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ARTICLE

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Angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers in hypertensive patients with myocardial infarction or heart failure: a systematic review and meta-analysis

Toshio Ohtsubo[1] · Rei Shibata[2] · Hisashi Kai[3] · Ryuji Okamoto[4] · Eita Kumagai[5] · Hiroaki Kawano[6] · Akira Fujiwara[7] · Takanari Kitazono[1] · Toyoaki Murohara[8] · Hisatomi Arima[9]

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Abstract

Angiotensin-converting enzyme inhibitors (ACEIs) are considered primary drugs for the secondary prevention of myocardial infarction (MI), and angiotensin receptor blockers (ARBs) are used when ACEIs cannot be tolerated. However, it is unclear whether ACEIs or ARBs are more appropriate first-line drugs in hypertensive patients with MI or heart failure (HF). The present study aimed to compare the effects of ACEIs and those of ARBs in these patients. Sixty randomized controlled trails (RCTs) that compared the effects of ACEIs and ARBs in patients with MI or HF were extracted by searching PubMed/MEDLINE, Cochrane Database, and the Medical Central Journal database according to the PRISMA guidelines. We finally selected six eligible RCTs and identified three systematic reviews and meta-analyses. The proportion of hypertensive patients ranged from 36 to 69%. Meta-analyses were performed for recurrence or new onset of MI (risk ratio 0.97 [95% confidence interval: 0.88, 1.06]), hospitalization for HF (0.98 [0.84, 1.14]), cardiovascular or total mortality (0.98 [0.91, 1.05]), cardiovascular events or stroke (1.02 [0.94, 1.11]), and adverse events (1.40 [1.11, 1.77]). There were no significant differences between ACEIs and ARBs for all outcomes, except adverse events. Study discontinuation owing to adverse events was significantly more common with ACEIs than with ARBs. Among hypertensive patients with MI or HF, it appears desirable to select the most appropriate drugs, ACEIs or ARBs, in each case by considering the function level, patient background, comorbidity presence, blood pressure target, drug price and other such factors comprehensively in addition to considering tolerability.

Keywords angiotensin-converting enzyme inhibitors · angiotensin receptor blockers · heart failure · hypertension · meta-analysis · myocardial infarction · systematic review

Introduction

The progress of the aging population in Japan is remarkable, and the proportion of elderly people aged 65 years or

These authors contributed equally: Toshio Ohtsubo, Rei Shibata

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✉ Toshio Ohtsubo
tohtsubo@intmed2.med.kyushu-u.ac.jp

✉ Rei Shibata
rshibata@med.nagoya-u.ac.jp

1 Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

2 Department of Advanced Cardiovascular Therapeutics, Nagoya University Graduate School of Medicine, Nagoya, Japan

3 Department of Cardiology, Kurume University Medical Center, Kurume, Japan

4 Department of Cardiology and Nephrology, Mie University Graduate School of Medicine, Mie, Japan

5 Division of Cardio-Vascular Medicine, Department of Internal Medicine, Kurume University School of Medicine, Kurume, Japan

6 Department of Cardiovascular Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

7 Division of Nephrology and Hypertension, Yokohama City University Medical Center, Yokohama, Japan

8 Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan

9 Department of Preventive Medicine and Public Health, Fukuoka University, Fukuoka, Japan

older among the total population, which is referred to as the population-aging rate, was 27.3% on October 1, 2016. It has been estimated that the population-aging rate will continue to increase in the future and will reach 33.3% in 2033 and 38.4% in 2065 (http://www8.cao.go.jp/kourei/whitepaper/w-2017/zenbun/29pdf_index.html). Additionally, it has been reported that the proportion of hypertensive patients increased with age and was 80.8% among men and 71.2% among women in their seventies in Japan [1]. Aging can influence the onset of heart failure (HF) as well as hypertension. It has been reported that chronic HF occurred at a rate of ~1% among people in their fifties and that the rate reached 10% among people aged over 80 years in the United States [2]. The number of patients hospitalized for acute HF or exacerbation of chronic HF is increasing in Japan (http://www.j-circ.or.jp/jittai_chosa/jittai_chosa2015web.pdf). Hypertension and HF are important issues, as Japan is becoming a "super-aging society."

