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Original Article

Role of angiotensin receptor blockers in chronic heart failure with reduced left ventricular ejection fraction: a meta-analysis

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Abstract: To identify the role of angiotensin receptor blockers in the treatment of chronic heart failure with reduced ejection fraction, we performed a meta-analysis of a total of 23 clinical trials involving 13,532 patients. A systematic search was conducted on MEDLINE, EMBASE and Cochrane Library. The pooled outcomes were all-cause mortality, cardiovascular mortality, and hospitalizations for heart failure. ARBs reduce all-cause mortality (RR 0.84, 95% CI 0.74-0.96), cardiovascular mortality (RR 0.86, 95% CI 0.74-0.99) and hospitalizations for heart failure (RR 0.68, 95% CI 0.59-0.78) compared with placebo without background ACEIs therapy. ARBs did not differ from ACEIs in reducing all-cause mortality (RR 0.87, 95% CI 0.54-1.41), cardiovascular mortality (RR 0.79, 95% CI 0.42-1.47), hospitalizations for heart failure (RR 1.09, 95% CI 0.74-1.60) but lowered withdrawals due to adverse effects versus ACEIs (RR 0.64, 95% CI 0.53-0.77). Combination of ARBs and ACEIs reduced cardiovascular mortality (RR 0.84, 95% CI 0.74-0.94). However, this combination failed to reduce total mortality (RR 0.86, 95% CI 0.62-1.20) or hospitalizations for heart failure compared with ACEIs alone (RR 0.83, 95% CI 0.59-1.16), and it increased the risk of withdrawals due to adverse effects (RR 1.33, 95% CI 1.15-1.53). This meta-analysis suggests the superiority of ARBs over placebo in reducing mortality and morbidity in patients with heart failure with reduced ejection fraction. ARBs are better tolerated than ACEIs. Close monitoring for adverse effects may be warranted in the combination therapy of ARBs and ACEIs.

Keywords: Angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, heart failure, reduced ejection fraction, meta-analysis

Introduction

Chronic heart failure (CHF) is a major cause of morbidity and mortality in the general population, and healthcare expenditure on it in developed countries consumes 1-2% of the total health care budget [1, 2]. Declining left ventricular ejection fraction (LVEF) of HF patients is an important and powerful predictor of cardiovascular outcomes, and every 10% reduction in LVEF below 45% was independently associated with a 39% increased risk for all-cause mortality [3]. The role of angiotensin receptor blockers (ARBs) in the treatment of chronic heart failure with reduced ejection fraction (HFREF) is controversial. Current evidence-based practice guidelines recommended that ARBs are a reasonable alternative in patients with HFREF intolerant of angiotensin-converting enzyme inhibitors (ACEIs) unless contraindicated, to reduce morbidity and mortality [4, 5]. This is in spite of the theoretical hypothesis that ARBs could potentially better suppress the effects of the renin-angiotensin-aldosterone system. A Cochrane review indicated that ARBs were no better than placebo or ACEIs in reducing the risk of death, disability, or hospital admission for any reason [6]. Nevertheless, this systematic review did not include data neither from Maggioni et al. [7], a subgroup analysis of the Valsartan Heart Failure Trial (Val-HEFT) nor from Cice et al. [8]. The former study would suggest a favorable effect of an ARB on mortality and morbidity in patients with HF not treated with ACEIs, and the latter study was published subsequent to Cochrane review. Moreover, in 3 prior meta-analyses [6, 9, 10], the effects of combination therapy of ARB and ACEI versus ACEI alone on clinical events in HF patients differed from each other despite the fact that

they all included the Val-HEFT and VALIANT (Valsartan In Acute Myocardial Infarction) trials. However, our study omitted VALIANT trial [11] given that it enrolled patients who were not with chronic HF (NYHA class II-IV) but with left ventricular dysfunction immediately post-myocardial infarction (Killip class I-IV). Therefore it would be possible for us to figure out the real add-on effects of ARBs on ACEIs in patients with chronic heart failure. Considering the limitations of current data and the potential superiority of ARBs by themselves in improving survival and reducing morbidity in HF patients, we conducted a comprehensive meta-analysis of all qualified randomized controlled trials to determine the theoretical benefit of ARBs in terms of clinically relevant outcomes particularly in patients with HFREF. We also undertook separate meta-analysis of subgroups of patients by their utilization of different types of ARBs.

Methods

Search strategy

This meta-analysis was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [12]. We systematically performed an electronic search of MEDLINE, EMBASE and Cochrane Library for studies published between January 1970 and December 2014, using key terms: chronic heart failure, congestive heart or cardiac failure, angiotensin-converting enzyme inhibitors, angiotensin receptor blocker and AT II antagonists. Data from randomized controlled trial were included in this meta-analysis. The searches were limited to English publications in humans. A manual search of all potentially relevant studies, meta-analyses, meeting abstracts, international guidelines and reference from selected trials were also screened.

Study selection

The eligibility criteria of studies were applied: (i) participants: patients diagnosed with chronic HF (NYHA class II-IV) and reduced EF; (ii) intervention: ARB versus placebo/ACEIs, combination of ARB and ACEI versus ACEI alone (100% patients receiving background ACEI therapy) (iii) studies provided with outcomes, such as all-cause mortality, cardiovascular mortality and hospitalizations for HF (iv) study design: RCTs available in a full paper article. (v) with duration of follow-up of at least six weeks.

