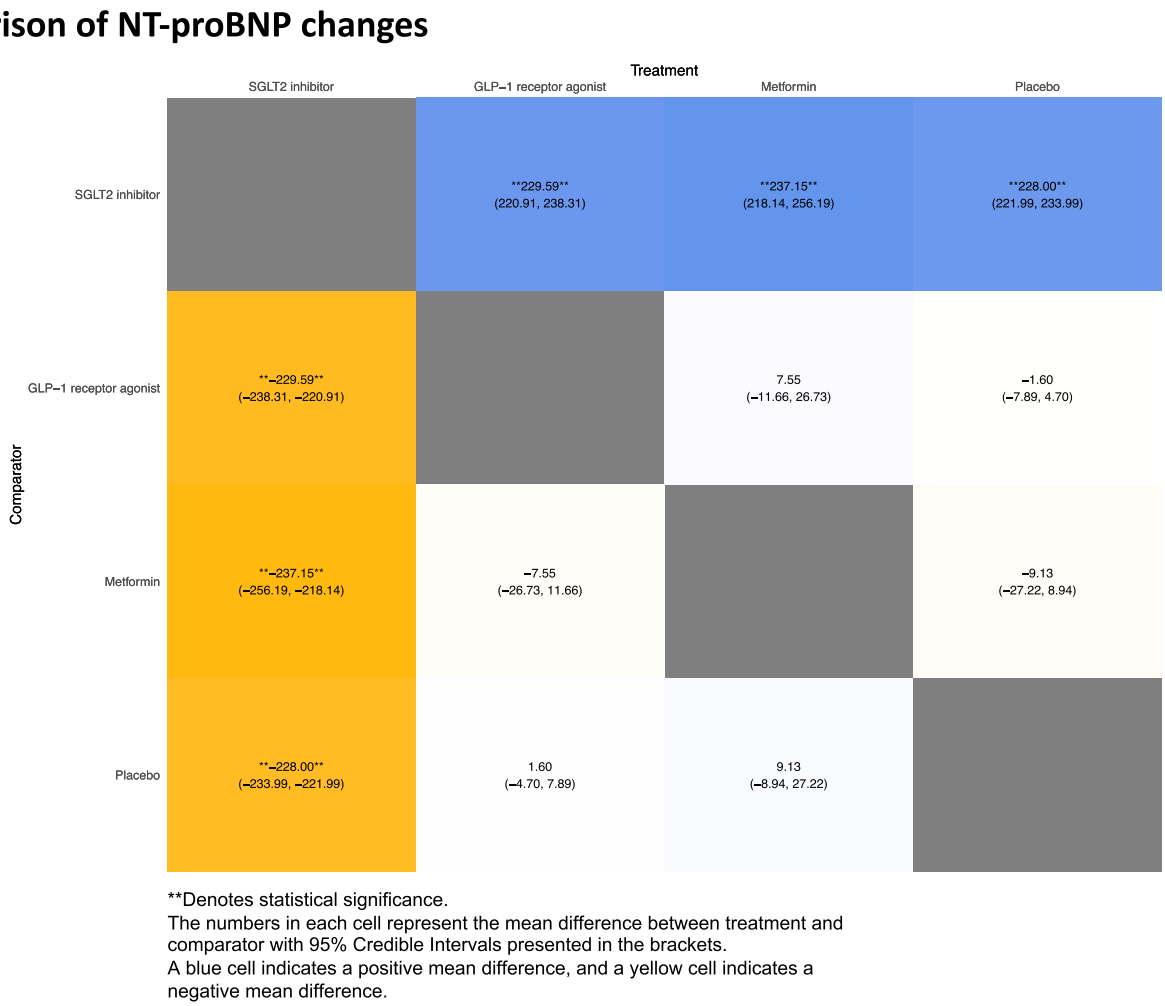
In non-diabetic patients with metformin use, Larsen *et al.*[27] reported two serious cardiac events in the metformin group: ventricular tachycardia was observed in one patient, while another patient experienced orthostatic hypotension. Furthermore, 12 patients in the metformin group and 9 in the placebo experienced gastrointestinal side effects, which typically occurred during dose initiation or up-titration. Ladeiras-Lopez *et al.*[30] reported the discontinuation of metformin in one patient due to gastrointestinal side effects, while another two were maintained on a low dose.

