



# Efficacy of Empagliflozin Therapy in Patient with Acute Heart Failure: Meta-analysis

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Received: August 16, 2023  
Revised: September 30, 2023  
Accepted: October 25, 2023  
Published: October 31, 2023

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DOI: [10.29303/jppipa.v9i10.5000](https://doi.org/10.29303/jppipa.v9i10.5000)

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**Abstract:** Heart failure is still a common disorder with a high morbidity and mortality rate around the world. New drugs sodium-glucose cotransporter 2 inhibitors (SGLT2i) such as empagliflozin are currently showing promising results across the HF spectrum. Based on this, the authors are interested in researching the efficacy of Empagliflozin Therapy in Patient with Acute Heart Failure. This study used a systematic search using PRISMA principle in several online databases (Pubmed, Cochrane library and Google scholar). The selected study was an RCT or clinical trial with a population of Acute HF patients. The intervention group is Empagliflozin in any dose compared to placebo. The primary outcome for this meta-analysis is the levels of BNP or NT-proBNP and mortality after intervention. Selected study will be assessed and analyzed using Review Manager software version 5.3 with 95% CI. The two studies selected in this meta-analysis had a total sample size of 290 in the intervention group and 285 in the placebo group. Heterogeneity test obtained [ $p=0.44$ ;  $I^2 0\%$ ], indicating the homogenous data and the study is recommended to use the fixed effect method. The pooled effect size of RR is 0.472 [CI95% 0.24-0.75,  $P=0.003$ ], meaning that there is a significant favorable outcome in empagliflozin group than in the placebo group. The results showed that empagliflozin had shown a favorable effect in reduction of the risk of death and reducing level of NT-proBNP in patient with acute heart failure.

**Keywords:** Empagliflozin, Acute Heart Failure, NT-proBNP, Mortality

## Introduction

The optimal treatment for patients with Heart failure is controversial. Heart failure is a complex clinical syndrome caused by a functional or structural heart disorder that impairs ventricular filling or ejection of blood into the systemic circulation. It is, by definition, a failure to meet the systemic demands of circulation. Heart failure is still a common disorder with a high morbidity and mortality rate around the world. It is estimated to affect 26 million people worldwide and contributes to increased healthcare costs (Greenberg, 2017). Heart failure can be caused by a number of different diseases. The etiology of heart failure influences the treatment plan to some extent; however, most treatment recommendations are based solely on the presence of heart failure, regardless of the cause (Ahmad, Daniel, Sarosh, & Lovely, 2022).

Angiotensin-converting enzyme inhibitors, beta-blockers, mineralocorticoids, or aldosterone receptor antagonists are recommended for HF patients, according to the guidelines (Ponikowski et al., 2016). New drugs, such as sodium-glucose cotransporter 2 inhibitors (SGLT2i) and vericiguat, are currently showing promising results across the HF spectrum. The drug SGLT2i has been used to treat type 2 diabetes (Kato et al., 2019). In recent years, SGLT2i has been demonstrated in clinical trials to be more effective than placebo in terms of all-cause mortality and heart failure hospitalization in patients with type 2 diabetes mellitus, independent of the presence or absence of heart failure (Steiner, 2016). SGLT2i lowered the incidence of all-cause death and heart failure hospitalizations by 23% in patients with diabetes mellitus. One of the most often used SGLT2i, empagliflozin, has been shown to be helpful in lowering HF hospitalizations, cardiovascular mortality, and biomarkers in patients with HF (Packer et

### How to Cite:

Pintaningrum, Y., & Pranayoga, K. (2023). Efficacy of Empagliflozin Therapy in Patient with Acute Heart Failure: Meta-analysis. *Jurnal Penelitian Pendidikan IPA*, 9(10), 849–853. <https://doi.org/10.29303/jppipa.v9i10.5000>

al., 2020). However, results from similar research revealed variation in several outcomes, such as N-terminal pro-brain natriuretic peptide (NT-proBNP) (Mordi et al., 2017). The effect of empagliflozin on patients with heart failure has not been studied in detail. Prior research has primarily focused on SGLT2i rather than empagliflozin. Previous large-sample trials found that empagliflozin produced different results for a composite cardiovascular endpoint (cardiovascular deaths, non-fatal myocardial infarction, or non-fatal stroke) when compared to dapagliflozin, implying that different drugs may produce different results even though they all belong to the SGLT2i class (Santos-Gallego et al., 2021). We, therefore, performed a systematic review and meta-analysis of randomized controlled trials (RCTs) to assess the efficacy of empagliflozin in patients with acute HF.

**Method**

The present analysis was conducted in accordance with Preferred Reporting, Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations (Arya, Kaji, & Boermeester, 2021) and was prospectively registered at the PROSPERO international prospective register of systematic reviews (ID CRD42023447036).