Eligibility and quality assessment

Potentially eligible studies and trial quality information were independently conducted by two investigators. Data were entered into a standardized data-collection form. Any disagreement was resolved by consensus. The methodological of each included study was evaluated with the validated Jadad scale, ranging from 0 to 5, and higher scores indicate better methodological quality [13]. We also extracted study characteristics for each trial. Data were recorded as follows: eligible studies, New York Heart Association Functional Class, ejection fraction, total number of participants, types of ARBs and ACEIs, mean follow-up, Jadad score and end-points.

Statistical analysis

The clinical endpoints were all-cause mortality, CV mortality and hospitalizations for HF. The meta-analysis was performed using Review Manager (Revman, version 5.0.25 for windows, Oxford, England, Cochrane Collaboration) and Stata (version 12.0, Texas, USA, Stata Corporation, College Station). A summary of relative risks (RRs) and their corresponding 95% confidence intervals (CIs) were computed for each dichotomous outcome using either fixed-effects models or, in the presence of obvious heterogeneity (I^2>50%), random-effects models [14]. Statistical heterogeneity across studies was evaluated with Q and I^2 statistics. Studies with an I^2 statistics of 25-50% were considered to have low heterogeneity, those with an I^2 statistics of 50%-75% were considered to have moderate heterogeneity, and those with an I^2 statistics of >75% were considered to have a high degree of heterogeneity [15]. Potential sources of heterogeneity were investigated using sensitivity analyses and each study involved in the meta-analysis was deleted each time to reflect the influence of the individual data set on the pooled RRs.

An estimation of potential publication bias was executed by the funnel plots in which the log RRs were plotted against their SEs. An asymmetrical plot suggests a possible publication bias. Funnel plot asymmetry was assessed by Egger's linear regression test [16]. The significance of the intercept was determined by the t test suggested by Egger. A P value <0.05 was considered statistically significant. Subgroup analysis was performed by drug types.

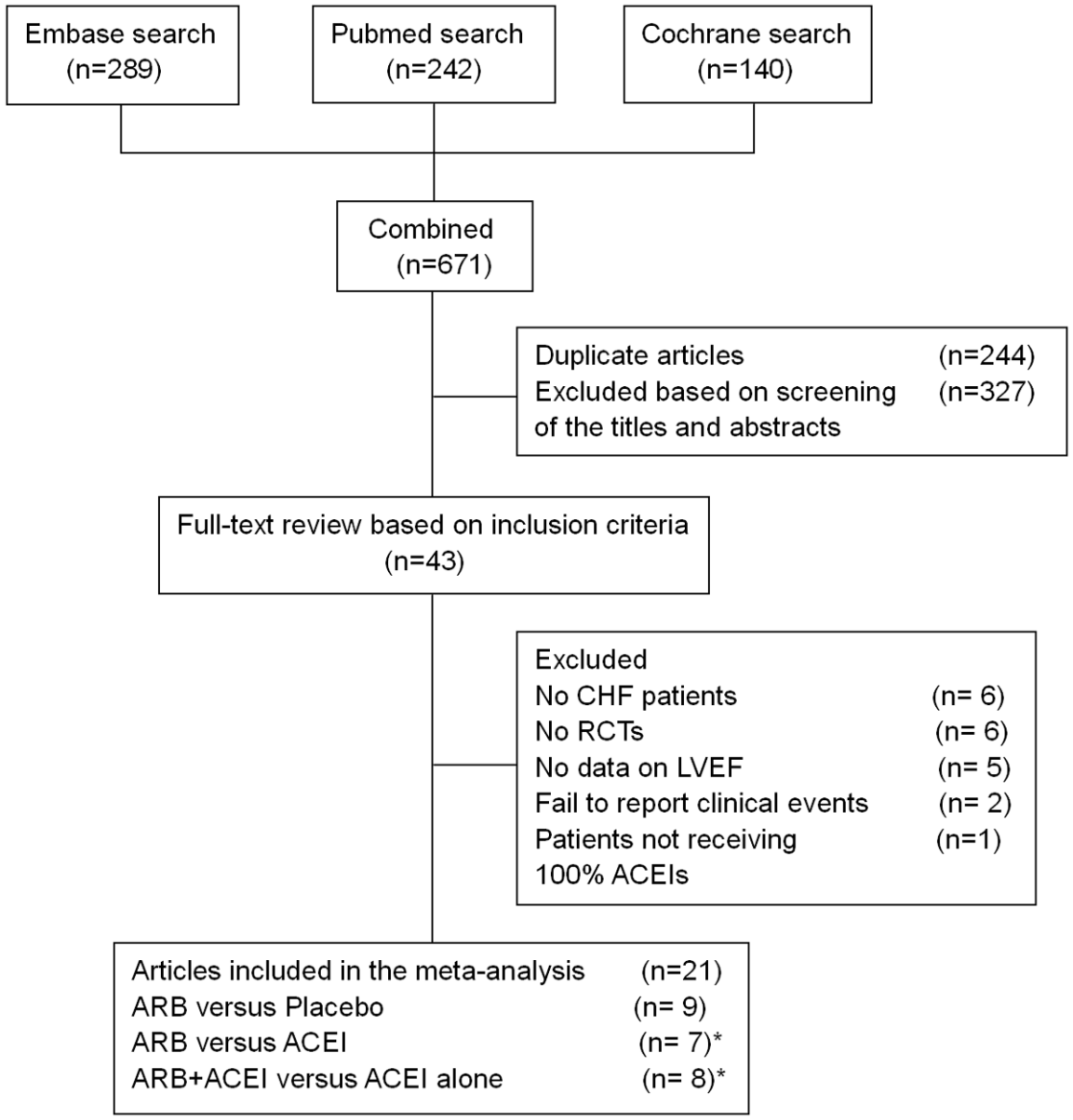

Figure 1. Flow chart of study selection. (*) One article reported both ARB versus ACEI and ARB + ACEI versus ACEI alone. CHF, chronic heart failure; RCT, randomized controlled trial; LVEF, left ventricular ejection fraction; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor.

