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Peer reviewed

# Renin–angiotensin blockade in heart failure with preserved ejection fraction: a systematic review and meta-analysis

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## Abstract

Studies with angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) in patients with heart failure with preserved ejection fraction (HFpEF) have yielded inconsistent results. To conduct a systematic review and meta-analysis of all evidence for ACE-I and ARBs in patients with HFpEF, we searched PubMed, Ovid SP, Embase, and Cochrane database to identify randomized trials and observational studies that compared ACE-I or ARBs against placebo or standard therapy in HFpEF patients. Random-effect models were used to pool the data, and  $I^2$  testing was performed to assess the heterogeneity of the included studies. A total of 13 studies (treatment arm = 8676 and control arm = 8608) were analysed. Pooled analysis of randomized trials for ACE-I and ARBs ( $n = 6$ ) did not show any effect on all-cause mortality [relative risk (RR) = 1.02, 95% confidence interval (CI) = 0.93–1.11,  $P = 0.68$ ,  $I^2 = 0\%$ ], while results from observational studies showed a significant improvement (RR = 0.91, 95% CI = 0.87–0.95,  $P = 0.005$ ,  $I^2 = 81.5\%$ ). In pooled analyses of all studies, ACE-I showed a reduction of all-cause mortality (RR = 0.91, 95% CI = 0.87–0.95,  $P = 0.01$ ). There was no reduction in cardiovascular mortality seen, but in pooled analysis of randomized trials, there was a trend towards reduced HF hospitalization risk (RR = 0.91, 95% CI = 0.83–1.01,  $I^2 = 0\%$ ,  $P = 0.074$ ). These data suggest that ACE-I and ARBs may have a role in improving outcomes of patients with HFpEF, underscoring the need for future research with careful patient selection, and trial design and conduct.

**Keywords** Heart failure; Preserved ejection fraction; Angiotensin-converting enzyme inhibitors; Angiotensin receptor blockers; Renin–angiotensin system

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## Introduction

Patients with heart failure with preserved ejection fraction (HFpEF) represent approximately half of all HF patients.<sup>1,2</sup> Although outcomes for these patients remain poor and similar to patients with HF with reduced ejection fraction (HFrEF), to date, there are no therapies known to improve outcomes in these patients.<sup>3,4</sup> As such, even a therapy for patients with HFpEF that provides only modest benefit may meet an important unmet need. Hypertension, diabetes mellitus, and chronic kidney diseases are highly prevalent and are

implicated in development and progression of HFpEF. All these comorbidities benefit from treatment with angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs). Angiotensin-converting enzyme inhibitor and ARB also improve outcomes in patients with HFrEF. Thus, it stands to reason that these drugs may benefit HFpEF as well. However, clinical trials<sup>5–7</sup> in HFpEF did not replicate benefits seen in HFrEF with ACE-I and ARB therapy, and multiple explanations for these discordant results have been proposed. There remains ongoing debate regarding patient selection, crossover rates, low event rates,

and open-label use of investigational agents in these trials; all factors potentially diminishing the power to show a difference.<sup>8</sup> In contrast to trial data, observational data, however, suggest potential benefit with ACE-I and ARB in HFpEF.<sup>9,10</sup> Prior systematic reviews and meta-analyses studying the role of ACE-I and ARBs in HFpEF have not included all evidence.<sup>11–13</sup> In an attempt to pool all the evidence quantitatively and qualitatively, we conducted this systematic review and meta-analysis of randomized clinical trials and observational studies to better understand the effect of ACE-I and ARBs on outcomes in HFpEF.