**Search Strategy**

We performed a systematic search of the PubMed, Cochrane and Google scholar from the start to March 2023. The search syntax is in the following: ["acute decompensated heart failure" OR "de novo heart failure"] AND ["Complications" OR "death" OR "BNP"]. Only articles released in English and clinical trial are included in this study.

**Inclusion Criteria**

Patient with diagnosis of acute heart failure by European Society of Cardiology 2021 with the presence of congestion and/or peripheral hypoperfusion followed by 1) sign of congestion such as peripheral edema, congestion in chest x-ray, or rales in lungs; 2) dyspneu on rest or minimal exercise; 3) BNP levels >19pg/mL or NT-proBNP >300pg/mL or MR-proANP >120pg/mL.

**Endpoints**

The primary efficacy endpoint for this meta-analysis is the levels of BNP or NT-proBNP and mortality after intervention.

**Data Extraction and Analysis**

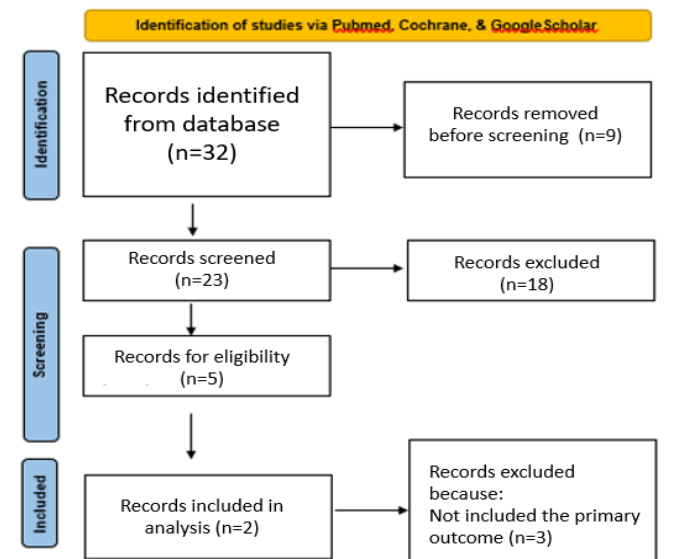
The studies which fully eligible after reviewing the articles then further analyzed. We extracted the

following data from each included study: author, year, type of study population, sex, ages, comorbidities, positive incidence rate, and mortality.

The datas were analyzed using RevMan 5.3 for forest plot of the BNP or NT-proBNP levels and mortality. We are using fixed effect model if the sample size are quite similar of each studies, otherwise we are using random effect model.

**Result and Discussion**

We found a total of 32 records from database then further assessed for eligibility only 23 records. Among 23 records, only 2 studies that fulfill the eligibility criteria for analysis, other records were excluded because those were not in our inclusion criteria. This Fig. 1 showed our selection of studies.



**Figure 1. PRISMA Flowchart**

A total of 2 included studies were analyzed. In the table 1 showed the characteristic of the included studies. The average ages of population was older than 70 years old, mostly consisted of male patient, and the highest comorbidities was hypertension followed by atrial fibrillation, diabetes, myocardial infarction and valvular heart diseases. the most common type of acute heart failure is acute decompensated heart failure. The NT-prBNP levels was more than 3000 pg/mL and even 6000 pg/mL in one study. only one study showed a changes in NT-proBNP levels in percent which is not significantly different between intervention and placebo group.

Authors, year	Population	Age (Q1-Q3)		Sex (male %)		Comorbidities (%)		NT-proBNP levels (mean Q1-Q3)		NT-proBNP changes (%/SD)		Heart failure type (%)	
		I	P	I	P	I	P	I	P	I	P	I	P
Voors et al, 2022	530	71(62-78)	70(59-78)	67.5	64.9	diabetes (46.8)	diabetes (43.8)	3229	3106	-	-	Decompensated (66.8), de novo (33.2)	Decompensated (67.2), de novo (32.8)
						HTN (77.4)	HTN (83.4)	13943	(1388-6013)				
Damman et al, 2020	79	73(73-83)	61(61-83)	60	74	diabetes (38)	diabetes (28)	4406/2873	6168/3180	46	42	decompensated (52), de novo (48)	decompensated (54), de novo (46)
						HTN (68), AF (78), MI (30)	HTN (56), AF (64), MI (38)	6979	10.489)				

Figure 2. The summarize of the studies

The total participant from empagliflozin is 290 and from the placebo group is 285 participant from 2 included studies. The pooled effect size of RR is 0.472 (CI95% 0.24-0.75, P=0.003), meaning that there is a significant favorable outcome in empagliflozin group than in the placebo group. The heterogeneity test showed a homogenous data (I<sup>2</sup>=0%, P=0.44). The funnel plot below showed that the studies were symmetrical and had a moderate significant impact.