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are widely used in patients with hypertension, renal impairment along with proteinuria, diabetes mellitus, and HF [3, 4]. Both these types of drugs are recognized as inhibitors of the renin-angiotensin system, but differences in their modes of action have been reported to be associated with clinically different outcomes [5]. The usefulness of ACEIs for the secondary prevention of cardiovascular events in patients with myocardial infarction (MI) and HF with reduced ejection fraction (HFrEF) has been established by many randomized controlled trails (RCTs) [6–16]. The rates of total death, sudden death, MI recurrence, hospitalization for HF, and other such poor outcomes were found to be significantly lower with ACEIs than with placebo in the ISIS-4 and GISSIS-3 trials for acute MI and in the SAVE, AIRE, and TRACE trials for HFrEF after MI [7–11]. On the other hand, the mortality rate was found to be slightly higher with the ARB losartan than with the ACEI captopril in the OPTIMAAL study after acute MI with high-risk HF [17]. In the VALIANT study that targeted patients with MI or HFrEF, there were no significant differences in total or cardiovascular death, MI recurrence, and hospitalization for HF between the ARB valsartan and the ACEI captopril [18]. In a meta-analysis of the BPLTTC study that examined the organ protection effects of ACEIs and ARBs beyond their antihypertensive effects, ACEIs were found to prevent coronary artery disease in addition to lowering blood pressure [5]. Based on these findings, ACEIs are considered as first-line drugs for the secondary prevention of MI in many guidelines, and ARBs are used only when ACEIs cannot be tolerated [3, 6]. In addition, ACEIs are less expensive than ARBs for the reason to prefer as first choice. However, it is unclear which of ACEIs or ARBs are more appropriate in hypertensive patients with MI or HF.

ACEI administration in HFrEF patients was found to significantly reduce the rates of total mortality and various cardiovascular events in many RCTs, including the CONSENSUS-1 and SOLVD trials [12, 13]. In addition, studies have shown that ACEIs improved the total mortality rate and reduced the number of hospitalization days associated with HF even in asymptomatic HFrEF patients [14, 15]. With respect to the effects of ARBs on HFrEF, the rates of cardiovascular death and hospitalization for HF were lower with candesartan than with placebo among patients who could not tolerate ACEIs in the CHARM-Alternative trial [19]. On the other hand, in the VALIANT trial of patients with HFrEF after acute MI and in the ELITE II trial of elderly HF patients, the number of adverse events was lower with ARBs than with ACEIs; however, ARBs had no advantage with regard to the suppression of cardiovascular events [18, 20]. Considering these findings, it is unclear which of ACEIs or ARBs are more appropriate first-line drugs in hypertensive patients with HF.

In fact, the use of ARBs is overwhelmingly greater than that of ACEIs, and ARBs are actually used as first-line drugs in clinical practice, especially in HFpEF patients with hypertension in Japan. Thus, it is important to clarify which of ACEIs or ARBs should be used preferentially in hypertensive patients with MI or HF. The present systematic review and meta-analysis assessed RCTs that directly compared the effects of ACEIs and ARBs in hypertensive patients with MI or HF in order to determine which of ACEIs or ARBs should be used preferentially in these patients.

Methods

Search strategy

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21]. The search was conducted using medical subject headings and relevant text words of MI/HF (myocardial infarction [MeSH], heart failure [MeSH] and various text words such as myocardial infarction, heart failure, left ventricular dysfunction etc.), ACEIs (angiotensin-converting enzyme inhibitors [MeSH] and various text words such as ACE inhibitor*, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril etc.), and ARBs (angiotensin II type 1 receptor blocker [MeSH] and various text words such as angiotensin receptor blocker, azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan etc.). We also checked the studies included in previous systematic review articles to find other eligible trials [5, 22, 23]. Language was restricted to English and Japanese.

Selection criteria

The literature search, data extraction and quality assessment were conducted independently by two systematic reviewers (TO and RS). In case of disagreement between the two reviewers, consensus was achieved after consulting with a third reviewer (HK).