Results

Eligible studies

The derivation of the included studies and the selecting process are described in **Figure 1**. After screening the abstracts and full texts, a total of 23 randomized controlled trials involving 13,532 patients with HFREF were included [7, 8, 17-36]. Of note, the Val-HEFT trial was excluded in our study in that there were still 7.3% of involved patients not receiving background ACEIs therapy [37]. The key characteristics of the selected studies are summarized in **Table 1**. Nine studies used placebo as controls. Seven studies used ACEI as controls. Eight studies compared ARB + ACEI with ACEI alone. One trial included both a placebo and an ACEI arm as controls. Of note, the subgroup analysis of Val-HEFT, Maggioni et al., which examined 366 (7.3%) of the 5,010 patients in VaL-HEFT trial and evaluated the effects of valsartan in patients with HFREF not receiving ACEI at baseline, was included in our meta-analysis to detect ARB versus placebo. Mean Jadad score for all eligible trials was 3.2 [2-5].

Table 1. Summary of randomized controlled trials included in the meta-analysis

Source	NYHA class	LVEF	n	ARB and target doses	Placebo	ACEI	Follow-up mean	Jadad score	End-points
ARB versus placebo									
Crozier I, et al. [17] (1995)	II-IV	<40%	134	Losartan 2.5 mg, 10 mg, 25 mg, 50 mg OD	Placebo	NA	12 weeks	3	Hemodynamics, neurohormones
STRECH [18] (1999)	II-III	30%-45%	844	Candesartan 4 mg, 8 mg, 16 mg OD	Placebo	NA	12 weeks	5	Primary: exercise time; Secondary: signs and symptoms of CHF, NYHA class, cardiothoracic ratdo, neuroendocrine parameters
SPICE [19] (2000)	II-IV	<35%	270	Candesartan 16 mg OD	Placebo	NA	12 weeks	3	Primary: tolerability; Secondary: NYHA class, 6MWD, QoL, laboratory tests
Sharma D, et al. [20] (2000), III-Int'l	II-IV	≤40%	385	Losartan 50 mg OD	Placebo	NA	12 weeks	2	Primary: exercise capacity
Sharma D, et al. [20] (2000), III-US	II-IV	≤40%	351	Losartan 50 mg OD	Placebo	NA	12 weeks	2	Primary: exercise capacity
Maggioni AP, et al. [7] (2002), Val-HeFT	II-IV	<40%	366	Valsartan 160 mg BID	Placebo	NA	24 months	3	Primary: all-cause mortality; Secondary: CV death, non-fatal morbid event, sudden death with resuscitation, hospital admission for HF, therapy for HF
CHARM-Alternative [21] (2003)	II-IV	≤40%	2028	Candesartan 32 mg OD	Placebo	NA	33.7 months	5	Primary: the composite of CV death, hospital admission for CHF; Secondary: CV death, hospital admission for CHF, non-fatal MI, non-fatal stroke, coronary revascularization, all-cause mortality, development for new diabetes
ARCH-J [22] (2003)	II-III	≤45%	305	Candesartan 8 mg OD	Placebo	NA	6 months	2	Primary: confirmed progression of CHF; Secondary: progression of CHF, cardiac death, life-threatening arrhythmias, MI, coronary artery disease
Mitrovic V, et al. [23] (2003)	II-III	≤40%	218	Candesartan 2 mg, 4 mg, 8 mg, 16 mg OD	Placebo	NA	12 weeks	2	Primary: PCWP, SVR, cardiac index ;Secondary: pulmonary arterial pressure, neurohormones, fatigue and ankle swelling, physicians' overall efficacy score, QoL, NYHA classification, heart rate
ARB versus ACEI									
Dickstein K, et al. [24] (1995)	III-IV	≤35%	166	Losartan 25 mg, 50 mg OD	NA	Enalapril 10 mg BID	8 weeks	4	Primary: symptoms of heart failure, exercise capacity, neurohormonal status
ELITE [25] (1997)	II-IV	≤40%	722	Losartan 50 mg OD	NA	Captopril 50 mg TID	48 weeks	4	Primary: renal dysfunction; Secondary: all-cause mortality, hospitalization for heart failure
Lang RM, et al. [26] (1997)	II-IV	≤45%	116	Losartan 25 mg, 50 mg OD	NA	Enalapril 10 mg BID	12 weeks	2	Primary: exercise tolerance, signs and symptoms of heart failure; Secondary: clinical and laboratory adverse events
RESOLVD [27] (1999)	II-IV	<40%	768	Candesartanf 4 mg, 8 mg, 16 mg OD	NA	Enalapril 10 mg BID	43 weeks	2	Primary: 6MWD; Secondary: ventricular volume, QoL, NYHA classification, neurohormone levels
ELITE II [28] (2000)	II-IV	≤40%	3152	Losartan 50 mg OD	NA	Captopril 50 mg TID	1.25 years	4	Primary: all-cause mortality; Secondary: composite of sudden death, hospital admission for heart failure, NYHA classification
REPLACE [29] (2001)	II-III	≤40%	378	Telmisartan 10 mg, 20 mg, 40 mg, 80 mg OD	NA	Enalapril 10 mg BID	12 weeks	3	Primary: exercise duration; Secondary: LVEF, QoL, BP, neurohormonal changes, NYHA classification
HEAVEN [30] (2002)	II-III	≤45%	141	Valsartan 160 mg OD	NA	Enalapril 10 mg BID	12 weeks	3	Primary: 6MWD; Secondary: QoL, LVEF, left ventricular end diastolic diameter, dyspnea fatigue index score
ARB + ACEI versus ACEI alone									
Hamroff G, et al. [31] (1999)	III-IV	≤35%	33	Losartan 50 mg OD	NA	Enalapril, Captopril, Fosinopril, Lisinopril	6 months	3	Primary: peak VO_2, NYHA functional class; Secondary: laboratory safety parameters and doses of concomitant background medications

