RESEARCH REPORT

CARDIOVASCULAR AND RENAL OUTCOME OF SODIUM GLUCOSE COTRANSPORTER-2 INHIBITOR (SGLT2I) VERSUS MINERALOCORTICOID RECEPTOR ANTAGONIST (MRA) IN HEART FAILURE WITH REDUCED EJECTION FRACTION (HFrEF) PATIENTS: SYSTEMATIC REVIEW AND META ANALYSIS

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INTERNATIONAL CLASS MEDICAL PROGRAM

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SURABAYA

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Research Report

To fulfill the undergraduate requirements of the International Medical Program

Faculty of Medicine Universitas Airlangga

Author

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FORM OF APPROVAL

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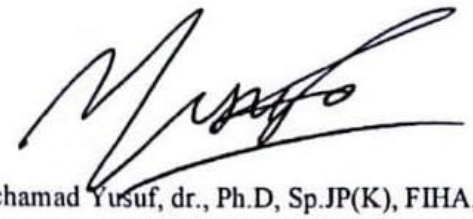

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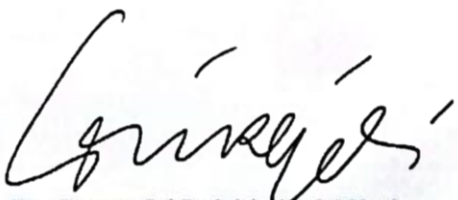

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STATEMENT OF ORIGINALITY

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Dengan ini menyatakan karya tulis ilmiah yang saya buat sebagai pemenuhan adalah benar-benar hasil karya saya sendiri dan buka plagiarisme, bukan jiplakan karya orang lain.

Demikian pernyataan ini dibuat dengan sebenarnya.

Surabaya, 22 Januari 2022

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I thoroughly understand this research is far from excellence also truly appreciate the advice and criticism given in order to further improve this research. Lastly, I earnestly apologize for my demeanor that may cause inconvenience. I hope this research is beneficial to society and furthermore.

Surabaya, 17 Januari 2022

I Putu Agus Arsana

SUMMARY

Overall number of people with heart failure is increasing because of a substantial increase in predisposing or comorbid diseases. It is now known that sodium glucose cotransporter 2 inhibitor (SGLT2i) has a favorable effect on the prognosis of heart failure reduced ejection fraction (HfrEF) patients. However, there are still no studies or trials that directly compare SGLT2i with other first-line HFrEF pharmacotherapy drugs.

This study is aimed to determine the effect of SGLT2i on cardiovascular and renal outcome in HFrEF, determine the effect of MRA on cardiovascular and renal outcome in HFrEF, compare the effect of SGLT2i with MRA, and find whether combination of SGLT2i and MRA is better than monotherapy.

This research is systematic review and meta-analysis with literature research using e-database such as Scopus, Pubmed, Science direct, and ClinicalTrial.gov. The primary efficacy outcome was the composite of cardiovascular death or hospitalization for heart failure. Study Quality Assessment was done by version 2 of the Cochrane risk of bias tool for randomized trial (RoB 2). Fixed or random effect Mantel-Haenszel model was used for dichotomous data to calculate the pooled risk ratio (RR) and 95% confidence interval (CI). Indirect treatment comparison (ITC) analysis and assessing confidence was performed on Confidence in Network Meta-Analysis (CINeMA) with a fixed model. The use of $P < 0.05$ was considered to indicate statistical significance.

Total of seven trials were included. SGLT2i was found to significantly in reduce the risk of cardiovascular death or hospitalization for heart failure by 24%

(RR 0.76, 95% CI 0.70-0.81), cardiovascular death by 15% (RR 0.85, 95% CI 0.75-0.96), hospitalization for heart failure by 28% (RR 0.72, 95% CI 0.65-0.80), and worsening renal function by 39% (RR0.61, 95% CI 0.47-0.80). The reduction in cardiovascular death or hospitalization for heart failure was of similar magnitude in patients with or without diabetes mellitus (RR 0.74, 95% CI 0.69-0.81 vs RR 0.78, 95% CI 0.68-0.89). MRA also was found to significantly in reduce the risk of cardiovascular death or hospitalization for heart failure by 22% (RR 0.78, 95% CI 0.68-0.90), cardiovascular death by 20% (RR 0.80, 95% CI 0.74-0.87), hospitalization for heart failure by 20% (RR 0.80, 95% CI 0.69-0.93), but non-significant on worsening function (RR 1.13, 95% CI 0.44-2.93). Indirect treatment comparison showed that MRA and SGLT2i had similar effects on primary outcome (RR 1.083, 95% CI 0.991-1.183). And combination of SGLT2i and MRA better than MRA monotherapy (RR 0.77, 95% CI 0.69-0.85).

In conclusion, SGLT2i and MRA could safely and give excellent prognosis on cardiovascular outcome in HFrEF patients. SGLT2i safely reduces worsening renal function, but not in MRA. SGLT2i and MRA demonstrate similar effects, while combination of SGLT2i and MRA results in a better cardiovascular protective effect.