We searched PubMed/MEDLINE (1966 to July 2017), Cochrane Database of Systematic Reviews (third quarter of 2017), and the Medical Central Journal database (1981 to July 2017). Inclusion criteria was: (A) RCTs that compared the effects of ACEIs and ARBs, (B) participants involve patients with MI/HF and hypertension, and (C) outcomes reported involve (1) recurrence or new onset of MI, (2) hospitalization for HF, (3) cardiovascular or total mortality, (4) cardiovascular events or stroke, (5) adverse events, (6) renal impairment or proteinuria, and/or (7) atrial fibrillation.

Data extraction and quality assessments

The following data were extracted from papers: publication year, age selection, mean age, inclusion criteria, number of patients, intervention (ACEIs), comparison (ARBs), and duration of follow-up, as well as number and proportion of hypertensive patients and baseline and achieved blood pressures with ACEIs or ARBs. The Cochrane Collaboration's tool was used for assessing risk of bias [24].

Statistical analysis

The risk ratios (RR) and 95% confidence intervals (CI) were estimated for each trial and each outcome. Random-effects model with the DerSimonian–Laird method were used to estimate pooled RR and 95% CI. The magnitudes of heterogeneity across studies were assessed using Cochrane χ^2 tests and I^2 statistics [24]. The publication bias of each outcome was analyzed using funnel plots. A P-value <0.05 was considered statistically significant. Review Manager 5 (RevMan 5) was used for the present analysis.

Results

Search results

The detailed steps of document retrieval are shown in Fig. 1. In the initial search, 658 articles that examined the effects of ACEIs or ARBs on outcomes were identified from PubMed/MEDLINE, Cochrane Database, and the Medical Central Journal database and two articles were identified from other sources. After screening the title and abstract, 601 irrelevant articles were excluded. Following full text review of the remaining 59 articles, 50 additional articles were excluded. Finally, six RCTs were identified.

Characteristics of the studies

This meta-analysis included three meta-analyses and six RCTs that directly compared ACEIs and ARBs in patients with MI or HF, including hypertensive patients [17, 18, 20, 25–27]. Of the three meta-analyses, two examined the effects of ACEIs and ARBs on various outcomes in hypertensive patients [5, 23] and one compared the effects of ARBs to those of placebo in patients with HF [27]. Among the six RCTs, the proportion of hypertensive patients ranged from 36 to 68.8% and the baseline blood

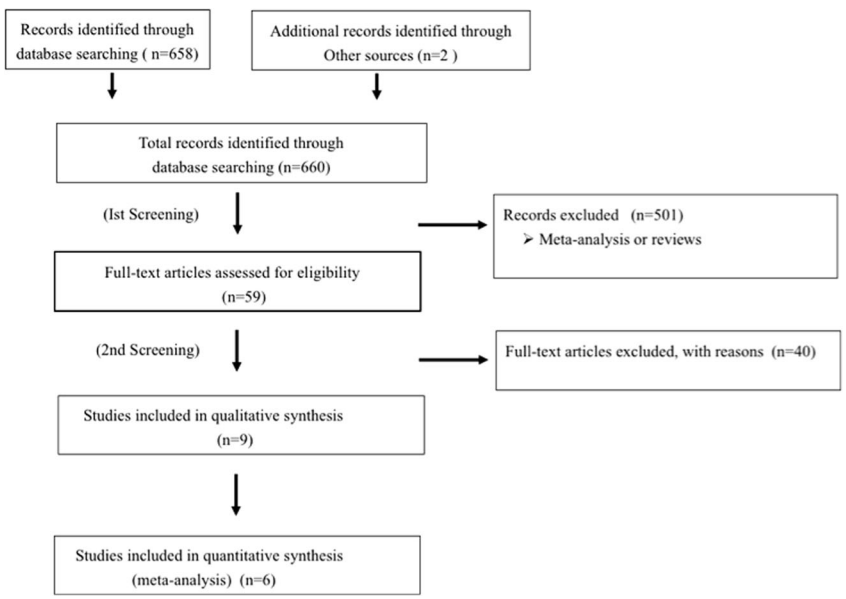

Fig. 1 Search strategy according to the PRISMA guidelines

pressure ranged from 122/72 to 142/82 mmHg (Table 1). Only one article was available for evaluating renal impairment or proteinuria and atrial fibrillation.