RESOLVD [27] (1999)	II-IV	<40%	768	Candesartan 4 mg, 8 mg, 16 mg OD	NA	Enalapril 10 mg BID	43 weeks	2	Primary: 6MWD; Secondary: ventricular volume, QoL, NYHA classification, neurohormone levels
Tonkon M, et al. [32] (2000)	II-III	≤40%	109	Irbesartan 150 mg OD	NA	Benazepril, Captopril, Enalapril, Fosinopril, Lisinopril, Quinapril	12 weeks	3	Primary: symptom-limited exercise tolerance time; Secondary: NYHA functional class, LVEF
ADEPT [33] (2001)	II-IV	≤35%	36	Eprosartan 400 mg BID	NA	Benazepril, Captopril, Enalapril, Fosinopril, Lisinopril, Perindopril Quinapril, Ramipril, Trandolapril	8 weeks	2	Primary: LVEF; Secondary: haemodynamics, neurohormones
CHARM-Added [34] (2003)	II-IV	≤40%	2548	Candesartan 32 mg OD	NA	Captopril, Enalapril, Perindopril, Quinapril, Trandolapril	41 months	5	Primary: the composite of CV death, hospital admission for CHF; Secondary: CV death, hospital admission for CHF, non-fatal MI, non-fatal stroke, coronary revascularization, all-cause mortality, development for new diabetes
White M, et al. [35] (2007)	II-IV	<40%	80	Candesartan 32 mg OD	NA	Enalapril	25 weeks	3	Primary: Nt-proBNP; Secondary: biochemical parameters selected markers of inflammation, oxidative stress, plasma insulin levels
Kum LC, et al. [36] (2008)	II-III	<50%	50	Irbesartan 300 mg/day	NA	Captopril, Enalapril, Fosinopril, Lisinopril, Perindopril	1.3 years	3	exercise capacity, NYHA class, QoL, left ventricular end systolic diameter, mortality and/or CV hospitalization
Cice G, et al. [8] (2010)	II-III	≤40%	332	Telmisartan 80 mg/day	NA	Enalapril, Ramipril	36 months	5	Primary: all-cause mortality, CV death, hospital admission for management of worsening CHF; Secondary: acute non-fatal MI, non-fatal stroke, CV mortality in addition to acute non-fatal MI, coronary revascularization, CV hospital admission, permanent premature treatment withdrawals