It is hoped that further meta-analysis research will be more in-depth and homogeneous in terms of methods, characteristics, inclusion and exclusion criteria, so as to minimize bias in further systematic studies. Further large trials are needed regarding the effectiveness and safety of several drugs such as canagliflozin, ertugliflozin, finerenone, and canrenone against HFrEF.

ABSTRACT

CARDIOVASCULAR AND RENAL OUTCOME OF SODIUM GLUCOSE COTRANSPORTER-2 INHIBITOR (SGLT2I) VERSUS MINERALOCORTICOID RECEPTOR ANTAGONIST (MRA) IN HEART FAILURE WITH REDUCED EJECTION FRACTION (HFrEF) PATIENTS: SYSTEMATIC REVIEW AND META ANALYSIS

Background: Overall number of people with heart failure is increasing because of a substantial increase in predisposing or comorbid diseases. It is now known that sodium glucose cotransporter 2 inhibitor (SGLT2i) has a favorable effect on the prognosis of heart failure reduced ejection fraction (HfrEF) patients. However, there are still no studies or trials that directly compare SGLT2i with other first-line HFrEF pharmacotherapy drugs.

Aims: This study is aimed to determine the effect of SGLT2i on cardiovascular and renal outcome in HFrEF, determine the effect of MRA on cardiovascular and renal outcome in HFrEF, compare the effect of SGLT2i with MRA, and find whether combination of SGLT2i and MRA is better than monotherapy.

Methods: This research is systematic review and meta-analysis with literature research using e-database such as Scopus, Pubmed, Science direct, and ClinicalTrial.gov. The primary efficacy outcome was the composite of cardiovascular death or hospitalization for heart failure. Study Quality Assessment was done by version 2 of the Cochrane risk of bias tool for randomized trial (RoB 2). Fixed or random effect Mantel-Haenszel model was used for dichotomous data to calculate the pooled risk ratio (RR) and 95% confidence interval (CI). Indirect treatment comparison (ITC) analysis and assessing confidence was performed on Confidence in Network Meta-Analysis (CINeMA) with a fixed model. The use of $P < 0.05$ was considered to indicate statistical significance.

Result: Total of seven trials were included. SGLT2i was found to significantly in reduce the risk of cardiovascular death or hospitalization for heart failure by 24% (RR 0.76, 95% CI 0.70-0.81), cardiovascular death by 15% (RR 0.85, 95% CI 0.75-0.96), hospitalization for heart failure by 28% (RR 0.72, 95% CI 0.65-0.80), and worsening renal function by 39% (RR0.61, 95% CI 0.47-0.80). The reduction in cardiovascular death or hospitalization for heart failure was of similar magnitude in patients with or without diabetes mellitus (RR 0.74, 95% CI 0.69-0.81 vs RR 0.78, 95% CI 0.68-0.89). MRA also was found to significantly in reduce the risk of cardiovascular death or hospitalization for heart failure by 22% (RR 0.78, 95% CI 0.68-0.90), cardiovascular death by 20% (RR 0.80, 95% CI 0.74-0.87), hospitalization for heart failure by 20% (RR 0.80, 95% CI 0.69-0.93), but non-significant on worsening renal function (RR 1.13, 95% CI 0.44-2.93). Indirect

treatment comparison showed that MRA and SGLT2i had similar effects on primary outcome (RR 1.083, 95% CI 0.991-1.183). And combination of SGLT2i and MRA better than MRA monotherapy (RR 0.77, 95% CI 0.69-0.85).

Conclusion: SGLT2i and MRA could safely and give excellent prognosis on cardiovascular outcome in HFrEF patients. SGLT2i safely reduces worsening renal function, but not in MRA. SGLT2i and MRA demonstrate similar effects, while combination of SGLT2i and MRA results in a better cardiovascular protective effect.

Keywords: Sodium glucose cotransporter 2 inhibitor, mineralocorticoid receptor antagonist, heart failure with reduced ejection fraction, meta-analysis

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LIST OF ABBREVIATIONS

HFrEF	: Heart Falure with reduced ejection fraction
HFpEF	: Heart Falure with preserved ejection fraction
HFmrEF	: Heart Falure mid-range ejection fraction
DM	: Diabetes Melitus
FDA	: Food Drug Administration
SGLT 2	: Sodium-Glucose Co-transporter-2
PICO	: Population, Intervention, Comparison, Outcome
PRISMA	: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
NIH	: National Institutes of Health's
WHO	: World Health Organization
NYHA	: New York Heart Association
LVEF	: Left Ventricular Ejection Fraction
QoL	: Quality of Life
RoB	: Risk of Bias
EMPEROR-Reduced	: Empagliflozin Outcome Trial In Patients With Chronic Heart Failure With Reduced Ejection Fraction

CANVAS	: Canagliflozin Cardiovascular Assessment Study
DECLARE-TIMI	: Dapagliflozin Effect on CardiovascuLAR Events
DAPA-HF	: Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure
SOLOIST WHF	: Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure
EMPHASIS-HF	: The Eplerenone in Mild Patients Hospitalization and Survival study in Heart Failure
EPHESUS	: Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigator
RALES	: Randomized Aldactone Evaluation Study Investigators