Outcomes

Recurrence or new onset of MI

We identified five RCTs for this outcome. The rates of recurrence or new onset of MI in all patients with MI or HF were 6.25% ($n = 836/13,374$) among those treated with ACEIs and 6.49% ($n = 866/13,336$) among those treated with ARBs. A meta-analysis involving the five RCTs found no significant difference in recurrence or new onset of MI between the ACEI and ARB groups (RR 0.97 [CI: 0.88, 1.06], $P = 0.45$) (Fig. 2a). There was no clear evidence of heterogeneity ($P = 0.70$, $I^2 = 0\%$).

Hospitalization for HF

We identified four RCTs for this outcome. The rates of hospitalization for HF in all patients with MI or HF were 12.2% ($n = 583/4798$) among those treated with ACEIs and 12.5% ($n = 599/4794$) among those treated with ARBs. A meta-analysis involving the four RCTs found no significant difference with regard to the improvement in prognosis evaluated according to hospitalization for HF between the ACEI and ARB groups (RR 0.98 [CI: 0.84, 1.14], $P = 0.79$) (Fig. 2b). There was slight heterogeneity ($P = 0.23$, $I^2 = 30\%$).

Cardiovascular or total mortality

We identified six RCTs for this outcome. The rates of cardiovascular or total mortality in all patients with MI or HF were 20.7% ($n = 3783/18,283$) among those treated with ACEIs and 21.0% ($n = 3831/18,245$) among those treated with ARBs. A meta-analysis involving the six RCTs found no significant difference in cardiovascular or total mortality between the ACEI and ARB groups (RR 0.98 [CI: 0.91, 1.05], $P = 0.49$) (Fig. 2c). Heterogeneity was moderate ($P = 0.08$, $I^2 = 49\%$).

Cardiovascular events or stroke

We identified five RCTs for this outcome. The rates of cardiovascular events or stroke in all patients with MI or HF were 19.3% ($n = 2579/13,374$) among those treated with ACEIs and 19.4% ($n = 2590/13,336$) among those treated with ARBs. A meta-analysis involving the five RCTs found no significant difference in cardiovascular events or stroke between the ACEI and ARB groups (RR 1.02 [CI: 0.94, 1.11]) (Fig. 2d). Moderate heterogeneity was observed ($P = 0.06$, $I^2 = 55\%$).

Table 1 Main characteristics of included studies

Study	Year	Age (Mean)	Inclusion criteria	Number	ACEI (mg/day)	ARB (mg/day)	Hypertension			Baseline BP		Achieved BP (After duration)		Duration of Follow up
							ACEI (%)	ARB (%)	Total (%)	ACEI	ARB	ACEI	ARB	
ELITE I	1997	65 years or more (73.5)	NYHA II-IV, EF<40%	722	Captopril (18.7-150)	Losartan (12.5-50)	212/370 (57.3)	201/352 (57.1)	413/722 (57.2)	137/79	137/79	N/D	N/D	48 weeks
ELITE II	2000	60 years or older (71.4)	NYHA II-IV, EF<40%	3152	Captopril (37.5-150)	Losartan (12.5-50)	780/1574 (49.6)	760/1578 (48.2)	1540/3152 (48.9)	134/78	134/78	N/D	N/D	Median follow up: 555days
OPTIMALL	2002	50 years or older (67.4)	after AMI, EF<35%	5477	Captopril (37.5-150)	Losartan (12.5-50)	987/2734 (36.1)	983/2744 (35.8)	1970/5478 (36.0)	123/71	122/72	114/66 (2 hour)	119/69 (2 hour)	Mean follow up: 2.7 years
VALIANT	2003	18 years or older (65)	after AMI, EF<35%	14703	Captopril (18.7-150)	valsartan (20-320)	2700/4885 (55.3)	2732/4909 (55.7)	5432/9794 (55.5)	122/72	123/72	122/76 (1 year)	127/75 (1 year)	Median follow up: 24.7 months
ONTARGET	2008	55 years or older (66.4)	High-risk patients	23400	ramipril (2.5-10)	telmisartan (40-80)	5918/8576 (69.0)	5862/8542 (68.6)	11780/17118 (68.8)	141/82	141/82	135/78 (6 week)	134/77 (6 week)	4.5 (3.5-5.5) years
T-VENTURE	2009	(62.9)	after AMI	241	ACEI	valsartan (40-160)	65/121 (53.7)	73/120 (60.8)	138/241 (57.3)	127/72	129/73	114/66	114/65	6 months