Discussion

While previous meta-analyses on glucose-lowering medications use in HF management have included both diabetic and non-diabetic patients,[16,18,19] the current meta-analysis demonstrates the efficacy and safety of glucose-lowering medications in the management of HF in non-diabetic patients. We were unable to assess clinical outcomes due to a paucity of data stratified in accordance to diabetic status, and hence we used the prognostic indicators of HF as surrogates of HF disease severity and risk for adverse clinical events. Raised serum NT-proBNP levels has been strongly correlated with reduced survival rates,[33,34] while lower LVEF is a potent predictor of all-cause and cardiovascular death for HFrEF.[35,36] Similarly, a diminished PVO_2 is indicative of high cardiovascular risk and increased mortality risk.[37]

The 2021 guidelines from the European Society of Cardiology recommend the use of dapagliflozin and empagliflozin, but not GLP1-RA, for all patients with chronic HFrEF as a Class I recommendation.[38] These guidelines were formulated with regards to the current evidence supporting SGLT2i use with a myriad of trials demonstrating decreased rates of HF

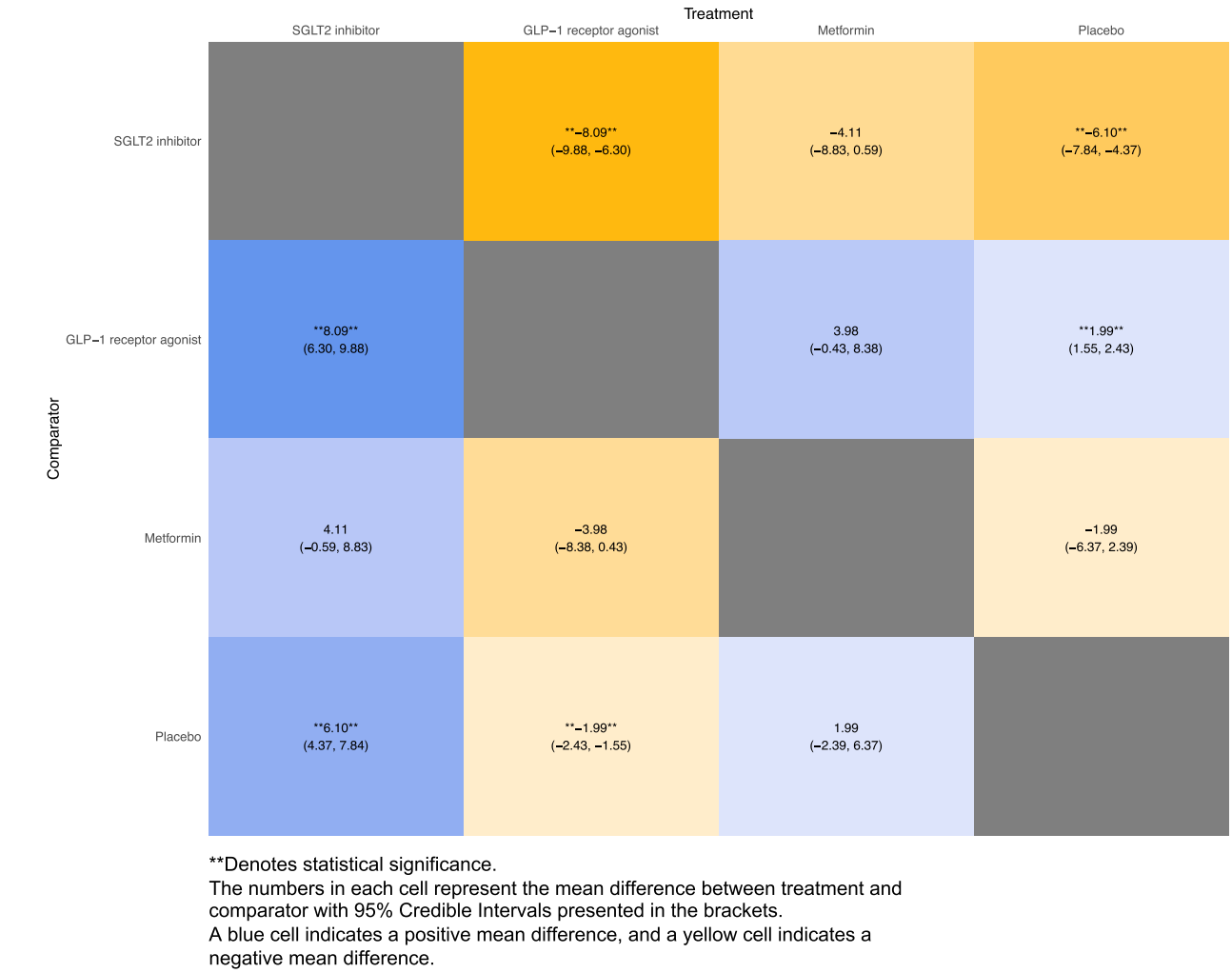
Figure 3 Comparison of changes in serum NT-proBNP levels. League table heatmap. The values in each cell represent the relative treatment effect (95%-CI) of the treatment on the top compared with the treatment on the left. NT-proBNP, N-terminal prohormone of brain natriuretic peptide.



