Clinical and Hemodynamic Effects of Endothelin Receptor Antagonists in Patients With Heart Failure: A Meta-Analysis of Randomized Controlled Trials

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Summary

The clinical benefit of endothelin receptor antagonists (ERA) for the management of heart failure (HF) remains controversial. To examine this question, we performed a meta-analysis of randomized controlled trials (RCTs) to investigate the clinical and hemodynamic effects of ERA in HF patients.

We searched the PubMed, Medline, Embase, and Cochrane Library from inception to March 20, 2016 to identify the pertinent studies. Risk ratio (RR) and weighted mean difference (WMD) were calculated using a fixed or random effect model.

A total of 15 RCTs with 3,624 HF patients were included. Compared with control groups, ERA might not improve the mortality (RR 1.12, 95%CI 0.81 to 1.54, P = 0.51) or incidence of worsening HF or cardiovascular events (WHF/CVE) (RR 1.06, 95%CI 0.94 to 1.19, P = 0.35) in HF patients. Subgroup analysis also suggested that neither nonselective nor selective ERAs had an impact on mortality and WHF/CVE. However, the hemodynamic variables of HF patients, including cardiac index (WMD 0.32, 95%CI 0.22 to 0.43, P < 0.01), pulmonary capillary wedge pressure (WMD -3.10, 95%CI -3.99 to -2.20, P < 0.01), mean pulmonary arterial pressure (WMD -4.42, 95%CI -5.50 to -3.33, P < 0.01), systemic vascular resistance (WMD -276.35, 95%CI -399.62 to -153.09, P < 0.01), and pulmonary vascular resistance (WMD -69.42, 95%CI -105.33 to -33.52, P < 0.01) were significantly improved by ERA.

In conclusion, this meta-analysis suggests that ERA therapy could effectively improve cardiac output and pulmonary and systemic hemodynamics, but with less benefit to the clinical outcomes of HF patients. (Int Heart J 2017; 58: 400-408)

Key words: Endothelin system, Systematic review

Heart failure (HF) is a major public health problem, with a prevalence of more than 23 million worldwide.1 Progression of HF is characterized by sustained deterioration in symptoms, cardiac function, and peripheral and pulmonary vascular resistance.2,3 Neurohormonal activation, an important factor of left ventricular (LV) remodeling, is likely to be a primary determinant for the progression. The roles of activation of the renin-angiotensin system (RAS) and sympathetic nervous system (SNS) in HF are well documented and inhibiting them with angiotensin-converting enzyme inhibitors (ACEI) and β blockers could effectively reverse the process of LV remodeling, relieve patient symptoms, and prolong life.4,5 Furthermore, it has been demonstrated that local activation of the endothelin (ET) system might also be linked with HF progression.6 ET-1 is thought to mediate potent vasoconstriction, proliferation of vascular smooth muscle, and myocardial hypertrophy through ET1 receptors.7 In contrast, activation of endothelial ETB receptors is primarily involved in vasodilatation, antithrombotic, and antiproliferative effects. Moreover, ET-1 also has a potential to enhance the activity of RAS and SNS pathways and induce the production of other neurohormonal factors.8 Plasma levels of ET-1 and big ET-1 are elevated and can significantly predict mortality in patients with HF.9,10 Hence, like ACEI and β blockers, blockade of the ET system with an endothelin receptor antagonist (ERA) might also improve the clinical outcomes and prognosis of HF.

The data of preclinical studies of ERA in HF are conflicting. In some animal models of chronic HF, ERA has been shown to correct hemodynamic abnormalities, decrease card-
ac fibrosis, and improve survival.\textsuperscript{12} However, a meta-analysis of experimental HF indicated that EARs may not improve the mortality of HF.\textsuperscript{13} Several randomized controlled trials (RCT) have suggested that both non-selective and selective ERAs could alleviate pulmonary and systemic vascular resistance, and increase cardiac index and left ventricular ejection fraction (LVEF) in patients with HF.\textsuperscript{14-16} In addition, a recent study has demonstrated that sitaxsentan might increase the exercise tolerance in patients of HF with preserved ejection fraction (HFpEF).\textsuperscript{11} However, these promising results were not found in other clinical trials.\textsuperscript{17,18} Hence, the effects of ERA for the management of HF remain to be clarified and there is lack of a complete overview. For this purpose, we performed a meta-analysis of RCTs to investigate the clinical and hemodynamic effects of ERA in patients with HF.