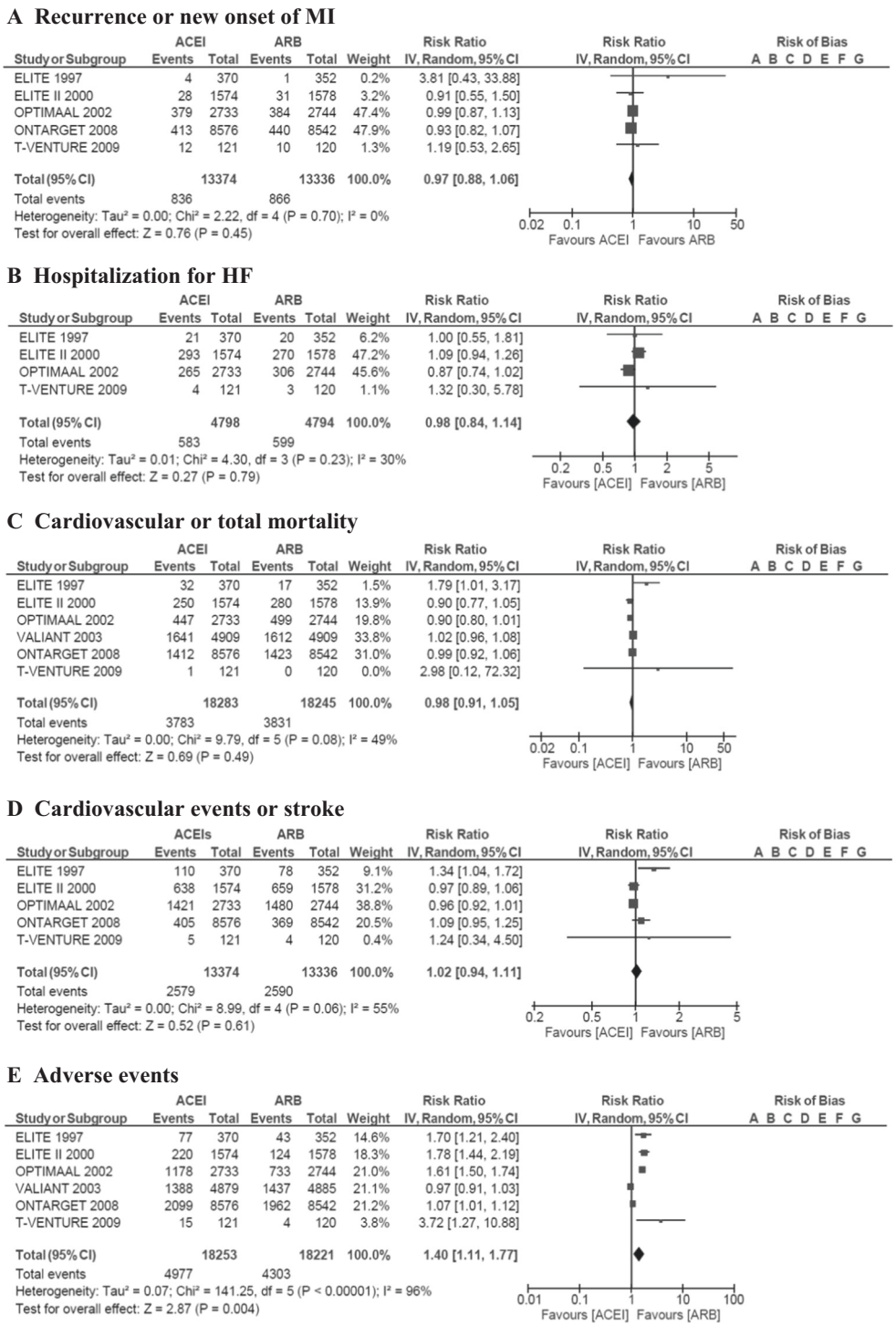

Fig. 2 Forest plots of ACEIs versus ARBs for various outcomes in hypertensive patients with MI or HF. **a** Recurrence or new onset of MI, **b** hospitalization for HF, **c** cardiovascular or total mortality, **d** cardiovascular events or stroke, **e** adverse events, **f** renal impairment or proteinuria, and **g** atrial fibrillation