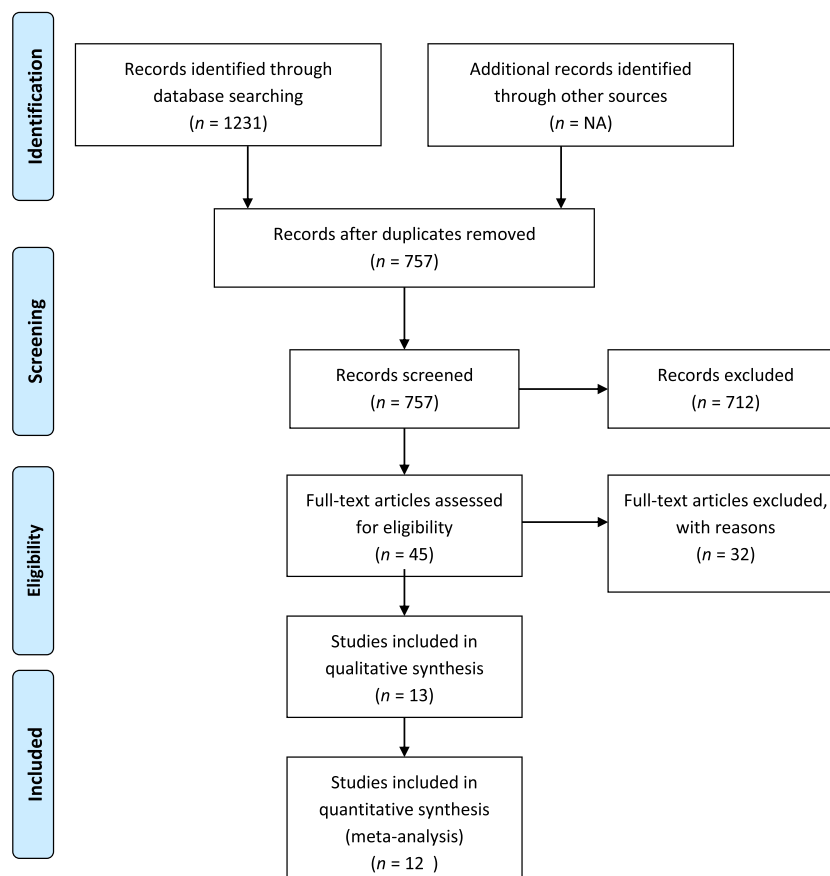
## Methods

An extensive literature search was conducted utilizing Medline (PubMed and Ovid SP, Embase, and Cochrane Central Register of Controlled Clinical Trials). A variety of search terms as Medical Subject Headings and keywords were employed including ‘heart failure with preserved ejection fraction, HFpEF, diastolic HF, HF with normal

ventricular systolic function, persevered cardiac function HF, angiotensin converting enzyme inhibitors, ACE inhibitors, ACE-I, angiotensin receptor blockers, ARBs, heart failure, enalapril, quinapril, imidapril, delapril, lisinopril, ramipril, perindopril, captopril, Irbesartan, valsartan, candesartan’, and a combination of all these terms. Original research including both prospective observational (prospective cohort and nested case control studies) and randomized controlled trials was selected. The search was conducted from the inception of these databases till January 2016. Only articles in English language were considered. To ensure no article was missed, we also hand searched the references of all pertinent retrieved articles.

Two independent reviewers carefully viewed all the retrieved publications. The exclusion criteria were as follows: (i) patients who had transient symptoms following a recent illness, (ii) studies that did not provide adequate details for clinical endpoints, (iii) report with less than 10 patients, (iv) single-arm studies, (v) editorials or review articles, (vi) subgroup analysis or interim analysis of landmark articles, and (vii) heart transplant patients. The inclusion criteria included comparison of ACE-I or ARBs against placebo or standard

**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram showing detailed search strategy.



therapy and a minimum of 3 month follow-up. Any disagreement was solved by mutual consensus.

Two authors extracted and verified the data. A standardized data collection form was used to extract data from each study. In case of any discrepancy, the original reference article was reviewed again. The following information was extracted: first author's name, year of publication, study design, sample size, name of drug used, baseline patient demographics, primary endpoints, secondary endpoints, and duration of follow-up.