hospitalization and cardiovascular death with SGLT2i use.[1,2,4–8,39] Evidence supporting the use of SGLT2i to reduce the risk of HF hospitalization and cardiovascular death is well established. However, the body of evidence supporting the use of GLP1-RA is less robust, given the unconvincing results from past trials. GLP1-RA had a neutral effect on parameters such as LVEF in one trial, while numerical increase in deaths and HF hospitalizations were observed in another.[40,41] However, with the completion of the recent AMPLITUDE-O trial,[42] an updated meta-analysis[43] found GLP1-RA to significantly reduce the risk of cardiovascular and even renal outcomes in diabetic patients. Whether this efficacy extends to the non-diabetic population remains unclear.

Our analysis found SGLT2i to be the favourable choice for HF in non-diabetic patients with significant improvements in all three parameters (NT-proBNP, LVEF, and PVO_2). These cardiovascular benefits could be mediated through an increased haematocrit, along with changes in cardiac and renal metabolism.[44–47] Volume regulation appears to play a role as well because osmotic diuresis secondary to SGLT2 inhibition causes greater fluid clearance and thereby alleviating cardiac congestion and HF symptoms.[48] These HF parameters are continuous variables, similar to diabetes itself which is a spectrum of glucose intolerance, rather than a binary disease. As such, the beneficial non-glycaemic effects of SGLT2i is likely to span across non-diabetic HF patients as well, as evidenced by the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 trial that demonstrated the superiority of SGLT2i across a broad spectrum of HbA1c.[49] Additionally, a favourable safety profile was found with SGLT2i in non-diabetic patients. The use of SGLT2i generally does not result in an increased risk of hypoglycaemia, acute kidney injury, and diabetic ketoacidosis.[50,51] However, reviews and meta-analyses have found SGLT2i use to be potentially associated with an increased risk of genital mycotic or urinary tract infections,

