

Comparing the effect of Angiotensin-Converting Enzyme Inhibitors versus Angiotensin Receptor Blockers in heart failure patients with type 2 diabetes mellitus: A systematic review



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ABSTRACT

Introduction: Heart failure is a debilitating disease with increasing prevalence worldwide and often treated with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB). However, their efficacy is never be compared in heart failure patients, especially those who have co-morbid disease such as type 2 diabetes mellitus. Therefore, the aim of this study was to determine the effect of the two drugs in heart failure patients with type 2 diabetes mellitus.

Methods: This meta-analysis was performed on research articles that focused on the drugs of heart failure patients published in PubMed, ProQuest and EBSCO database between 2008-2018. Pooled odds ratio (OR) are calculated using fixed and random effects models. Data were processed using Review Manager 5.3 (RevMan 5.3).

Results: From total 209 articles, ten studies were met the criteria for the systematic review. The meta-analysis result showed that there was no difference in the effect of angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers in heart failure patients with type 2 diabetes mellitus (RR = 1.73 [95% CI 0.88-3.40], p=0.11). However, heterogeneity test for studies (P-heterogeneity = <0.00001) showed there was some variation within the articles used which indicated heterogeneous research. Nevertheless, there was no publication bias in this study according to Egger's test (p = 0.334) and Begg's test (p = 0.180).

Conclusion: This analysis confirmed there was no difference in the effect of angiotensin-converting enzyme inhibitors (ACEi) versus angiotensin receptor blockers (ARBs) in heart failure patients with type 2 diabetes mellitus.

Keywords: heart failure, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, type 2 diabetes mellitus

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INTRODUCTION

Heart failure (HF) is a clinical syndrome in cardiovascular patients whose prevalence and the incidence continues to increase.¹ This condition associated with high morbidity and mortality rates. Based on available data from the United States and Europe, the prevalence of heart failure is estimated from 1% to 12% of the adult population and is projected to increase with ageing population.² Heart failure is a significant public health problem accounting for 5% of emergency hospital admissions in the United Kingdom and is associated with substantial mortality with five-year survival estimated at only 50%.³

Type 2 diabetes mellitus is a major risk factor for all types of heart failure and causes an increase in mortality and morbidity in patients with HF.^{4,5} Among T2D patients, it is estimated that the prevalence rate of unrecognised HF is as high as 25% in the community aged 60 years and over. This fact underlines the importance of T2D in HF. Furthermore, T2D could also pose a challenge

in HF patients because of its extensive metabolic disorder and associated complications that possibly hamper HF treatment.

Angiotensin-converting enzyme inhibitors (ACEi) are indicated as first-line treatment for HF.⁶⁻⁸ It has been conclusively demonstrated in major clinical trials to be able to reduce mortality as well as rates of reinfarction and hospitalisations for heart failure.⁹ In asymptomatic patients, ACEi is given to prevent heart failure and also to reduce the risk of myocardial infarction as well as sudden death. The other drugs, angiotensin receptor blockers (ARB), currently only recommended for ACE-intolerant patients, often manifested as coughing. ARB does not inhibit kininase, so it rarely causes coughing and angioedema.⁸

In the previous study, ARB had similar efficacy as ACEi in reducing total mortality and all-cause hospitalizations.¹⁰ However, this study did not evaluate specifically heart failure patients with diabetes comorbidities and, thus, the difference of efficacy of

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these drugs in this specific type of patients remain poorly understood. Therefore, this study was determined to compare the effectiveness of ACEi and ARB in heart failure patients with type 2 diabetes mellitus.

MATERIAL AND METHODS

Study design and research sample

A meta-analysis study was conducted by following the preferred reporting items from the Systematic Reviews and Meta-Analysis (PRISMA) guideline.¹¹ The research samples were original articles published between January 2008 and December 2018 in online article databases of PubMed, ProQuest and EBSCO. The flowchart of this study is described in [figure 1](#).¹²⁻²⁰

The literature searching was conducted using following keywords in literature title or abstract: (“Heart Failure” AND (“Diabetes Mellitus Type 2” OR DM Type 2) AND (“Angiotensin-Converting Enzyme Inhibitors” OR “Angiotensin Receptor Antagonists”) AND (“randomized clinical trials” OR “RCT” OR “random* control* trial”). Two hundred nine articles appeared initially which then assessed by reviewing through the titles of the articles, continued by reviewing the abstracts, and then the full-text form. The article was excluded if: (a) having no relevant subject outcome, (b) not randomised clinical trials, and/or (c) the information provided in the results was not enough or insufficient for data extraction.