Quality assessment of studies was performed through Jadad scale.<sup>14</sup> Hazard ratios, risk ratios, and odds ratios were assumed to approximate the same measure of relative risk (RR) across studies. Relative risks with 95% confidence interval (CI) were used as the common measures of association. Summary RRs were pooled using a random-effects meta-analysis. Statistical heterogeneity across studies was quantified using Cochran  $\chi^2$  and the  $I^2$  statistics, respectively. Clinical endpoints used in our analysis were all cause mortality, HF hospitalization, cardiovascular death, total hospitalizations, and composite endpoint of HF hospitalization and all-cause mortality. We assessed the potential for publication bias through formal tests, namely, Begg's funnel plots and Egger's regression symmetry test.<sup>15</sup> All statistical tests were two-sided and used a significance level of  $P < 0.05$ . All data were analysed using STATA 10 (Stata Corporation, Lakeway Drive, College Station, TX, USA).

## Results

A total of 13 studies were included,<sup>5–7,10,16–24</sup> cumulatively representing 8676 patients in the treatment and 8608 in the control groups. The literature search strategy is highlighted in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow sheet (Figure 1). Seven studies were with ACE-I,<sup>6,17–21,23</sup> four on ARBs,<sup>5,7,22,24</sup> and two<sup>10,16</sup> used both. Of these, six<sup>10,17,18,20,21,24</sup> were observational studies. Yi *et al.*<sup>16</sup> reported data separately for ACE-I and ARBs making it a total of 14 entries in Table 1. Studies were generally of good quality with a mean Jadad score of 4. No evidence of publication bias was noted as shown by the funnel plot (Figure 2). Egger's test value for publication bias was  $P = 0.69$ . The demographic and clinical characteristics of all studies are shown in Table 1. Definition of HFpEF varied among studies. The average follow-up period was 24.8 months (3–72 months). The mean age of the pooled sample was 79 years, and 42% of patients were male.

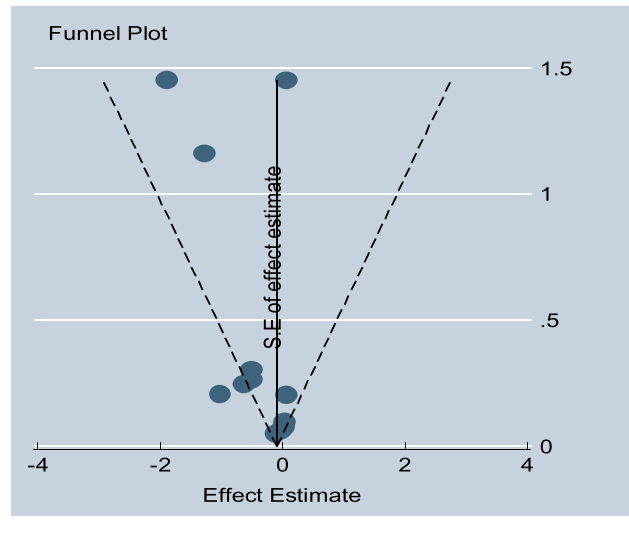
Pooled analysis of randomized trials did not show an improvement in all-cause mortality (RR = 1.02, 95% CI = 0.93–1.11,  $P = 0.68$ ,  $I^2 = 0\%$ ), while results from observational studies showed a benefit (RR = 0.91, 95% CI = 0.87–0.95,  $P = 0.005$ ,  $I^2 = 81.5\%$ ). When results of randomized trials and