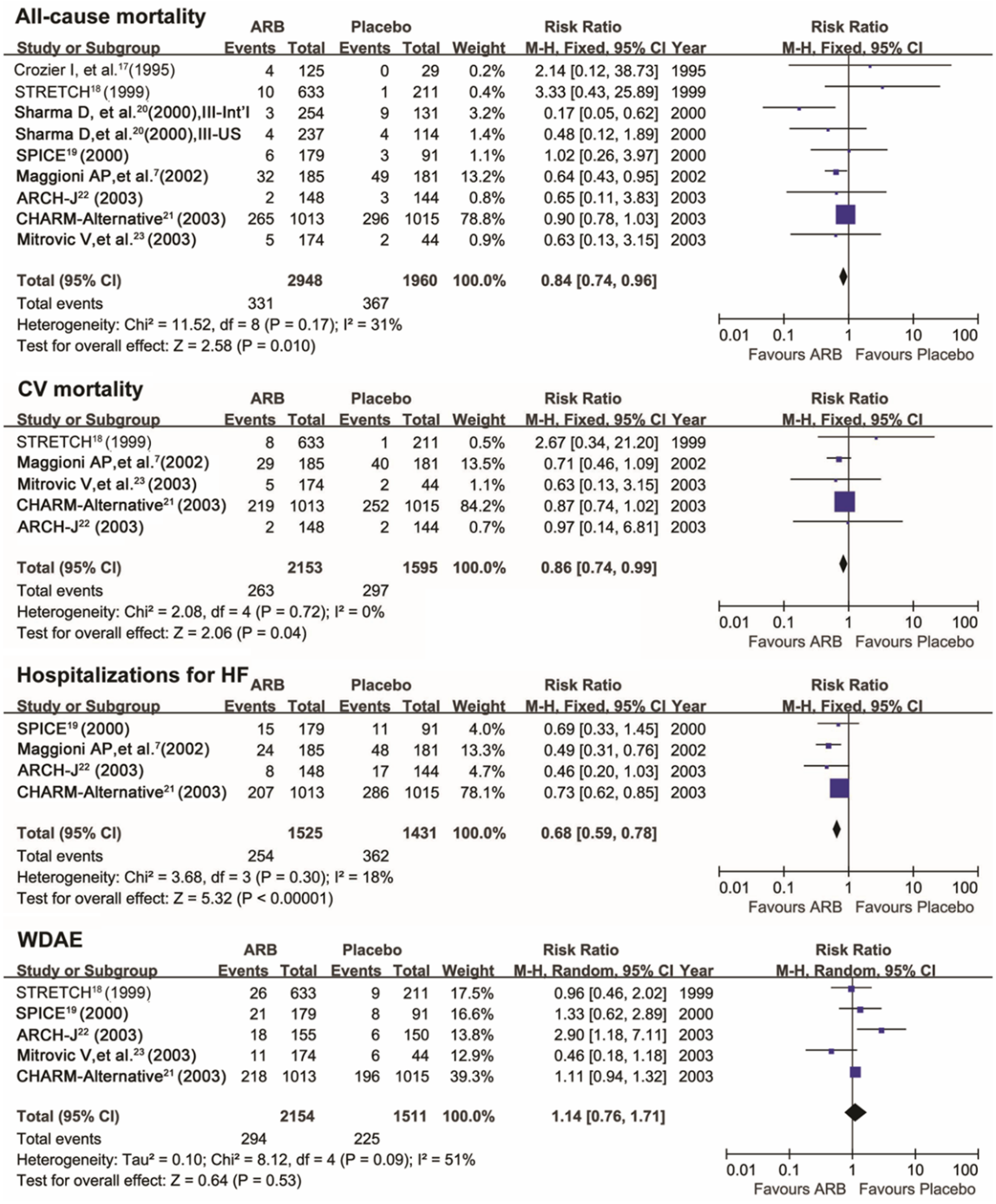

Figure 2. ARB versus placebo on all-cause mortality, CV mortality and hospitalizations for HF in patients with CHFrEF. ARB, angiotensin receptor blocker; CV, cardiovascular; HF, heart failure; CHFREF, chronic heart failure with reduced ejection fraction; WDAE, withdrawals due to adverse effects.

All cause mortality

Among trials of ARB versus placebo where background ACEI was not given, the overall mortality was significantly reduced in the ARB arm (RR 0.84, 95% CI 0.74-0.96, I^2=31%, P=0.010) (**Figure 2**). Nevertheless, no obvious difference was seen in improving survival, neither among trials that directly compared ARB with ACEI (RR 0.87, 95% CI 0.54-1.41, I^2=46%, P=0.57) (**Figure 3**), nor among trials compared combination therapy of ARB and ACEI with ACEI therapy alone (RR 0.86, 95% CI 0.62-1.20, I^2=55%, P=0.37) (**Figure 4**).