Two independent investigators carefully extracted information from all studies that fulfilled the inclusion criteria following a standardised protocol. Disagreements were resolved by three other investigators. Quality assessment was conducted Jadad

score and papers with a total score of ≥ 3 points were specified as sufficient quality.²¹

DATA ANALYSIS

The analysis was conducted to acquire the value of pooled risk ratio which is the combined analysis of risk ratio value from each research. The results of the study were expressed as pooled risk ratio with corresponding 95% confidence intervals (CIs). Significant heterogeneity was indicated by $P > 50\%$ because these tests had minimal statistical power in cases with few studies and small sample sizes. A random-effect model was used when significant heterogeneity was observed; otherwise, a fixed-effect model was performed. Publication bias was visually evaluated by using funnel plots and statistically assessed through Egger’s and Begg’s tests. The overall analysis was conducted using Review Manager 5.3 (RevMan) and Stata version 14.2 (Stata Corporation). A two-tailed p -value of < 0.05 was considered statistically significant.

RESULTS

The identification of the published articles was conducted and we obtained ten studies with the number of samples 41,234 patients related to the effect of angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers in heart failure patients with type 2 diabetes mellitus ([Table 1](#)). The origins of the studies were considered diverse enough to represent all races and variability across different population worldwide and this problem was countered especially by two studies which included population from 40 countries. There were three studies with small populations included,

Table 1 Systematic review on effect of angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers in heart failure patients with type 2 diabetes mellitus

First author, year	Region	Type of study	Number of samples	
			ACE-I	ARB
Seferovic et al, 2017	USA	randomised active-controlled trial	3,778	3,778
Kristensen et al, 2017	UK	randomized trial	1,134	1,134
Yamashita et al, 2013	Japan	randomized clinical trial	417	417
Muramatsu et al, 2012	Japan	randomized clinical trial	575	545
Redon et al, 2012	40 countries	multicenter double blind trial	9,603	9,603
Kawai et al, 2011	Japan	randomized clinical trial	68	68
Imai et al, 2011	Japan and China	randomized clinical trial	282	282
NAVIGATOR study group et al, 2010	40 countries	double-blind, randomized clinical trial	4,631	4,631
Ertek et al, 2010	Turkey	randomized clinical trial	87	87
Henry et al, 2009	USA	randomized controlled trial	57	57
Number of samples			20,632	20,602