**Table 1.** Baseline characteristics of studies included in the meta-analysis

Author	Publication year	Design	Treatment	Sample	Age (years)	Male (%)	Follow-up (months)	Mean LVEF	Number of deaths	HFpEF definition	Jadad score
Philbin <i>et al.</i> <sup>17</sup>	1997	Cohort	ACE-I	190/160	75	43	6	51	53	40	3
Philbin <i>et al.</i> <sup>18</sup>	2000	Cohort	ACE-I	284/245	75	45	6	50.4	79	40	3
Grigorian <i>et al.</i> <sup>20</sup>	2006	Cohort	ACE-I	210/206	73	49	30	—	210	50	3
Tribouilloy <i>et al.</i> <sup>21</sup>	2007	Cohort	ACE-I	120/120	76	52	60	62.6	131	50	4
Lund <i>et al.</i> <sup>10</sup>	2012	Cohort	ACE-I/ARBs	3329/3329	79	47	20	—	3194	40	5
Patel <i>et al.</i> <sup>24</sup>	2012	Cohort	ARBs	296/296	80	31	72	55	375	40	4
Cleland <i>et al.</i> <sup>6</sup>	2006	RCT	ACE-I	424/426	75	45	26	64.5	109	40	6
Yip <i>et al.</i> <sup>16</sup>	2008	RCT	ACE-I	45/50	73	41	12	65.6	3	45	3
Yip <i>et al.</i> <sup>16</sup>	2008	RCT	ARBs	56/50	74	38	12	67.4	4	45	3
Kitzman <i>et al.</i> <sup>23</sup>	2010	RCT	ACE-I	35/36	69	15	12	50	—	50	6
Zi <i>et al.</i> <sup>19</sup>	2003	RCT	ACE-I	36/38	78	44	6	58.6	2	40	4
Massie <i>et al.</i> <sup>7</sup>	2008	RCT	ARBs	2067/2061	72	40	49	59.5	881	45	5
Yusuf <i>et al.</i> <sup>5</sup>	2003	RCT	ARBs	1514/1509	67	60	8	54	481	40	6
Parthasarathy <i>et al.</i> <sup>22</sup>	2009	RCT	ARBs	70/82	62	51	3	71	—	40	4

ACE-I, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; RCT, randomized clinical trial.

**Figure 2** Funnel plot representing publication bias for all-cause mortality.

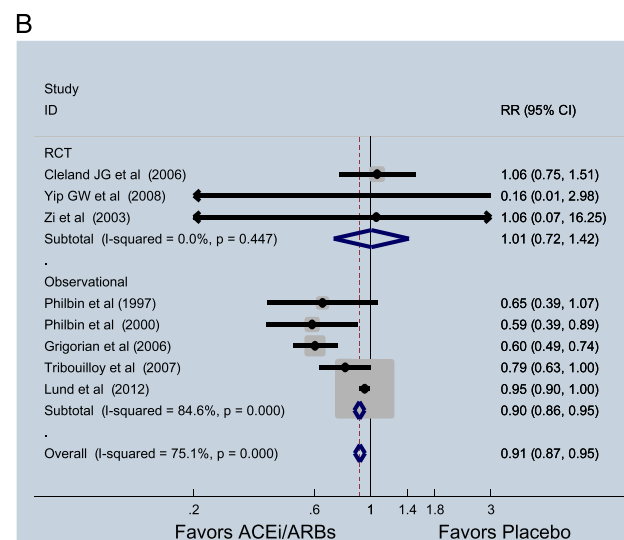
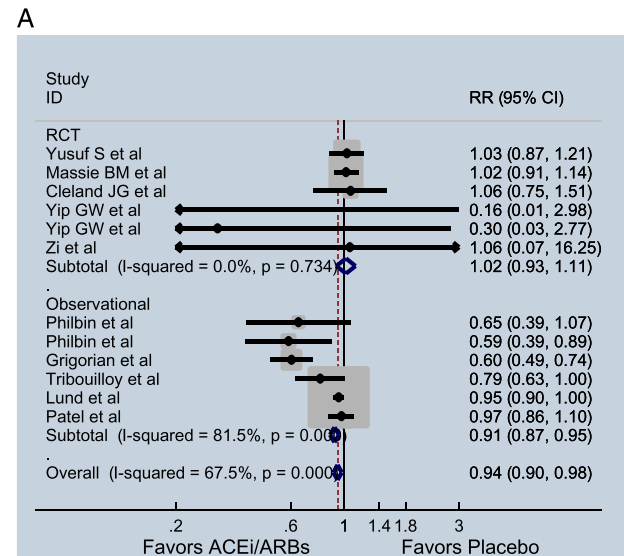