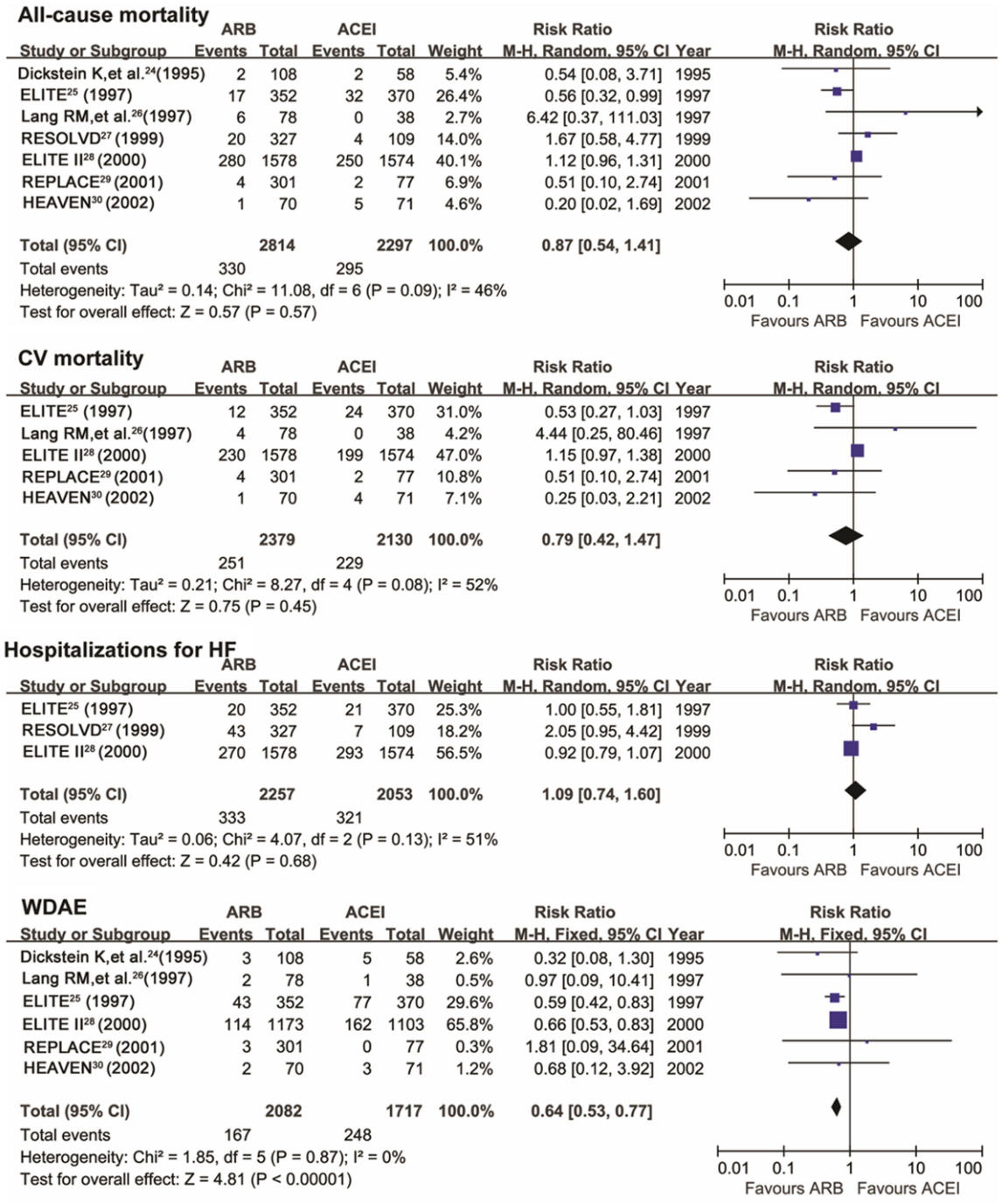

Figure 3. ARB versus ACEI on all-cause mortality, CV mortality and hospitalizations for HF in patients with CHFREF. ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; CV, cardiovascular; HF, heart failure; CHFREF, chronic heart failure with reduced ejection fraction; WDAE, withdrawals due to adverse effects.

Cardiovascular mortality

ARB therapy was associated with a 14% reduction in cardiovascular mortality compared with placebo without background ACEI treatment (RR 0.86, 95% CI 0.74-0.99, I^2=0%, P=0.010) (**Figure 2**). In five trials comparing ARB versus ACEI, there was a beneficial trend towards ARBs, but no statistical significance reached (RR 0.79, 95% CI 0.42-1.47, I^2=52%, P=0.45) (**Figure 3**). Dual therapy of ARB and ACEI revealed benefit on cardiovascular mortality compared with ACEI alone (RR 0.84, 95% CI 0.74-0.94, I^2=0%, P=0.003) (**Figure 4**).