Adverse events

We identified six RCTs for this outcome. ACEIs caused many adverse events, such as cough, taste disturbance, rash, angioedema, and other such issues, while ARBs frequently caused hypotension and renal dysfunction. The rates of adverse events in all patients with MI or HF were 21.1% ($n = 4644/18,253$) among those treated with ACEIs and 18.3% ($n = 3867/18,245$) among those treated with ARBs. A meta-analysis involving the six RCTs found that

treatment discontinuation owing to adverse events was significantly more common in the ACEI group than in the ARB group (RR 1.40 [CI: 1.11, 1.77], $P = 0.0004$) (Fig. 2e). Large heterogeneity was detected ($P < 0.00001$, $I^2 = 96\%$).

Renal impairment or proteinuria

We identified only one article for renal impairment or proteinuria and examined the results. There was no significant difference in renal impairment or proteinuria between the ACEI and ARB groups (RR 0.96 [CI: 0.88, 1.05]) [25].

Atrial fibrillation

We identified only one article for atrial fibrillation. There was no significant difference in new onset atrial fibrillation between the ACEI and ARB groups (RR 1.03 [CI: 0.92, 1.16]) [25].

Publication bias

One study was identified as high risk of bias among included intervention studies (Supplementary Table 1). The possibility of publication bias was suggested in recurrence or new onset of MI, hospitalization for HF, and adverse events, with some asymmetries on analysis involving funnel plots (Fig. 3a, b, e). Publication bias was not suggested in cardiovascular or total mortality and cardiovascular events or stroke (Fig. 3c, d).

Discussion

The present study found no significant difference in the effectiveness of ACEIs and ARBs with regard to recurrence or new onset of MI in hypertensive patients with MI or HF. In a Cochrane Review [22] that examined the effects of ARBs in new-onset MI patients with HF, there was no significant difference between the ACEIs and ARBs groups on direct comparison involving two RCTs (RR 1.00 [CI: 0.62, 1.63], $P = 0.99$) (http://minds4.jcqhc.or.jp/minds/guideline/pdf/manual_all_2.0.pdf) [20]. Interestingly, placebo was significantly more effective when compared with candesartan in patients with chronic heart failure and reduced left ventricular systolic function intolerant to ACEIs in a meta-analysis of two RCTs (SPICE and CHARM-Alternative trials) (RR 1.44 [CI: 1.03, 2.01], $P = 0.033$) [19, 22, 28]. On the other hand, ACEIs had cardiovascular protective effects beyond blood pressure reduction when compared with ARBs in the BPLTTC trial [5]. Thus, few results have indicated that ARBs are more effective than ACEIs. It has been recommended that the use of ARBs for the prevention of recurrence or new onset of MI should be restricted only to patients who cannot tolerate ACEIs.

There was no significant difference in the effectiveness of ACEIs and ARBs with regard to improvement in hospitalization for HF in this study. Previously, ARBs were found to be significantly more effective than placebo regardless of the blood pressure level among HFpEF patients with left ventricular ejection fraction (LVEF) >40% (RR 0.90 [CI: 0.81, 1.00], $P = 0.048$) in two RCTs