observational studies were pooled (Figure 3A), ACE-I and ARBs were found to modestly reduce all-cause mortality (RR = 0.94, 95% CI = 0.90–0.98,  $P = 0.01$ ,  $I^2 = 67.5\%$ ). After removing the four studies with ARB, the significant lower mortality with ACE-I remained (RR = 0.91, 95% CI = 0.87–0.95,  $P = 0.01$ ,  $I^2 = 75.1\%$ ) (Figure 3B).

Six studies consisting of 8626 patients (treatment = 4332 and control = 4294) reported data on cardiovascular mortality. ACE-I and ARBs did not benefit cardiovascular mortality (RR = 1.00, 95% CI = 0.90–1.12,  $P = 0.953$ ,  $I^2 = 0\%$ ) (Figure 4). Of these, five were randomized trials that showed similar results (RR = 1.01, 95% CI = 0.90–1.13,  $P = 0.906$ ,  $I^2 = 0\%$ ). When only ACE-I studies were considered, no significant reduction in cardiovascular mortality was noted, (RR = 0.90, 95% CI = 0.63–1.28,  $P = 0.543$ ,  $I^2 = 0\%$ ).

Pooled analysis of randomized trials showed a trend towards reduced HF hospitalization risk (RR = 0.91, 95% CI = 0.83–1.01,  $I^2 = 0\%$ ,  $P = 0.074$ ). Three observational studies reported data on HF hospitalization and did not show a significant association (RR = 0.99, 95% CI = 0.86–1.13,  $I^2 = 0\%$ ). Combined analyses of randomized and observational data found similar results (RR = 0.93, 95% CI = 0.86–1.01,  $I^2 = 0\%$ ,  $P = 0.11$ ) (Figure 5A). The effect of ACE-I and ARBs on composite endpoint of death and HF hospitalization showed a non-significant trend (RR = 0.95, 95% CI = 0.91–1.01,  $P = 0.085$ ,  $I^2 = 0\%$ ) (Figure 5B). In both cases, removing ARB studies did not meaningfully affect results (HF hospitalization: RR = 0.90, 95% CI = 0.72–1.14,  $P = 0.39$ ,  $I^2 = 0\%$ ; death or HF hospitalization: RR = 0.93, 95% CI = 0.83–1.05,  $P = 0.25$ ,  $I^2 = 0\%$ ). Angiotensin-converting enzyme inhibitor and ARBs did not reduce all-cause hospitalization (RR = 0.99, CI = 0.96–1.02,  $P = 0.52$ ,  $I^2 = 0\%$ ).

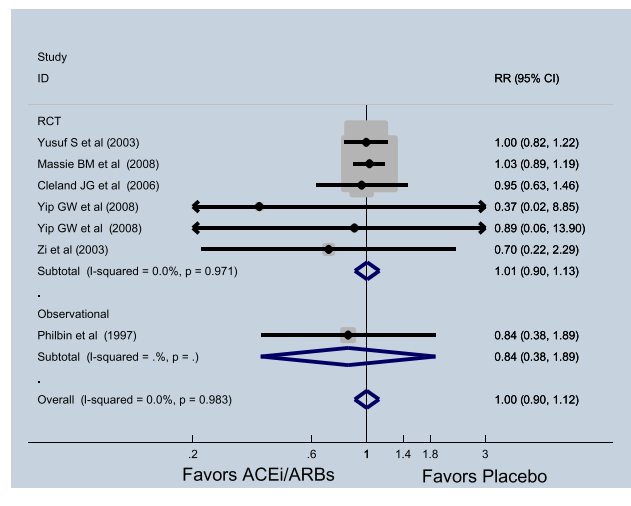
**Figure 3** (A) Effect of angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) on all-cause mortality in patients with heart failure with preserved ejection fraction. (B) Effect of ACE-Is on all-cause mortality in patients with heart failure with preserved ejection fraction. CI, confidence interval; RCT, randomized clinical trial; RR, relative risk.