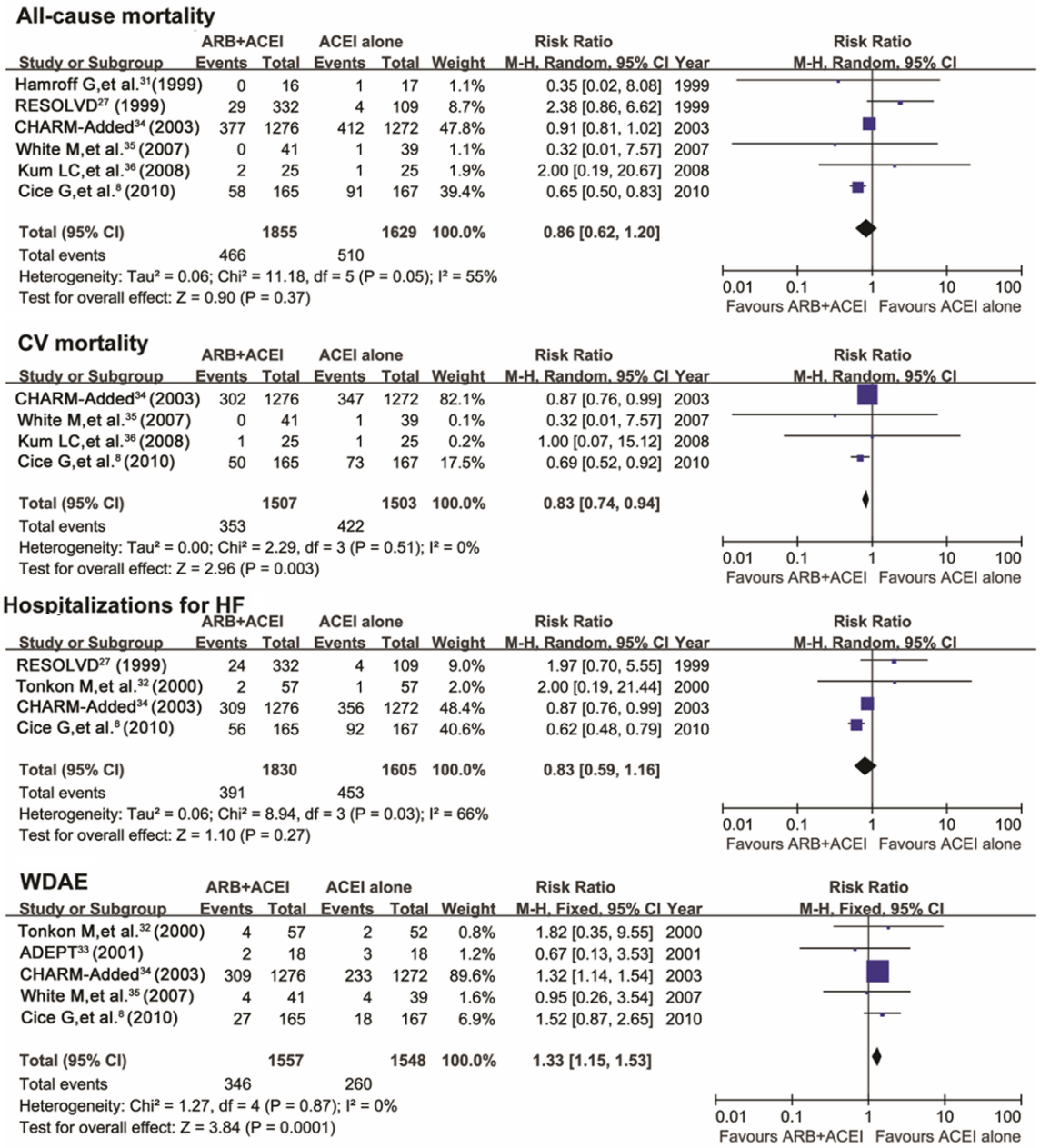

Figure 4. ARB + ACEI versus ACEI on all-cause mortality, CV mortality and hospitalizations for HF in patients with CHFREF. ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; CV, cardiovascular; HF, heart failure; CHFREF, chronic heart failure with reduced ejection fraction; WDAE, withdrawals due to adverse effects.

Hospitalizations for HF

The pooled estimate favored ARB over placebo across the trials in reducing admissions to hospital for HF (RR 0.68, 95% CI 0.59-0.78, I^2=18%, P<0.001) (**Figure 2**). There was no statistical difference in hospitalizations for HF between ARB and ACEI therapy (RR 1.09, 95% CI 0.74-1.60, I^2=51%, P=0.68) (**Figure 3**). The combination therapy of ACEI plus ARB showed no benefit for hospitalizations for HF in comparison with ACEI therapy alone (RR 0.83, 95% CI 0.59-1.16, I^2=66%, P=0.27) (**Figure 4**). There was insufficient data for the endpoints myocardial infarction and stroke.

Withdrawals due to adverse events (WDAE)

No statistical significance was observed in ARB versus placebo for WDAE (RR 1.14, 95% CI

0.76-1.71, I^2=51%, P=0.53) (**Figure 2**). Significantly fewer patients in the ARBs group withdrew due to AE than those in the ACEIs group (RR 0.64, 95% CI 0.53-0.77, I^2=0%, P<0.001) (**Figure 3**). Combined ARB plus ACEI therapy was associated with a 33% increased risk of WDAE (RR 1.33, 95% CI 1.15-1.53, I^2=0%, P<0.001) in comparison with ACEI alone therapy (**Figure 4**).

Subgroup analysis

Considering that different types of ARBs or ACEIs can have different effects on clinical outcomes, we further performed subgroup analysis stratified by drug types. Due to limited data available, only the comparison between ARBs and placebo in total mortality was examined. Compared with placebo, the overall estimate of losartan significantly showed beneficial effect on all-cause mortality (RR 0.35, 95% CI 0.15-0.80, I^2=31%, P=0.01). Candesartan appeared to be superior to placebo (RR 0.91), but it failed to attain statistical significance in pooled five trials (95% CI 0.79-1.04, I^2=0%, P=0.16). Maggioni et al., the subgroup analysis of VAL-HEFT, suggested a favorable effect of valsartan on all-cause mortality in patients with HFREF not treated with ACEIs.

Sensitivity analyses and publication bias

Sensitivity analyses were conducted to explore potential sources of heterogeneity among these groups. Moderate heterogeneity was observed among trials of ARB plus ACEI versus ACEI alone. We noticed that Cice et al. involved CHF patients with hemodialysis, given the potential sources of heterogeneity resulting from the the potential pathophysiological effect of hemodialysis on patients with CHF, we performed further analysis without counting Cice et al. trial. Interestedly, little difference in pooled estimate was revealed for total mortality (RR 1.04, 95% CI 0.68-1.59, I^2=13%, P=0.87), CV mortality (RR 0.87, 95% CI 0.76-0.99, I^2=0%, P=0.03), and HF hospitalizations (RR 1.07, 95% CI 0.62-1.86, I^2=30%, P=0.81), whereas heterogeneity suggested by I^2 was significantly reduced to below 50%. Further exclusion of any single study did not materially alter the overall combined RR. The Egger's test indicated no evidence of publication bias in each group.

Discussion

Summary of main results

ARBs versus placebo: Our findings show a clear benefit in favor of ARBs to treat HFREF compared with placebo in improving survival and reducing cardiovascular death and hospitalizations for HF, which hence disagree with a previous meta-analysis that suggested ARBs were no better than placebo in HF. One source of this difference is the addition of the results from the subgroup analysis of Val-HEFT trial, Maggioni et al. Notably, though this trial represented only 7% of the Val-HEFT population, its favorable mortality result have much impact on the overall outcomes of the analysis in ARB versus placebo without background ACEI.