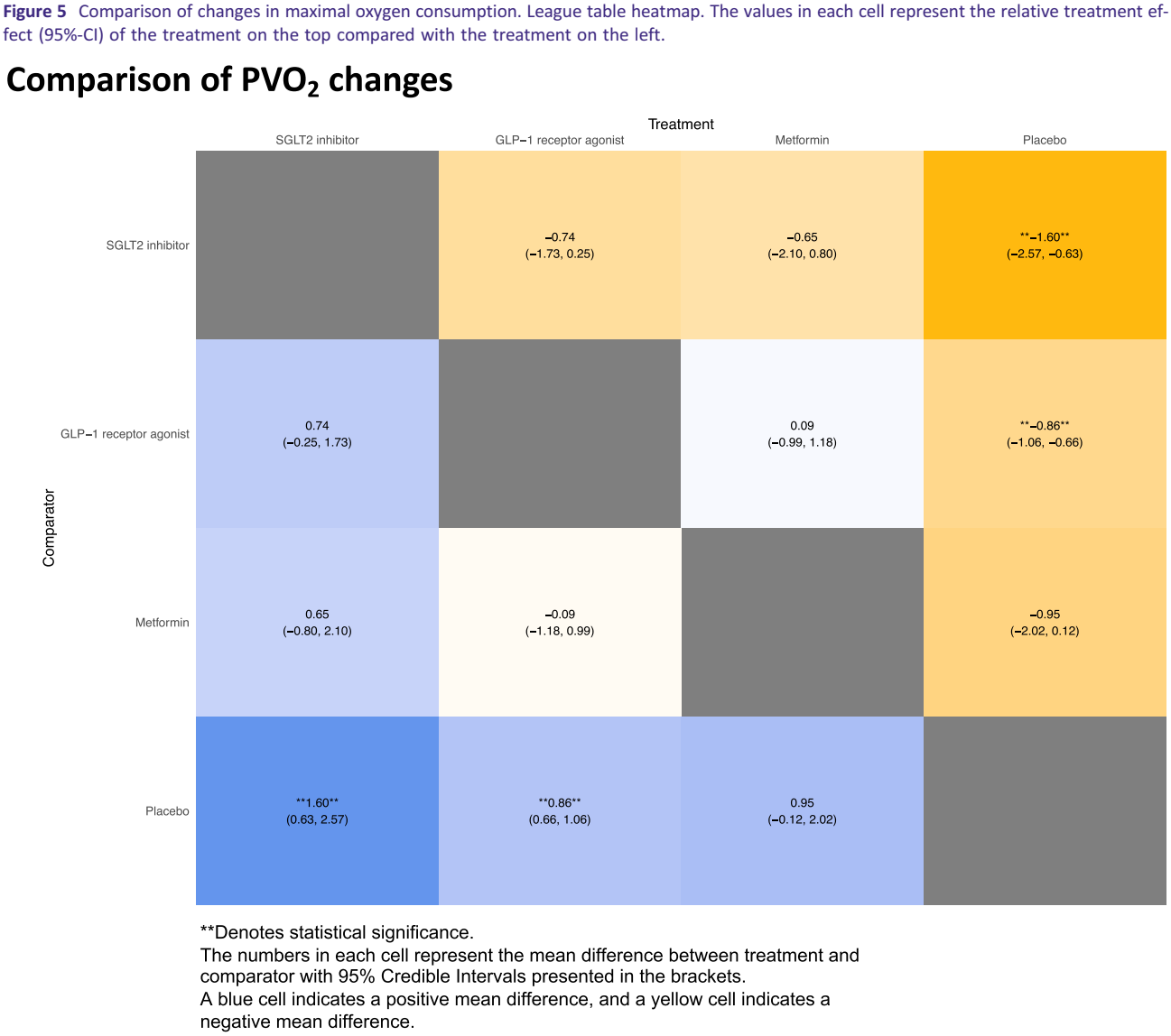
Figure 4 Comparison of changes in left ventricular ejection fraction. League table heatmap. The values in each cell represent the relative treatment effect (95%-CI) of the treatment on the top compared with the treatment on the left. LVEF, left ventricular ejection fraction.



volume depletion, and bone fractures.[50,52–54] Particularly, canagliflozin was observed to increase fracture risk in the Canagliflozin Cardiovascular Assessment Study.[5,55] Fracture incidence was comparable with placebo in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation trial,[56] and the underlying cause of this disagreement remains unknown.

Our analysis revealed PVO_2 to be the only parameter that demonstrated improvement when comparing GLP1-RA to placebo in non-diabetic patients. This is in discordance from evidence from several meta-analyses, which found significant cardioprotective effects of GLP1-RA, such as reduced rates of cardiovascular mortality, stroke, and hospital admissions for HF in diabetic patients.[43,57–59] This suggests that the cardioprotective benefits conferred by GLP1-RA may be associated with its use in diabetic patients only. These benefits are likely mediated through modifications of metabolic parameters such as reductions in blood glucose and lipids.[57–60] This may limit the applicability of GLP1-RA for the management of HF in non-diabetic patients. However, our results should be interpreted with caution, especially with regards to the effects of GLP1-RA in non-diabetic patients, due to the short duration of GLP1-RA administration in our included studies. Nearly, a quarter of the GLP1-RA cohort was exposed to the drug for only 2 days, which is unlikely to have a therapeutic effect on systolic function. In comparison, diabetic patients in a recent meta-analysis of eight trials, which reported reduced HF hospitalizations, were treated with GLP1-RA for an adequate time period ranging from 1.3 to 5.6 years.[43]

Figure 5 Comparison of changes in maximal oxygen consumption. League table heatmap. The values in each cell represent the relative treatment effect (95%-CI) of the treatment on the top compared with the treatment on the left.