\section*{METHODS}

This meta-analysis of ERA in HF patients was performed according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines.\textsuperscript{19} Search strategy and study selection: We identified potentially relevant articles by a computerized literature search of PubMed, Medline, Embase, and Cochrane Library without any restrictions from inception to March 20, 2016. The following search terms were used: (endothelin receptor antagonists OR darusentan OR bosentan OR sitaxsentan OR atrasentan OR ambrisentan OR enrasentan OR macitentan) AND (heart failure) OR (HF). In addition, the reference lists of retrieved articles were reviewed to identify additional relevant studies.

Studies were included if they met the following criteria: 1) the study was a RCT; 2) the study was performed in adult patients (≥ 18 years) with HF; 3) patients were treated with ERA versus placebo or active controls; and 4) the primary outcomes including mortality and incidence of worsening HF or cardiovascular events (WHF/CVE) and/or the secondary outcomes including cardiac index, pulmonary capillary wedge pressure (PCWP), mean pulmonary arterial pressure (mPAP), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) were reported.

Data extraction and quality assessment: Two authors independently extracted the available information from included studies with disagreements resolved by discussion. The following data were extracted: main characteristics of the study (authors, publication year, journal, country, study design), characteristics of HF patients (population number, gender, age, New York Heart Association class, LVEF, background medications, medical history), intervention and control treatments (dose, duration, mean follow-up time), and outcomes (mortality, WHF/CVE, cardiac index, PCWP, mPAP, SVR, PVR). If several articles reported the same study, the one with the most complete data was included. The corresponding author was contacted by email if any data were not available.

Risk of bias of the RCTs was evaluated by two authors using the Cochrane risk of bias tool in Review Manager 5.2 (The Cochrane Collaboration 2012, Nordic Cochrane Centre Copenhagen, Denmark), according to the following 7 items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias.

\section*{Statistical analysis:} Heterogeneity of the RCTs was evaluated using the chi-square test (P ≤ 0.10 representing significant heterogeneity) and I\textsuperscript{2} test (I\textsuperscript{2} > 50\% representing significant heterogeneity). Risk ratio (RR) and 95\% confidence interval (CI) for mortality and WHF/CVE were calculated using a fixed effect model, if there was no significant heterogeneity. Otherwise, a random effect model was chosen. The fixed effect model was also used to calculate the weighted mean difference (WMD) and 95\% CI for cardiac index, PCWP, mPAP, SVR, and PVR when there was no significant heterogeneity. Otherwise, a random effect model was used. We also performed sensitivity analysis to determine the stability of our estimates by omitting each study one by one. Publication bias was assessed using funnel plots and Egger’s test. All P values were two-tailed, and statistical significance was defined as P < 0.05. All statistical analyses were undertaken using STATA 12.0 (Stata Corp, College Station, TX, USA).

