INPLASY PROTOCOL

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Review Stage at time of this submission: **The analysis has been started, search is done, we are in process of drafting the manuscript, all the analysis are almost completed but not published.**

Conflicts of interest:
None declared.

Side effects and treatment initiation barriers of SGLT2 inhibitors in heart failure: A systematic review and meta-analysis

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Review question / Objective: **Is the risk of hypotension, volume depletion and acute kidney injury higher in patients on SGLT2-inhibitors in comparison with placebo?**
Condition being studied: **Our endpoints of interest are hypotension(defined as SBP<100mmHg or <110mmHg with symptoms), volume depletion (one of the follows: hypotension, hypovolemia, dehydration) and acute kidney injury (doubling of serum creatinine).**
Information sources: **Electronic databases (MEDLINE, Embasy), the current ESC Guidelines for Heart failure 2020.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 06 February 2022 and was last updated on 06 February 2022 (registration number INPLASY202220012).

INTRODUCTION

Review question / Objective: **Is the risk of hypotension, volume depletion and acute kidney injury higher in patients on SGLT2-inhibitors in comparison with placebo?**

Rationale: **There are some concerns regarding use of SGLT2-inhibitors in heart failure patients, which result in under treatment of these patients. Some of the main concerns are hypotension, volume depletion and deterioration of kidney function on SGLT2-i. Therefore we aimed to**

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explore the rate and risk of these side-effects by performing a systematic analysis by including the randomized, controller clinical trials in order to provide more objective findings regarding these side effects. Our results should encourage clinicians to use this life-prolonging therapy in appropriate patients.

Condition being studied: Our endpoints of interest are hypotension(defined as SBP<100mmHg or <110mmHg with symptoms), volume depletion (one of the follows: hypotension, hypovolemia, dehydration) and acute kidney injury (doubling of serum creatinine).

METHODS

Search strategy: We used the following keywords and medical subject headings (MeSH) terms : SGLT2 inhibitor OR empaglifozin OR dapaglifozin OR sotaglifozin OR canaglifozin OR ertuglifozin AND heart failure OR left ventricular dysfunction AND randomised controlled trial. The search was performed in MEDLINE and Embasy via OVID@. Furthermore we crosschecked the new Heart Failure guidelines of European Society of Cardiology in order not to miss the eligible study.

Participant or population: Patients with heart failure and reduced ejection fraction (EF<40%), from randomised, controlled clinical trials.

Intervention: Treatment with SGLT2-inhibitor vs. placebo on top of standard medication for heart failure (Betablocker, ACE-I/ARB, Sacubitril/Valsartan, MRA).

Comparator: Placebo group.

Study designs to be included: Randomized, controlled clinical trials.

Eligibility criteria: Randomized, controlled clinical trials with patients with heart failure and reduced ejection fraction (<EF 40%), in which SGLT2-inhibitors were compared with placebo treatment.

Information sources: Electronic databases (MEDLINE, Embasy), the current ESC Guidelines for Heart failure 2020.

Main outcome(s): The main outcome of interest were hypotension, volume depletion and acute kidney injury. We determined the summary risk by pooling the data from the included trials using random-effects model. Summary effect measure was relative risk.

Additional outcome(s): See above.

Data management: After search for eligible studies has been done, we extracted data of interest (study design, primary outcome, duration of follow-up, sample size, included population, rate of hypotension, volume depletion and acute kidney injury) in order to describe the included population and to use them for appropriate synthesis of the data.

Quality assessment / Risk of bias analysis: We used Cochrane tool for assessment of risk of bias. For assessment of publication bias we used Funnel plot (log of RR against SE).

Strategy of data synthesis: We performed a study-level, pairwise meta analysis based on intention-to-treat analysis. We determined the summary risk by pooling the data from the included trials using random-effects model. Summary effect measure was relative risk. The results were visualised with Forest plot. Furthermore, we presented the absolute difference (defined as excess on SGLT2-i or placebo) in incidence for each outcome between treatment and control group using Dot plot. Above that we performed benefit-risk assessment by computing benefit-risk ratio by dividing NNT-H(number needed to treat for harm) /NNT-B (number needed to treat for benefit). Benefit/Risk > 1 indicates a favorable benefit/risk balance. We used programme RevMan and GraphPad Prism for data management. We explored the robusstnes of the results for each outcome by computing fragility index (FI) by applying the calculator available online (http://

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clinicalepidemio.fr/fragility_ma/). FI >20 we considered as robust FI.

Subgroup analysis: None.

Sensitivity analysis: None.

Language: Englisch language.

Country(ies) involved: Germany, USA, Italy, Serbia.

Keywords: SGLT2 inhibitors, adverse events, heart failure population

Contributions of each author:

Author 1 - Davor Vukadinovic - design the trial, performed the search and statistical analysis, wrote and drafted the manuscript and is responsible for key intellectual content.
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Author 2 - Amr Abdin - performed the search, drafted the manuscript and is responsible for key intellectual content.
Author 3 - Stefan D. Anker - study design, drafted the manuscript, and is responsible for key intellectual content.
Author 4 - Giuseppe MC Rosano - study design, drafted the manuscript, and is responsible for key intellectual content.
Author 5 - Felix Mahfoud - wrote the manuscript, study design, drafted the manuscript, and is responsible for key intellectual content.
Author 6 - Milton Packer - study design, drafted the manuscript, and is responsible for key intellectual content.
Author 7 - Javed Butler - study design, drafted the manuscript, and is responsible for key intellectual content.
Author 8 - Michael Böhm - study design, wrote and drafted the manuscript, and is responsible for key intellectual content.

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