## Discussion

Despite pathophysiologic rationale, randomized trials with ACE-I and ARB in patients with HFpEF failed to improve outcomes. However, multiple issues other than the efficacy of the intervention may have confounded these results. In this systematic meta-analysis that included both randomized trials and observational studies, we found that ACE-I and ARBs were associated with a modest, but statistically significant, reduction in all-cause mortality in HFpEF patients. The

**Figure 4** Effect of angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) on cardiovascular mortality in patients with heart failure with preserved ejection fraction. CI, confidence interval; RCT, randomized clinical trial; RR, relative risk.

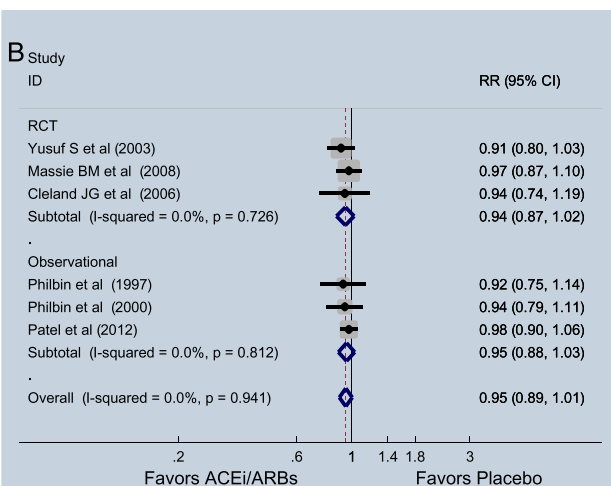
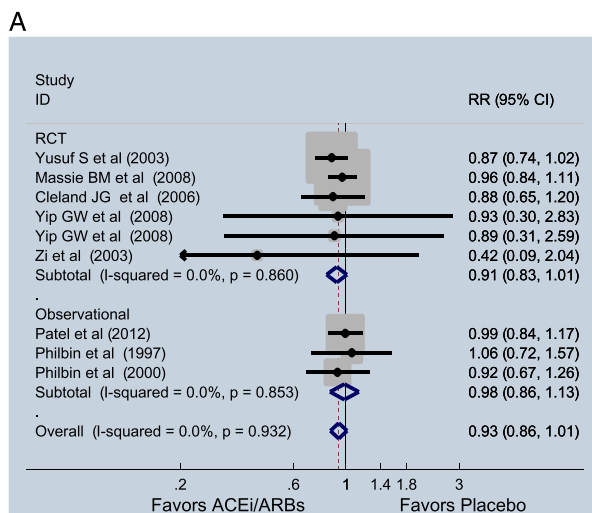


magnitude of benefit was larger when analysis was limited to ACE-I. In randomized trials alone, this effect was not seen. In pooled analysis, although no overall benefit on cardiovascular mortality was seen, data limited to ACE-I demonstrated a similarly modest reduction in risk, albeit statistically non-significant and also driven by the results from observational studies. Similar trends were seen for HF hospitalization. While a systematic meta-analysis does not obviate the aforementioned limitations of trials design and conducts issues with ACE-I and ARB for patients with HFpEF or the general concerns with observational data, these results suggest that further, more refined approaches to studying these drugs in HFpEF may yield different conclusions.

The only large randomized trial (perindopril in elder people with chronic HF study) of ACE-I in patients with HFpEF did not suggest any improvement in clinical outcomes.<sup>6</sup> However, it is important to recognize the many trial factors that might have caused the therapy to fail. There was a very high dropout rate of almost 40% owing to a prolonged recruitment period. Moreover, almost one-third of the patients also received open-label ACE-I after first year of follow-up.<sup>25</sup> This can potentially explain the lack of ACE-I effect found in the latter part of the trial, in contrast to the positive signal earlier in the trial.