\section*{RESULTS}

Study characteristics: The literature research process and reasons for exclusion are described in Figure 1. A total of 3,012 articles were identified through a database search. After title and abstract screening, 2,972 were excluded and 40 potentially relevant articles were retrieved for full text evaluation. In the end, 25 were excluded (Supplementary Table I) and 15\textsuperscript{19,20,21,22,23,24,25,26} RCTs that met the predetermined criteria were included in the present study. Major characteristics of the included RCTs are summarized in the Table. In general, the 15 studies, covering a total of 3,624 patients, were published between 1998 and 2013. Most of the baseline characteristics of each RCT were similar between the intervention and control...
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Study design</th>
<th>Study subject</th>
<th>ERA Administration of ERA</th>
<th>Control</th>
<th>NYHA class</th>
<th>LVEF (%) (Mean ± SD)</th>
<th>Follow-up (Months)</th>
<th>Outcomes of meta-analysis</th>
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<tr>
<td>McMurray, et al 2007</td>
<td>727</td>
<td>RCT</td>
<td>AHF</td>
<td>Tezosentan Intravenous, 1 mg/hour for 3 days</td>
<td>Placebo</td>
<td>NA</td>
<td>24 (10)</td>
<td>1</td>
<td>Mortality, WHF/CVE, CI, PCWP, mPAP, SVR, PVR</td>
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<td>Cotter, et al 2004</td>
<td>103</td>
<td>RCT</td>
<td>AHF</td>
<td>Tezosentan Intravenous, 0.2-25 mg/hour for 1 day</td>
<td>Placebo</td>
<td>NA</td>
<td>27.4 (12.5)</td>
<td>1</td>
<td>Mortality, WHF/CVE, CI, PCWP, mPAP, SVR, PVR</td>
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<tr>
<td>Torre-Amione, et al 2003</td>
<td>191</td>
<td>RCT</td>
<td>AHF</td>
<td>Tezosentan Intravenous, 50-100 mg/hour for 1 day</td>
<td>Placebo</td>
<td>NA</td>
<td>23.5 (14.3)</td>
<td>1</td>
<td>Mortality, WHF/CVE, CI, PCWP, mPAP, SVR, PVR</td>
</tr>
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<td>O’Connor, et al 2003</td>
<td>97</td>
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<td>AHF</td>
<td>Tezosentan Intravenous, 50 mg/hour for 2 days</td>
<td>Placebo</td>
<td>NA</td>
<td>(10) (9)</td>
<td>1</td>
<td>Mortality, WHF/CVE, CI, PCWP, mPAP, SVR, PVR</td>
</tr>
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<td>Kaluski, et al 2003</td>
<td>42</td>
<td>RCT</td>
<td>AHF</td>
<td>Tezosentan Intravenous, 50-100 mg/hour for 1 day</td>
<td>Placebo</td>
<td>NA</td>
<td>42.2 (11.9)</td>
<td>1</td>
<td>Mortality, WHF/CV</td>
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<td>Schalcher, et al 2001</td>
<td>18</td>
<td>RCT</td>
<td>AHF</td>
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<td>Placebo</td>
<td>3</td>
<td>24.9 (5.0)</td>
<td>1</td>
<td>Mortality, CI, PCWP, mPAP, SVR, PVR</td>
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<tr>
<td>Torre-Amione, et al 2003</td>
<td>46</td>
<td>RCT</td>
<td>AHF</td>
<td>Tezosentan Intravenous, 1-100 mg/hour for 7 hours</td>
<td>Placebo</td>
<td>3-4</td>
<td>21.1 (6.4)</td>
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<td>Mortality, CI, PCWP, mPAP, SVR, PVR</td>
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<td>Givertz, et al 2000</td>
<td>32</td>
<td>RCT</td>
<td>CHF</td>
<td>Sitaxsentan Oral, 1-5 mg/kg for 5 minutes for 15 minutes</td>
<td>Placebo</td>
<td>3-4</td>
<td>21.3 (9.2)</td>
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<tr>
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<td>60</td>
<td>RCT</td>
<td>CHF</td>
<td>Bosentan Oral, 1-250 mg/day for 20 weeks</td>
<td>Placebo</td>
<td>3-4</td>
<td>23.8 (6.6)</td>
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<td>Mortality, WHF/CVE, CI</td>
</tr>
<tr>
<td>Packer, et al 2005</td>
<td>244</td>
<td>RCT</td>
<td>CHF</td>
<td>Bosentan Oral, 1,000 mg/day for 26 weeks</td>
<td>Placebo</td>
<td>3-4</td>
<td>23.8 (6.6)</td>
<td>1</td>
<td>Mortality, WHF/CVE, CI</td>
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<td>Süttsch, et al 1998</td>
<td>24</td>
<td>RCT</td>
<td>CHF</td>
<td>Bosentan Oral, 50 mg/day for 2 weeks</td>
<td>Placebo</td>
<td>3</td>
<td>23.1 (5.2)</td>
<td>0.5</td>
<td>CI, PCWP, mPAP, SVR, PVR</td>
</tr>
<tr>
<td>Anand, et al 2004</td>
<td>375</td>
<td>RCT</td>
<td>CHF</td>
<td>Darusentan Oral, 1-100 mg/day for 24 weeks</td>
<td>Placebo</td>
<td>3-4</td>
<td>26 (11.5)</td>
<td>0.5</td>
<td>CI, PCWP, mPAP, SVR, PVR</td>
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<tr>
<td>Lüscher, et al 2002</td>
<td>124</td>
<td>RCT</td>
<td>CHF</td>
<td>Darusentan Oral, 30-100 mg/day for 28 weeks</td>
<td>Placebo</td>
<td>2-4</td>
<td>26 (11.5)</td>
<td>0.5</td>
<td>Mortality, WHF/CVE, CI</td>
</tr>
<tr>
<td>Prasad, et al 2006</td>
<td>36</td>
<td>RCT</td>
<td>CHF</td>
<td>Enrasentan Oral, 60-90 mg/day for 24 weeks</td>
<td>Enalapril</td>
<td>1</td>
<td>61 (12)</td>
<td>0.5</td>
<td>Mortality, WHF/CVE, CI</td>
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</table>