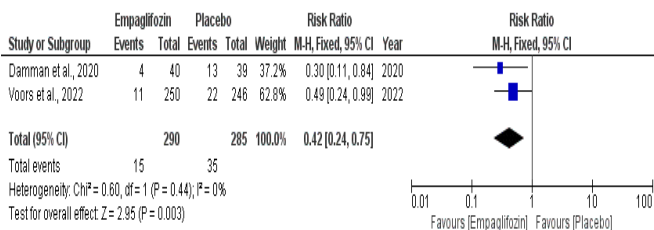


Figure 3. Forest plot of mortality

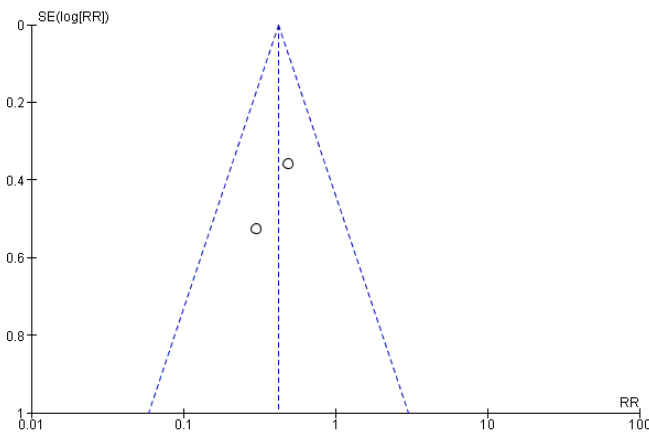


Figure 4. Funnel plot of mortality

In this meta-analysis we included two randomized clinical trial studies which are from EMPULSE trial and EMPA-RESPONSE-AHF trial with 575 participants in total. The primary outcomes in this study are mortality and NT-proBNP levels change. Unfortunately, the studies included NT-proBNP change is only one study from EMPA-RESPONSE-AHF which showed 46%±31 reduction in empagliflozin group and 42%±31 in placebo group. It is also worth noting that the findings of a previous trial with dapagliflozin intervention revealed

no significant difference in NT-proBNP change (Nassif et al., 2019). SGLT2i, particularly empagliflozin or dapagliflozin, were associated with a reduction in plasma NT-proBNP levels in some trials (Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, 2019). Empagliflozin has been shown to improve left ventricular diastolic function and reduce mortality in mice, most likely by reducing spontaneous diastolic sarcoplasmic reticulum calcium release. The mechanism of diastolic dysfunction was thought to be leakage (Moellmann et al., 2020). Furthermore, empagliflozin improved cardiac function in non-diabetic rats, which could be related to improved cardiac metabolism and cardiac ATP production. If BNP/NT-proBNP levels fall by less than 50%, the risk of rehospitalization or death within 12 months increases by 40% (Hummel, Empen, Dörr, & Felix, 2015).

In our study, the mortality is significantly lower in empagliflozin group than the placebo group. This result is consistent with the Dapagliflozin trial that showed a reduction in mortality and morbidity in patient with chronic heart failure (Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, 2019). Sotagliflozin therapy initiated either before (in nearly half of the population) or shortly after hospital discharge significantly reduced cardiovascular deaths and HF hospitalizations in the SOLOIST-WHF trial, which recruited diabetic patients with AHF (Bhatt et al., 2021).

Our study found that most of the populations are acute decompensated HF. Cardiovascular comorbidities are mainly hypertension, atrial fibrillation, ischemic heart disease, and valvular heart disease. Arrhythmias, valvular dysfunction, and acute cardiac ischemia were the most common causes of acute decompensation, accounting for approximately 30% of cases (Hummel et al., 2015). These comorbidities may worsen the heart failure. Non-valvular atrial fibrillation (NVAf) worsens cardiac hemodynamics by lowering LV performance and is linked to an increased risk of death, hospitalization, and a lower quality of life, especially in subjects with a low ejection fraction (EF) (Cherian et al., 2017).

### Conclusion

The acute heart failure is associated with poor prognosis and the risk of hospitalization and death. From the present updated systematic review and meta-analysis, the new drug such as empagliflozin had shown a favorable effect in reduction of the risk of death in patient with acute heart failure. Although the effect on reducing level of NT-proBNP showed a favorable result, but the result is still inconsistent. Further research with more participants is need to be done to assess the effectiveness of empagliflozin in reduction of NT-

proBNP. This study has its limitations such as not enough studies is included and the risk of bias in the study is possibly high.

#### Acknowledgments

The author thanks all who contributed to the writing of this article.

#### Author Contributions

The data were accessible to all authors, who also gave the work a thorough review before submission. Before submission, this article was reviewed and approved by all authors. Conception and design contributed by YP; Analysis and interpretation contributed by YP, KP; Data collection contributed by YP, KP; Writing the article contributed by YP, KP; Critical revision of the article contributed by YP; Final approval of the article contributed by YP, KP; Statistical analysis contributed by YP, KP; Overall responsibility contributed by YP.

#### Funding

Not applicable

#### Conflicts of Interest

There is no conflict of interest

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