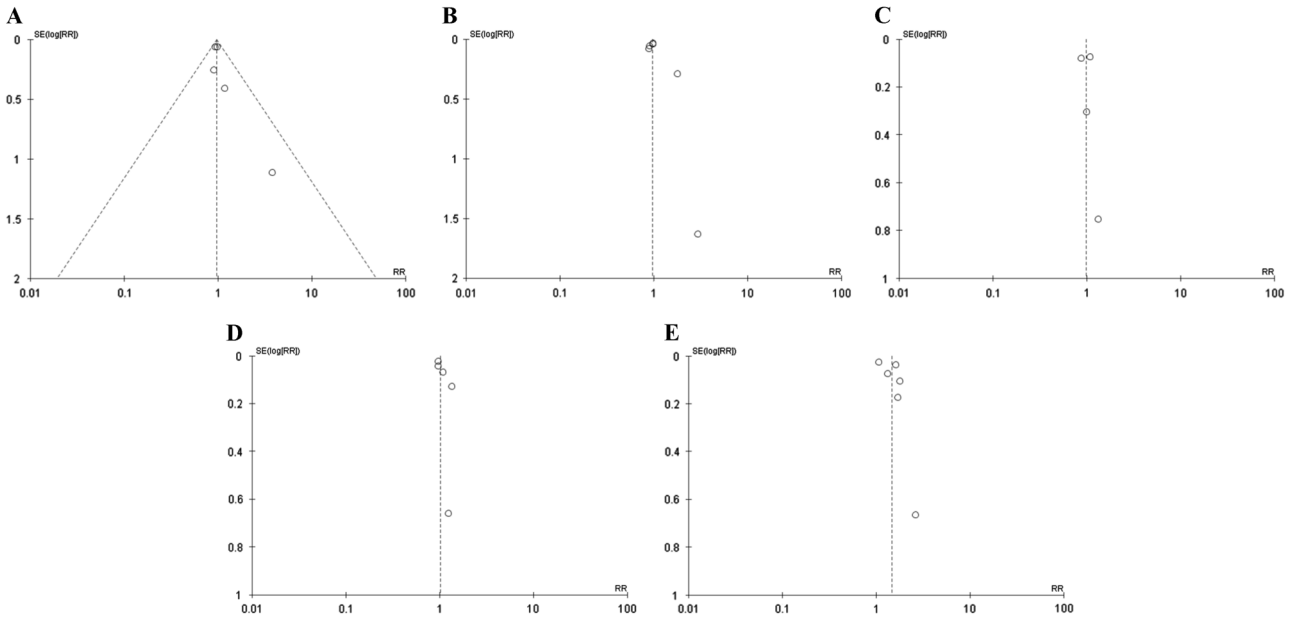

Fig. 3 Funnel plots for various outcomes. **a** Recurrence or new onset of MI, **b** hospitalization for HF, **c** cardiovascular or total mortality, **d** cardiovascular events or stroke, and **e** adverse events

(CHARM-Preserved and I-PRESERVE trials) [29, 30] and among HFrEF patients with LVEF <40% (RR 0.71 [CI: 0.61, 0.82], $P < 0.00001$) in three RCTs (ARCH-J, SPICE, and CHARM-Alternative trials) [19, 28, 31] that examined the effects of ARBs on HF. On the other hand, there was no significant difference in the effectiveness of ACEIs and ARBs (RR 0.96 [CI: 0.83, 1.11], $P = 0.58$) in three RCTs (RESOLVD, ELITE, and ELITE II trials) that compared ACEIs and ARBs [20, 25, 32]. Additionally, improvement in HF was equivalent between ARBs and ACEIs in the BPLTTC trial [5]. These results suggest that ARBs are as useful as ACEIs in patients with HF and that ARBs can be used instead of ACEIs to improve the prognosis of HF, even in hypertensive patients with HF or MI.

There was no significant difference in the effectiveness of ACEIs and ARBs with regard to the reduction of cardiovascular or total mortality in this study. Previously, no significant difference in the effectiveness of ARBs and placebo was found with regard to total mortality (RR 1.02 [CI: 0.93, 1.12], $P = 0.67$) and cardiovascular death (RR 1.02 [CI: 0.90, 1.14], $P = 0.79$) among HFpEF patients in the Cochrane Review [22]. Six RCTs considering total mortality (RR 1.05 [CI: 0.91, 1.22], $P = 0.48$) and four RCTs considering cardiovascular death (RR 1.08 [CI: 0.91, 1.28], $P = 0.36$) showed no significant difference between ACEIs and ARBs; however, ACEIs tended to be somewhat useful in direct comparisons. In addition, there was no significant difference between ACEIs and ARBs with regard to the onset of cerebral cardiovascular disorders in this study. Similarly, there was no significant difference between ACEIs and ARBs with regard to stroke onset and all hospitalizations among HF patients in the Cochrane Review [22].