AHF indicates acute heart failure; CHF, chronic heart failure; CI, cardiac index; ERA, endothelin receptor antagonist; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; NA, not available; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RCT, randomized controlled trial; SVR, systemic vascular resistance; and WHF/CVE, worsening heart failure or cardiac vascular events.
groups. Patients were suffering from HF with reduced ejection fraction (HFrEF) in most studies with the exception of 2 studies that included patients with HFrEF. ERAs were administered intravenously or orally and tezosentan was most frequently used in these studies. The mean follow-up duration ranged from 0.5 to 6 months. With regard to the quality of the studies included, according to the Cochrane risk of bias tool, most items indicated a low or unclear risk of bias (Supplementary Figure 1).

Effect of ERA on mortality and incidence of WHF/CVE: A total of 12 RCTs, involving 3,503 participants, reported the mortality of HF after ERA therapy. Compared to the control groups, ERA therapy seemed to have no impact on the mortality of HF patients \( (RR = 1.12, 95\% CI = 0.81 \text{ to } 1.54, P = 0.51) \) \( \text{(Figure 2)} \). No significant heterogeneity was found (\( I^2 = 0.0\% \), \( P = 0.95 \)). Furthermore, subgroup analysis suggested that the mortality of both HFrEF (RR 1.10, 95%CI 0.79 to 1.53, \( P = 0.56 \)) and HFrEF (RR 1.12, 95%CI 0.81 to 1.54, \( P = 0.60 \)) patients was not improved by ERA (Figure 2). Since selective ET\(_B\) receptor blockade was likely to worsen the hemodynamic variables of HF patients, non-selective ETA/B and selective ETA receptor antagonists may have different effects on the clinical outcomes of HF. However, the results of subgroup analysis indicated that neither non-selective ETA/B (RR 1.03, 95%CI 0.91 to 1.16, \( P = 0.62 \)) and selective ETA receptor antagonists showed that neither had the potential to reduce the incidence of WHF/CVE in HF patients (Supplementary Figure 3).

Hemodynamic effect of ERA in patients with HF: Cardiac index is a good indicator of whether the cardiac function of HF patients is improved after ERA treatment. In the present meta-analysis, since significant heterogeneity was observed (\( I^2 = 67.1\% \), \( P < 0.01 \)), we used a random effect model to analyze the change of cardiac index in 10 RCTs that included 971 HF patients. Cardiac index was significantly increased in the ERA groups, as compared with control treatments (WMD 0.32, 95%CI 0.22 to 0.43, \( P < 0.01 \)) \( \text{(Figure 4)} \).