ARBs versus ACEIs: In the HFREF population, despite the fact that there were no significant differences in all-cause mortality or cardiovascular mortality or hospitalizations for HF between the two treatment groups, ARBs were found to be more tolerant compared with ACEIs. The clearest indication of intolerance an ACE inhibitor is a cough or angioedema because of increased levels of bradykinin or other kinins and they do not seem to be caused by an ARB [38]. However, possible reasons for lack of ARB advantages include insufficient dosing of ARBs. For instance, in the ELITE II trial, when 50 mg doses of losartan compared to 150 mg captopril, the outcomes favored captopril. Likewise, the trend went towards the preference of 150 mg captopril when compared to 50 mg losartan in the OPTIMAAL trial [39]. Furthermore, the HEAAL study evaluating effects of high-dose versus low-dose losartan for patients with HFrEF suggested that losartan 150 mg daily was superior to 50 mg daily with respect to the composite outcome of death or admission for heart failure [40]. According to our sensitivity analysis, after excluding ELITE II, ARBs were then associated with a 46% reduction in cardiovascular mortality versus ACEIs. The potential more benefit of higher doses of ARBs compared with ACEIs is therefore needed to be proven.

ARBs + ACEIs versus ACEIs alone: Our study suggested that combination therapy reduces CV mortality for HFREF, notwithstanding, it has more adverse events. A growing body of studies focused on whether patients would benefit from having both types of medication. The

premise theory was that angiotensin II could be generated through ACE independent pathways (e.g. chymase) and the ARBs add-on effects on ACEIs could offer more complete blockade of the renin-angiotensin system than that could be obtained by ACE inhibitors alone [41, 42]. However, one meta-analysis suggested that the combination therapy of ARBs and ACEIs was associated with an excessive risk of adverse events such as hyperkalaemia, hypotension, and renal failure compared with monotherapy [43]. Therefore, not only strict patient monitoring for adverse effects may be warranted in this combination therapy but also the specific indications for dual therapy are needed to be explored.

Subgroup analysis of ARBs versus placebo: Owing to the differences between the various ARBs in the characteristics of their antagonism of angiotensin II at the AT1 receptor site, they display marked differences in pharmacokinetics and receptor-binding properties that may contribute to observed differences in clinical outcomes [44, 45]. In our stratified analysis, candesartan failed to demonstrate superiority to placebo in improving the survival in HFREF patients mainly ascribed to Charm-Alternative trials. Insufficient evidence to date precluded us from examining additional outcomes of subgroup analysis.

Sources of heterogeneity: Moderate heterogeneity was seen among studies of ARBs versus ACEIs and ARB + ACEI versus ACEIs alone, which was not surprising given the disparities in characteristics of HFREF population, different types of ARBs and ACEIs, duration of drug utility, and their drug doses. In the absence of individual patient data, we can not further stratify the included studies by their different doses of drug utility and duration of drug utility to detect the sources of heterogeneity. However, our sensitivity analyses indicate that one study enrolling CHF patients with hemodialysis probably contributed to the heterogeneity, in that these patients could be sicker than patients simply with CHF.

Improvements over prior meta-analysis: Compared with Cochrane review [6] and other previous meta-analyses, this meta-analysis exclusively evaluate of role ARBs focusing on patients with CHF with reduced EF. In our analysis of ARB + ACEI versus ACEI alone, by excluding studies in which not all patients were taking ACEIs, we could avoid biasing the results toward overestimating the overall disadvantages in the ARB + ACEI combination group. However, this critical selection process is largely ignored by prior meta-analysis and reviews in which potential biased conclusion may exist among their analysis. Meanwhile, Maggioni et al., the subgroup analysis of Val-HEFT, is the very study we should attach more significance to rather than Val-HEFT itself in virtue of the fact that not all patients in the Val-HEFT study received background ACEIs treatment. This is the reason why our meta-analysis incorporates Maggioni et al. trial when investigating the ARB versus placebo group and omits the Val-HEFT when investigating ARB + ACEI versus ACEI alone group. Finally, our subgroup analysis additionally confirmed the role of losartan in reducing overall mortality compared with placebo.

Limitations

Although we add Maggioni et al. trial to assess the effects of the ARBs on clinical end points in a population not receiving an ACEI. The number of patients included in this trial was relatively small and several characteristics of the selected population may varied from the general study population, for instance, the non-ACEI subgroup were older, more likely to be female, had higher average ejection fraction and systolic blood pressure rates, and these may limit the universal application of our present findings in chronic heart failure patients.

The mean Jadad score for the included RCTs was 3.2, which would denote high reliability for this meta-analysis. However, seven RCTs had a Jadad score of 2, indicating low quality. Besides, some RCTs with a much smaller sample size in comparison with CHARM study rendered CHARM study powerful to evaluate the mortality and morbidity effect of ARBs. Adequately-powered methodology and sample sizes therefore calls the attention to future clinical trials.

On one hand, the lack of individual patient data prevented us from pooling relevant subgroups which may still benefit from ARBs. On the other hand, inconsistent and limited reports from included trials made it difficult to extract other important clinical outcomes, like myocardial infarction, stroke and so on. Despite these limi-

tations, our study remains as the best overview of the current evidence concerning the use of ARBs in HFREF compared with placebo and ACEIs. There is a need for more solid clinical trials concerning the types, economic analysis and doses utility of ARBs to help us know the truly efficacy of them in CHF more and better.

Conclusion

This meta-analysis suggests the superiority of ARBs over placebo in reducing mortality and morbidity in patients with heart failure with reduced ejection fraction. ARBs are better tolerated than ACEIs. Close monitoring for adverse effects may be warranted in the combination therapy of ARBs and ACEIs.

Disclosure of conflict of interest

None.

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