INPLASY PROTOCOL

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None declared.

Scientific Evidence of Sodium-glucose Cotransporter-2 Inhibitors for Heart Failure: An Overview of Systematic Reviews and Meta-Analyses

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Review question / Objective: **The efficacy of sodium-glucose cotransporter-2 inhibitors (SGLT-2is) in the treatment of heart failure with preserved ejection fraction (HFpEF) remains controversial. We aim to provide a systematic overview that summarizes the efficacy and safety of SGLT-2is in the treatment of HFpEF.**
Condition being studied: **In response to the increasing interest in the treatment of heart failure with preserved ejection fraction (HFpEF) with sodium-glucose cotransporter-2 inhibitors (SGLT-2is), researchers conducted systematic reviews and meta-analyses (SRs/MAs) to assess its clinical benefits. The SRs/MAs provide high-quality evidence-based medical findings based on reasonable and correct adherence to relevant research reporting guidelines. Unfortunately, the current lack of evidence and methodological quality evaluation of SRs/MAs associated with SGLT-2is in the treatment of HFpEF affects the strength of the findings to some extent. The overview utilizes a new strategy to integrate multiple SRs/MAs by evaluating their quality and reestimate outcomes, which can provide comprehensive evidence for clinical decision-making and identify critical gaps in evidence use. Therefore, the aim of our study was to summarize existing evidence, to evaluate the quality of previous SRs/MAs related to the effect of SGLT-2is in patients with HFpEF, and to reestimate the effect size through a systematic overview.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 December 2022 and was last updated on 19 December 2022 (registration number INPLASY2022120083).

INTRODUCTION

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summarizes the efficacy and safety of SGLT-2is in the treatment of HFpEF.

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METHODS

Participant or population: Type of participants: patients identified as having heart failure with preserved ejection fraction (HFpEF) based on acknowledged diagnostic criteria, regardless of age, gender, race, nationality or age of onset.

Intervention: The intervention group received sodium-glucose cotransporter-2 inhibitors (SGLT-2is).

Comparator: The control group received placebo or additional conventional treatment.

Study designs to be included: This overview included formally published systematic reviews and meta-analyses (SRs/MAs) based on randomized controlled trials (RCTs).

Eligibility criteria: The inclusion criteria were as follows: (a) type of research: this overview included formally published SRs/MAs based on randomized controlled trials (RCTs) regarding the efficacy of SGLT-2is in the treatment of patients with HFpEF; (b) type of participants: patients identified as having HFpEF based on acknowledged diagnostic criteria, regardless of age, gender, race, nationality or age of onset; (c) type of intervention: the control group received placebo or additional conventional treatment (CT), whereas the intervention group received SGLT-2is; (d) types of outcomes: first or total hospitalization for heart failure (HHF), CVD, all-cause death and the composite of HHF or CVD. On this basis, other outcomes, such as plasma B-type natriuretic peptide (BNP) level, plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) level, 6-min walk distance (6MWD), Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, the ratio of early mitral inflow velocity to mitral annular early diastolic velocity (E/e') and adverse events (hypoglycaemia, diabetic ketoacidosis, renal events, urinary infection, and any unfavourable or unintended sign, symptoms, or disease, including abnormal laboratory values) were acceptable.

Information sources: Eligible studies were identified from PubMed, EMBASE, and the Cochrane Library. To identify other pertinent studies for this overview, we also manually searched the reference lists of included studies as well as the websites for study registration. No language or publication country restriction was applied.

Main outcome(s): First or total hospitalization for heart failure (HHF), cardiovascular death (CVD), all-cause death, and the composite of HHF or CVD. On this basis, other outcomes, such as plasma B-type natriuretic peptide (BNP) level, plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) level, 6-min walk distance (6MWD), Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, the ratio of early mitral inflow velocity to mitral annular early diastolic velocity (E/e') and adverse events

(hypoglycaemia, diabetic ketoacidosis, renal events, urinary infection, and any unfavourable or unintended sign, symptoms, or disease, including abnormal laboratory values) were acceptable.

Quality assessment / Risk of bias analysis: The Cochrane risk of bias criteria.

Strategy of data synthesis: In a short period of time, a large number of SRs/MAs focusing on a specific research hotspot may include many overlapping primary RCTs, which may cause bias in the overall conclusions. The degree of overlap was measured using the validated corrected cover area (CCA) method to assess the potential impact of overlap induced by the inclusion of the same primary RCTs. In accordance with the method described by Pieper et al., the matrix was constructed by taking the primary RCTs as the row and the included SRs/MAs as the column. If the total number of RCTs included in SRs/MAs is taken as "N" (repetition allowed), the total number of RCTs is "r", and the number of included SRs/MAs is "c", then CCA= (N - r)/[(r x c) – r]. A CCA value of 0% to 5% indicates a minor degree of overlap, 6% to 10% indicates a moderate degree of overlap, 11% to 15% indicates a high degree of overlap, and >15% indicates a very high degree of overlap.
Additional excess significance tests were conducted for categorical variable outcomes in the included SRs/MAs using the $\chi 2$ test to assess whether the significance of the combined effect size could have been due to chance or bias. The observed number (O) and expected number (E) of significant RCTs were calculated and compared; the larger the difference between the observed and expected values is, the higher the degree of excess significance bias. Excess significance for a single SR/MA was indicated by $P < 0.10$.
We repooled multiple outcome indicators with inconsistent SR/MA effect sizes (e.g., risk ratio [RR], hazard ratio [HR], odds ratio [OR] or standard mean difference [SMD] where appropriate, the confidence interval [CI] will also be recorded) using data from individual RCTs. The level of significance was set as $P < 0.05$. A fixed effects model was used if there was no evidence of heterogeneity; otherwise, the random effects model was applied. Heterogeneity was considered to be present if the p-value for the Q test was <0.10 and the I2 value was 25% or higher. The evidence for small-study effects was evaluated using Egger's test. In addition, we evaluated the robustness and reliability of the combined results by conducting a sensitivity analysis. All statistical analyses were conducted using R 4.1.1 (http://www.R-project.org, The R Foundation) and Stata 16.0 (StataCorp LLC).

Subgroup analysis: Subgroup analysis will include subgroup analysis of different types of sodium-glucose cotransporter-2 inhibitors, different doses, and duration of administration.

Sensitivity analysis: Sensitivity analysis will be performed to ensure that no single study over-influenced the analysis by excluding each individual study and reanalyzing the overall effect on the remaining studies.

Country(ies) involved: China.

Keywords: overview; sodium-glucose cotransporter-2 inhibitor; heart failure with preserved ejection fraction; meta-analysis as topic; evidence quality assessment.

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