In addition, 8 RCTs reported changes in PCWP and mPAP that were associated with the symptoms, such as dyspnea, of HF patients. No statistical heterogeneity was found in the analyses of PCWP (\( I^2 = 0.0\% \), \( P = 0.46 \) and mPAP (\( I^2 = 37.0\% \), \( P = 0.13 \)), hence we used a fixed effect model. In contrast to placebo, ERA therapy could effectively decrease the PCWP of HF patients (WMD -3.10, 95%CI -3.99 to -2.20, \( P < 0.01 \)) \( \text{(Figure 5A)} \). The mPAP was also likely to be significantly reduced by ERA (WMD -4.42, 95%CI -5.50 to -3.33, \( P < 0.01 \)) \( \text{(Figure 5B)} \). Moreover, in comparison to placebo, both the SVR (WMD -276.35, 95%CI -105.33 to -153.09, \( P < 0.01 \)) \( \text{(Figure 6A)} \) and PVR (WMD -69.42, 95%CI -105.33 to -33.52, \( P < 0.01 \)) \( \text{(Figure 6B)} \) in patients with HF were significantly improved by ERA, without significant heterogeneity.

Publication bias and sensitivity analysis: Based on the results
of funnel plots and Egger’s tests, no publication bias was observed for WHF/CVE, cardiac index, mPAP, SVR, or PVR. However, in the analyses of mortality and PCWP, significant publication bias was observed (Supplementary Figure 4, Supplementary Figure 5). To test the stability of our estimates, we performed sensitivity analyses for all outcomes. All estimates in our meta-analysis were not substantially modified after omitting each study one by one (Supplementary Table II).
Results from this meta-analysis showed that ERA could not reduce the mortality and incidence of WHF/CVE among patients with HF. However, compared with placebo, all of the hemodynamic variables of HF patients including cardiac index, PCWP, mPAP, SVR, and PVR were significantly improved by ERA therapy.

ET-1 is a potent vasoconstrictor, primarily released by endothelial cells, to maintain endogenous vascular tone.\textsuperscript{27} At least two subtypes of ET receptors, ETA and ETB, have been identified in human myocardium and the ET-1 related pathologic hypertrophy, fibrosis, and increased contractility were mainly mediated by ETA.\textsuperscript{28} Previous experimental studies have suggested that increased ET-1 and subsequent activation of ETA receptors played a key role in the pathophysiological changes in HF and blockade of the ET system with ERA could effectively ameliorate survival, LV dysfunction, and ventricular remodeling in acute or cardiomyopathy HF models.\textsuperscript{29-31} Furthermore, several clinical trials confirmed the ability of ERA to improve the hemodynamics of HF\textsuperscript{14-16} and a recent study\textsuperscript{11} found that sitaxsentan was likely to increase exercise tolerance in HFpEF patients. However, the effect of ERA on clinical outcomes of HF patients needs to be further evaluated.

In accordance with most RCTs, our study demonstrated that the mortality and WHF/CVE of HF patients were not likely to be improved by ERA therapy. Although we did not analyze the HF symptoms due to different evaluation criteria in

**Figure 5.** Forest plot depicting the effect of ERA on the PCWP (A) and mPAP (B) in patients with heart failure.
each RCT, data from most studies included indicated that ERA may have had no impact on the improvement of major HF symptoms. Several possible reasons may explain these negative effects. First, like ACEIs and β blockers, a biphasic pattern of response to ERA therapy may exist in HF patients. Acute administration of ERA could lead to worsening HF and long-term treatment may produce favorable effects on clinical outcomes. In β blocker or ACEI/ARB therapy, at least 1 to 2 years treatment is needed to improve the mortality and morbidity among HF patients. However, the duration of ERA therapy in the reports studied only ranged from 0.5 to 6 months and hence this short treatment time may not meet the criteria of the duration for evaluating the effects of ERA on the mortality and incidence of WHF/CVE. Second, physiologically, the ETα receptor in human myocardium was reported to be involved in the inotropic effects. Hence, ERA administration might reduce this important compensatory effect in HF patients to offset the potential clinical benefits on symptoms and outcomes. Third, ACEI and β blockers were used as background treatments for most HF patients and might have caused maximum clinical effects. Thus, ERA therapy might not bring any additional clinical benefits in those already treated with ACEI or β blockers.