In this study, ACEIs had significantly more adverse events with study discontinuation when compared with ARBs (RR 1.48 [CI: 1.16, 1.88], $P = 0.001$). In two previous reviews, adverse events were significantly less frequent with ARBs than with ACEIs (RR 0.63 [CI: 0.52, 0.76], $P < 0.00001$ and RR 0.83 [CI: 0.74, 0.93], $P = 0.001$, respectively) [22, 23]. These results indicate the superior safety and tolerability of ARBs when compared to those of ACEIs.

Among the six RCTs used for meta-analyses in this study, ONTARGET was the only study in which the mean systolic blood pressure at registration was over 140 mmHg (Table 1). In the ONTARGET study, the mean systolic blood pressure was 141.7 mmHg and the proportion of hypertensive patients was 69%. However, blood pressure data limited to the old MI group accounting for about 50% of the registered patients were obscure, and individual analysis was not possible. In the OPTIMAAL, VALIANT, and T-VENTURE trials for acute MI, the proportions of hypertensive patients were 36%, 55%, and 57%, respectively; however, the mean systolic blood pressures at registration ranged from 120 to 130 mmHg. In the ELITE and ELITE II trials for chronic HF, the proportions of hypertensive patients were 50% and 57%, respectively, and the systolic blood pressures at registration were 137 and 134 mmHg, respectively. Therefore, we could not clarify which of ACEIs or ARBs should be used preferentially in hypertensive patients with MI or chronic HF. It is well known that hypertension is often associated with HFpEF [33], but there is limited evidence that strict blood pressure control improves prognosis. The results of the I-PRESERVE, PEP-CHF, and CHARM-PRESERVED trials that involved HFpEF patients did not show the usefulness of RA inhibitors [29, 30, 34]. Thus, evidence limited to patients with hypertension is insufficient. The main limitation of this study is the indirect assessment of hypertensive patients with MI or HF owing to the absence of RCTs that directly compared the effects of ARBs and ACEIs in hypertensive patients with MI or HF. Therefore, we adopted RCTs that included hypertensive patients; however, the proportion of hypertensive patients was low at around 50%. Additionally, only six RCTs were considered for the meta-analysis.

In conclusion, the findings of the effects of ACEIs and ARBs on recurrence or new onset of MI, hospitalization for HF, cardiovascular or total mortality, and cardiovascular disease or stroke in patients with MI or HF were not different from the results of previous systematic reviews and meta-analyses identified in this study. However, study discontinuation owing to adverse events was clearly more common with ACEIs than with ARBs. There was not enough evidence to confirm which of ACEIs or ARBs are more appropriate first-line drugs in hypertensive patients with MI or HF. Presently, ACEIs should be preferentially used for MI or HF with reduced ejection fraction, as there is abundant evidence to support their benefits. It is desirable to select the most appropriate drugs in each case by considering the function level, patient background, comorbidity presence, blood pressure target, drug price and other such factors comprehensively in addition to considering tolerability. In the future, it is expected that a clear answer will be provided for the present clinical question by a large-scale RCT focusing on hypertensive patients with MI and/or HF.

Study limitations

There were several limitations in the present study as follows: (1) the proportion of hypertensive patients ranged from 36 to 69% in RCTs analysed in the present study, (2) normotensive subjects were included in all study group, and (3) the definitions of cardiovascular events and stroke were not identical in the RCTs.

Compliance with ethical standards

Conflict of interest TO received honoraria from Sanwa Kagaku Kenkyusho. RS received honoraria from Medtoronic, Boehringer Ingelheim, Eli Lilly, and Otsuka Pharmaceutical Factory. HK received honoraria from Daiichi Sankyo Co., Mitsubishi Tanabe Pharma Co., Shionogi & Co., Dainippon Sumitomo Pharma Co., and Takeda Pharmaceutical Co. TK received honoraria from Daiichi Sankyo and research funding from Daiichi Sankyo, Takeda Pharmaceutical, Astellas Pharma, Chugai Pharmaceutical, MSD, Boehringer Ingelheim, EA Pharma, Sanofi Aventis, Pfizer, Kissei Pharmaceutical, Kyowa Hakko Kirin, Asahi Kasei Medical, Otsuka Pharmaceutical, Torii Pharmaceutical, and Bayer.

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