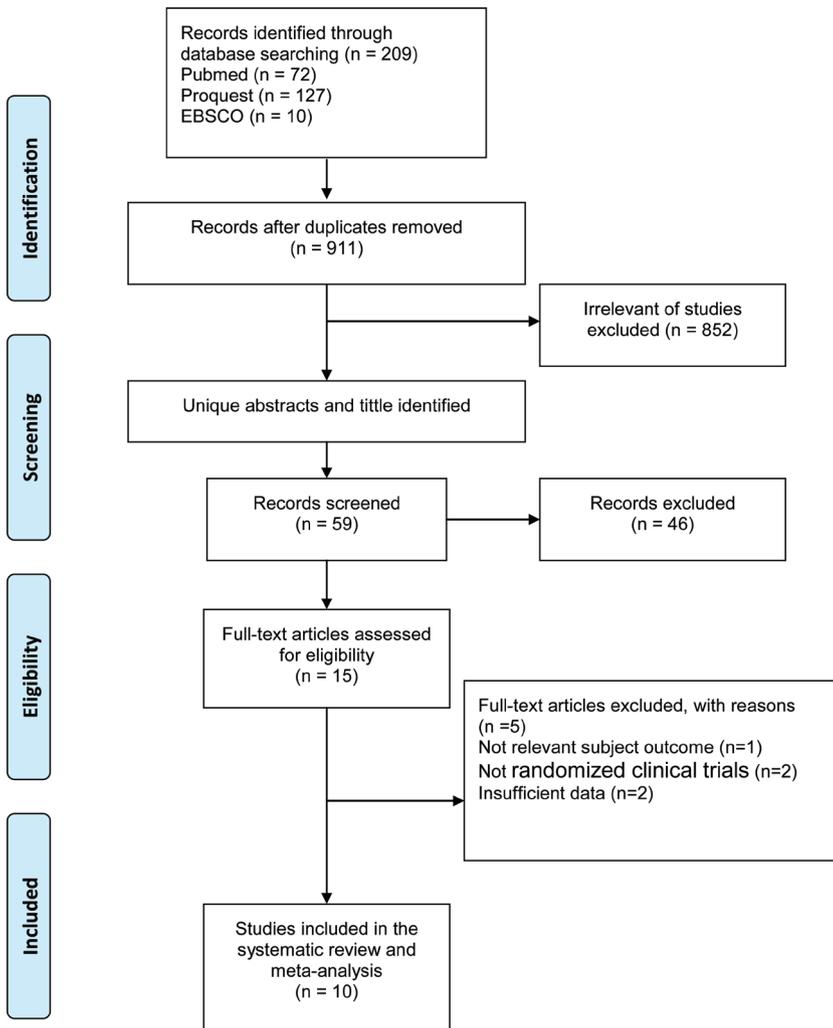


Figure 1 Flow diagram research procedure

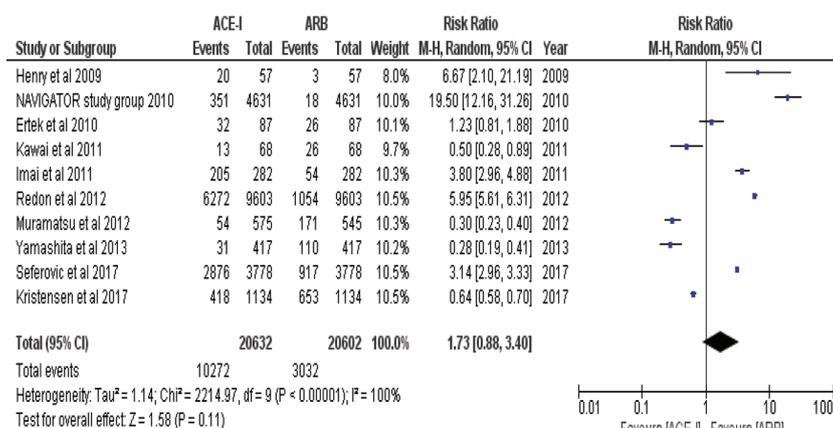


Figure 2 Forest plots effect of angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers in heart failure patients with type 2 diabetes mellitus

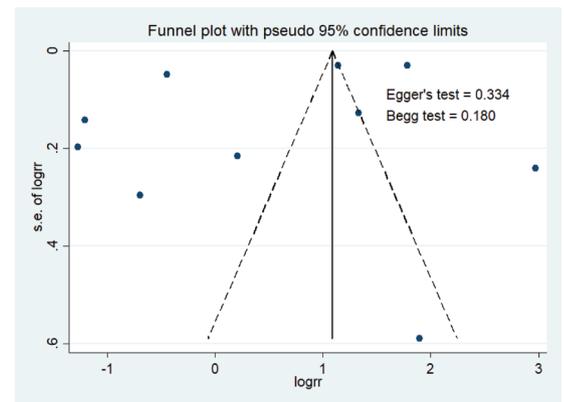


Figure 3 Publication bias on effect of angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers in heart failure patients with type 2 diabetes mellitus

DISCUSSION

Heart failure and T2DM are often coexisting and posed challenges to clinicians to provide optimal treatments to the patients. As the mainstay of therapy of heart failure, ACEi and ARB are commonly used interchangeably, especially if the patients develop intolerance toward ACEi. Unlike ACEi, ARB is more recently developed and, thus, more expensive than ACEi. However, because both drugs interfere same system (RAAS), they often considered having similar effects. This notion is difficult to judge because most studies used heart failure patient without declaring accompanying disease or heart failure patients without co-morbidities. Therefore, the efficacy of both drugs in heart failure patients, especially those with T2DM, are challenging to determine.

Nevertheless, some relevant studies that assessed the efficacy of ACEi and ARB in heart failure with T2DM showed several variations in their findings. As reported in this study, half of articles included in this study indicated that ARB had superior effects compared to ACEi. These include three large studies with sample population exceeding 1000 subjects. However, four other reported findings favouring ACEi over ARB, but they were relatively small study compared to 3 studies that are mentioned earlier. Nevertheless, after analysing the data, it was found that whether the value of relative risk favouring the ARB, the confidence interval showed that the finding was not significant.