Although there are important pharmacological differences between non-selective ETαβ and selective ETα receptor antagonists, the results of subgroup meta-analysis suggested that both of these two types of ERA did not have the potential to decrease the mortality and incidence of WHF/CVE in HF patients. Hence, there might not be any important clinical difference between non-selective ETαβ and selective ETα receptor antagonists. However, it is noteworthy that so far, there is a lack of high-quality RCTs with which to directly evaluate and
compare their clinical effects and hence whether these two different ERAs have similar clinical effects in HF patients needs to be further investigated.

The significant elevation of cardiac index was identified in our meta-analysis and this positive effect was a uniform trend across the entire group of most studies included, except two of them. As compared with other RCTs that reported an improvement of the cardiac index, the dosage of bosentan or tezosentan in these two studies was low and the PCWP or SVR in these two studies were not significantly improved either. Hence, the dose-dependent effect of ERA on the hemodynamics of HF patients and higher SVR which could hinder cardiac ejection may explain the negative effect on the cardiac index.

Our meta-analysis of hemodynamic variables also indicated that ERA could effectively reduce the PCWP and mPAP of HF patients. However, why did ERA fail to improve dyspnea and clinical outcomes, despite evidence of improved pulmonary hemodynamics? This contradictory consequence may partly be attributed to the fact that the potentially beneficial effect on dyspnea of reducing PCWP with ERA may be neutralized by other detrimental effects of ET blockade, such as the induction of pulmonary venous-arterial shunting leading to desaturation. In addition, as with other agents, a beneficial hemodynamic effect does not always translate into improved clinical outcomes because complicated mechanisms are involved in the development of HF. Recently, LaRue et al found that bosentan could significantly decrease the PAP and PVR in patients after left ventricular assist device (LVAD) implantation. Hence, even though ERA is not commonly recommended for the treatment of HF presently, with its promising hemodynamic effects, it may be used as adjunctive therapy for refractory pulmonary hypertension in LVAD or advanced HF patients.

With regard to the PVR and SVR, according to the results of our meta-analysis, both were likely to be decreased by ERA therapy. However, in 4 studies, ERA had little or no effect on the SVR or PVR of HF patients. Previous studies have demonstrated that intra-arterial or intravenous infusion of an ETα receptor agonist could cause constriction of the systemic vasculature in HF patients. Hence, ETα receptors may mediate the systemic vasoconstrictor response of HF. It is noteworthy that the ERAs used in two of the 4 studies were the selective ETA receptor antagonists sitaxsentan and darusentan. Although they could selectively inhibit the contraction of pulmonary arteries, predominantly mediated by the ETα receptor, but it had little impact on the activity of vasoconstrictor ETα receptors located on systemic resistance vessels. Moreover, considering the dose-dependent hemodynamic effects of EAR, the negative effects in the other two studies might be attributed to the fact that the HF patients in these studies were administered low dose or oral ERAs.

The present study has several limitations. First, significant heterogeneity and publication bias which may decrease the strength of our estimates were observed in the analyses of cardiac index, mortality, and PCWP. Second, the types and durations of ERA were variable in each of the RCTs, which may produce confound bias for the evaluation of ERA benefits in patients with HF. Third, we were not able to assess whether ERA could improve the symptoms of HF, due to the different evaluation criteria in the studies we analyzed. Fourth, the drug–drug interactions of background medications, especially ACEI and β blockers, may have influenced the accuracy of our estimates. Finally, as we only included published RCTs, we could not exclude the possibility that publication bias may have affected our results.

Conclusion: In summary, this meta-analysis provides evidence that ERA therapy could effectively enhance cardiac output and improve pulmonary and systemic hemodynamics, but with no benefit to clinical outcomes in patients with HF. Hence, at present, we do not recommend the use of ERA as a routine treatment for the management of HF. In the future, additional well-designed RCTs with long-term follow-up duration are needed to confirm our findings.

Acknowledgments

We acknowledge all the original authors of the studies included in our analysis for their excellent work.

Disclosure

Conflict of interest: The authors have no conflicts of interest to disclose.

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