Further, long-term studies examining the effects of GLP1-RA in the non-diabetic population are warranted to confirm the current findings.

There is ample evidence supporting the use of SGLT2i and GLP1-RA in patients with concomitant HF and diabetes, because both of these agents reduce the risks of adverse clinical events.[1,2,4–8,39,43,57–59] While the DAPA-HF,[1] EMPEROR-Reduced,[2] and EMPEROR-Preserved[3] trials demonstrated lower risk of cardiovascular death or HF hospitalizations compared with placebo regardless of diabetic status, the data of each individual outcome were not stratified in accordance to diabetic status. In addition, there was a lack of trials on metformin or GLP1-RA in non-diabetic HF patients with clinical outcomes; hence, this present study was unable to perform a network analysis of clinical hard outcomes for all the glucose-lowering medications. Nevertheless, the study reported surrogate prognostic measures of HF severity, which observed significant improvements only with SGLT2i use. Moving forward, further large-scale prospective studies with longer follow-up are needed to examine the impact of glucose-lowering medications on HF outcomes in the non-diabetic cohort. Additionally, another important subgroup of patients to consider would be pre-diabetics. These patients in HF have been shown to be associated with increased risk of adverse clinical outcomes, irrespective of ejection fraction phenotype, and even prior to the diagnosis of diabetes and initiation of glucose-lowering medications. To our knowledge, the trials that included non-diabetic patients did not report the number of pre-diabetics in the

study, and future prospective studies examining the role of glucose-lowering treatment in pre-diabetic HF patients will be the next important step.[61,62]

Strengths and limitations

Our network meta-analysis is the first to examine the efficacy of glucose-lowering medications in improving HF parameters for non-diabetic patients. The findings of this study provide evidence supporting the use of glucose-lowering medications in non-diabetic HF patients and serve to guide physicians in their clinical decisions. This study comprised only of randomized controlled trials to minimize confounding factors and heterogeneity. Nonetheless, this study has its limitations. As is with any meta-analysis, the design and quality of the included studies remain a limiting factor. There were also unavoidable differences in study protocols, inclusion, and exclusion criteria, as well as definitions of outcomes and the clinical presentation of individual patients. Hence, we restricted our study inclusion criteria to only randomized controlled trials. Secondly, our analysis may have limited statistical power because of the small sample size, especially for GLP1-RA and metformin treatment arms, along with only two trials examining SGLT2i. Nevertheless, this would be the largest study to date in evaluating these outcomes between glucose-lowering medications used in non-diabetic HF patients. Further studies with larger populations are needed for greater statistical power. To the best of our knowledge, there were no randomized controlled trials examining the cardiovascular effect of dipeptidyl peptidase-4 inhibitor and sulfonylureas in a non-diabetic cohort; hence, these drug classes were not included in the analysis. Lastly, there may have been differences within drugs of the same drug class, such as for GLP1-RA.[9,40,41,63,64] Undertaking within-group analysis to detect differences between drugs would not be feasible owing to the paucity of data.

Conclusions

This Bayesian network meta-analysis demonstrated the favourable metabolic profile of SGLT2i relative to GLP1-RA and metformin in non-diabetic HF patients. SGLT2i was the most efficacious in increasing LVEF in HFrEF patients, as well as in increasing PVO_2 and decreasing NT-proBNP. The inclusion of larger prospective studies evaluating the improvement of the metabolic profile specifically in non-diabetic patients with glucose-lowering medications is an important next step.

Conflict of interest

All authors declare that they have no conflicts of interest.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Search Strategy for Medline.
Table S2. Diagnostic Criteria for Heart Failure for Each Included Randomised Controlled Trial.
Table S3. Summary of Included Articles.
Table S4. Comparisons summary of each study endpoint.
Table S5. Change in outcomes from baseline to endpoint for outcomes.
Figure S1. Mean and standard deviation of placebo arm at baseline for NT-proBNP.
Figure S2. Mean and standard deviation of placebo arm at baseline for LVEF.
Figure S3. Mean and standard deviation of placebo arm at baseline for peak VO_2.

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