There is no different effect of result of angiotensin-converting enzyme inhibitors versus

angiotensin receptor blockers in heart failure patients with type 2 diabetes mellitus. In the previous study stated that there was no significant difference between ACEi and ARBs in terms of mortality and all causes of hospitalisation.^{10,22} However, that study does not distinguish between patients with comorbid DM and non-DM. In heart failure patients with T2DM, diabetes may be the primary cause of cardiac dysfunction and in others, it may play a more critical role. The importance of T2DM in heart failure patients has been delineated in several studies. Kristensen et al. evaluated the clinical outcomes of heart failure patients with T2DM has over a median follow-up of 4.1 years. They reported that hospitalisation caused by cardiovascular death or heart failure was at 34% of patients with T2DM versus 22% of those without T2DM (adjusted HR: 1.75; 95%CI: 1.49–2.05). Additionally, they also reported that 28% patients with heart failure and T2DM died compared to just 19% in patients without diabetes mellitus (adjusted HR: 1.59; 95%CI: 1.33–1.91).¹⁶

Regarding the usage of ACEi and ARB in heart failure with T2DM, as found in this study, several previous reports also emphasise on the similar efficacy of ACEi and ARB. Yamashita et al. reported that there were no differences in outcomes of hospitalisation and death rate between treatment arms in heart failure patients with T2DM. The median follow-up period was 3.2 years and primary outcome had occurred in 54 patients in the valsartan group and 56 in the amlodipine group (HR: 0.97 [95% CI: 0.66–1.40]; P=0.85).¹⁵ Our findings and the other reports suggest that ACEi and ARB can be used interchangeably and ARB will provide same efficacy and advantages as ACEi albeit the three large studies suggested that ARB might be superior.^{11,20}

Inhibition of the renin-angiotensin-aldosterone system is one of the mainstay therapies of heart failure. The use of ACEi which inhibits the production of angiotensin II in HF patients has been shown to improve clinical symptoms and reduce mortality. The drug works by blocking an enzyme responsible for converting angiotensin I to angiotensin II.^{6–8} However, most patients are intolerant to ACEi, which often manifested as coughing due to lung angioedema and, thus, the drug often replaced by ARB. Of note, according to the international guideline, ACEi could not be given in combination with ARB.⁶ However, there is also a newly developed drug designated as ARNI (Angiotensin receptor-neprilysin inhibitor) which consists of sacubitril and valsartan. This fixed-dose combination drug has been shown to reduce the incidence

of mortality and morbidity of heart failure patients, especially in HF, where the ejection fraction is reduced.²³ With this development, there will be more alternative therapy for heart failure patients in the future which potentially will improve the clinical outcome.

However, it is essential to note that our review is heterogeneous because it did not evaluate or focused on specific region or population. The studies included in this review came from several areas namely United States, UK and Asia (Japan, China and Turkey). The diversity of studies in this study shows that differences in outcomes in patients with heart failure with type 2 diabetes are not influenced by ethnicity and region. However, future studies are needed to evaluate the effects of ACEi or ARB in specific population due to potential influence of genetic diversity between populations.

Nevertheless, this study has some limitations, such as the exclusion of several studies due to unavailability of free access to full article or irrelevant outcomes. In this study, the outcome was determined based on clinical outcome which represented as total mortality and hospital admission. We did not analyse other clinical outcomes such as cardiovascular mortality, total hospitalisations, and hospitalisations for other causes, stroke, MI, and withdrawals due to adverse effects. Other useful indexes of morbidity would be total length of hospital admission or days in ICU or on a ventilator; however, these outcomes were not reported in any of the studies. We also did not see the drugs used in the treatment of DM specifically; we only analysed the study subjects included in RCTs with DM as comorbid.

CONCLUSION

According to our study, it can be concluded that ACEi-based therapy has similar efficacy as ARB-based treatment in terms of mortality and all causes of hospitalisation in HF patients with T2DM. We recommend further research on the effects of using those HF treatments with comorbidities other than diabetes mellitus.

CONFLICT OF INTEREST

The author declared no conflicts of interest regarding the publication of this study.

AUTHOR CONTRIBUTION

All authors contributed equally in the writing of this article.

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