The two large randomized trials of ARBs (Candesartan in Heart Failure—Assessment of Mortality and Morbidity-Preserved Trial and Irbesartan in Heart Failure with Preserved Systolic Function-Preserved Trial) had heterogeneity in the enrolled patient population.<sup>5,7</sup> Both trials used lower EF threshold for HFpEF and neither used diastolic function as an entry criterion. In fact, in the Candesartan in Heart Failure—Assessment of Mortality and Morbidity-Preserved

**Figure 5** (A) Effect of angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) on hospitalizations due to heart failure in patients with heart failure with preserved ejection fraction. (B) Effect of ACE-I and ARBs on hospitalizations or mortality in patients with heart failure with preserved ejection fraction. CI, confidence interval; RCT, randomized clinical trial; RR, relative risk.



Echocardiographic Substudy, nearly two-thirds of patients had no or mild diastolic dysfunction, a feature generally believed as central to the HFpEF condition.<sup>26</sup> Stage of the disease may also impact results because ARB was more effective in patients who with lower natriuretic peptide levels.<sup>27</sup>

Our pooled analysis did not reveal any effect of ACE-I/ARB on cardiovascular mortality. As suggested by Fu *et al.*,<sup>12</sup> the mortality benefit from renin-angiotensin modulation might arise from non-cardiac benefit. Their analysis<sup>12</sup> showed that ACE-I did not lower all-cause mortality in subset of patients >75 years indicating that old age and comorbidities might influence mortality rate in elderly. We also did not find any significant results with regard to all-cause hospitalizations

or readmission due to HF. This is in contrast to Zhang *et al.*<sup>11</sup> who reported that these drugs reduce HF hospitalizations. Their pooled analysis consisted of spironolactone trials as well. Nevertheless, we also noted a trend, and our results trended significance with ACE-I.

Because of paucity of data, we included non-randomized studies that had small sample sizes with limited follow-up. The studies included in our analysis had significant heterogeneity, and many studies did not provide any data on subsets of patients limiting our analysis to the overall cohort. In addition, we were unable to perform consistent multivariate adjustments across studies by combining models with the same set of potential confounders owing to our reliance on published data with variable levels of adjustments. Despite our efforts to provide results in a consistent manner, there remained heterogeneity among the available studies that require further investigation. Importantly, the observational data may be impacted by selection bias and confounding with may impact the results. Lastly, there were no uniform doses of ACE-I and ARBs in all of the studies included that may have affected efficacy of the drugs.

These findings indicate that it may be important to further investigate ACE-I and ARB in patients with HFpEF in prospective randomized clinical trials with longer follow-

ups, more defined population (ideally with higher event rates), and possibly stratified by phenotype or stage of disease progression. Also, such trials need to be large in size and avoid significant crossover all in an effort to be adequately powered.

## Conflict of interest

G.C.F. has received research support from National Heart Lung Blood Institute and consults for Amgen, Bayer, Janssen, Novartis, and Medtronic. S.D.A. is a consultant for Amgen. M. G. has been a consultant for Abbott Laboratories, Astellas, AstraZeneca, Bayer HealthCare AG, Corthera, Cytokinetics, Debiopharm S.A., Errekappa Terapeutici, GlaxoSmithKline, Ikaria, Johnson & Johnson, Medtronic, Merck, Novartis Pharma AG, Otsuka Pharmaceuticals, Palatin Technologies, PeriCor Therapeutics, Protein Design Laboratories, Sanofi-Aventis, Sigma Tau, Solvay Pharmaceuticals, Takeda Pharmaceutical, and Trevena Therapeutics. J.B. has received research support from the National Institutes of Health, European Union, and PCORI and served as a consultant for Amgen, Bayer, Boehringer Ingelheim, BMS, CVRx, Gilead, Medtronic, Novartis, Relypsa, and Stealth Peptide.

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