ORIGINAL ARTICLE

Renin-angiotensin-aldosterone system blockers and cardiovascular outcomes: a meta-analysis of randomized clinical trials

Renin-anjiyotensin-aldosteron sistemi blokerleri ve kardiyovasküler sonuçları: Randomize klinik çalışmaların meta-analizi

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ABSTRACT

Objective: Hypertension is the most prevalent modifiable risk factor for cardiovascular (CV) and cerebrovascular morbidity and mortality. This study aimed to assess the effects of renin-angiotensin-aldosterone system (RAAS) blockade on CV outcomes.

Methods: This study was designed according to the Preferred Reporting Items for Systemic reviews and Meta-Analyses statement. Databases were searched for articles published as of December 2014. Two sets of studies were selected. One set included randomized clinical trials comparing RAAS blocker (angiotensin II receptor blocker [ARB] or angiotensin-converting enzyme inhibitor [ACEI]) with placebo or active treatment. Second set included head-to-head randomized clinical trials comparing an ARB with an ACEI. Studies in both sets had reported any CV outcome parameter or death, i.e., all-cause mortality, CV mortality, emergence of CV events, myocardial infarction, cerebrovascular event, stroke, heart failure, and hospitalization for heart failure.

Results: Fifty-four pairwise comparisons of 51 trials with 277,609 patients were included. Statistically significant differences in favor of RAAS blockers vs non-RAAS blockers (risk ratio [RR] ranging from 0.805 to 0.967) were observed in terms of most CV outcomes, including all-cause mortality, CV mortality, CV events, myocardial infarction, heart failure and stroke. ARBs and ACEIs were found to be completely comparable (RR ranging from 0.923 to 1.090, all non-significant).

Conclusion: RAAS blockers are superior to medications other than RAAS blockers with respect to impact on CV outcomes in patients with hypertension. ARBs and ACEIs are comparable in terms of these outcomes.

ÖZET

Amaç: Hipertansiyon kardiyovasküler (KV) ve serebrovasküler morbidite ve mortalite için en yaygın değiştirilebilir risk faktörüdür. Bu çalışma renin-anjiyotensin-aldosteron sistemi (RAAS) blokajının KV sonuçlar üzerine etkilerini belirlemeyi amaçlamaktadır.

Yöntemler: Bu çalışma PRISMA (Preferred Reporting Items for Systemic reviews and Meta-Analyses) yöntemine uygun şekilde planlandı. Veri tabanları Aralık 2014 tarihine kadar yayımlanan makaleleri araştırmak üzere tarandı. İki farklı çalışma grubu seçildi. Birincisi RAAS blokeri (anjiyotensin reseptör blokeri [ARB] veya anjiyotensin-dönüştürücü enzim inhibitörü [ACEİ]) ile plasebo veya aktif tedaviyi kıyaslayan randomize klinik çalışmaları içerdi. İkinci grup ARB ile ACEİ'yi kıyaslayan randomize klinik çalışmaları içerdi. Her iki gruptaki çalışmalarda da tüm nedenlere bağlı mortalite, KV mortalite, aniden ortaya çıkan KV olay, miyokart enfarktüsü, serebrovasküler olay, inme, kalp yetersizliği ve kalp yetersizliği nedeniyle hastaneye yatış gibi KV sonuç parametresi veya ölüm bildirildi.

Bulgular: 277.609 hastayı içeren 51 çalışmanın 54 çiftli kıyaslanması alındı. RAAS blokerleri ile RAAS blokeri olmayan ilaçlar arasında en sık görülen KV sonuçlar (tüm nedenlere bağlı mortalite, KV mortalite, KV olay, miyokart enfarktüsü, kalp yetersizliği ve inme dahil) açısından istatistiksel anlamlı farklılık (risk oranları 0.805–0.967) olduğu gözlendi. ARB'ler ve ACEİ'ler tümüyle benzer bulundu (risk oranları 0.923-1.090; tümü anlamlı değil).

Sonuç: Hipertansiyonlu hastalarda KV sonuçlar açısından RAAS blokerleri RAAS blokeri olmayan diğer ilaçlara kıyasla üstündür. ARB ve ACEİ'ler bu sonuçlar açısından benzerdir.

Received: August 11, 2016 *Accepted:* November 24, 2016

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Hypertension is the most prevalent modifiable risk factor for cardiovascular (CV) and cerebrovascular morbidity and mortality. An estimated 30% of the adult population in the United States has hypertension.[1] The importance of lowering blood pressure to reduce the risk of CV events has been demonstrated in numerous clinical trials. More drugs will likely be required for individuals with coronary artery disease, chronic kidney disease, or diabetes, for whom goals lower than 140/90 mmHg have been recommended.[2,3] Blockade of the renin-angiotensin-aldosterone system (RAAS) is one of the therapeutic targets in patients with hypertension. The most clinically relevant pharmacological agents that block the RAAS system are angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs).

Trials comparing ACEI or ARB with other antihypertensive drugs, standard treatment, or placebo in hypertensive patients have not always produced similar results with regard to the prevention of emergence of CV outcomes. Therefore, meta-analyses performing indirect comparisons of ACEI and ARB based on these trials do not reach homogeneous conclusions. On the other hand, clinical trials comparing ACEI and ARB with other drugs, which are very limited in number, generally showed no difference in primary CV outcome. In a meta-analysis of randomized comparative trials between ARBs and ACEIs conducted by Reboldi et al.,[4] ARBs were found to be as effective as ACEIs on risk of myocardial infarction, CV mortality, and total mortality. It was concluded that ARB- and ACEI-based treatments provide a similar protective effect for overall risk of fatal CV events and all-cause mortality, but blockade of RAAS by antagonizing Angiotensin II receptor type 1 (AT1) stimulation might be associated with a slightly superior cerebrovascular protective effect than blockade of ACE. In a recent meta-analysis of over 160,000 patients in 20 clinical trials, van Vark et al.[5] concluded that the significant effect of RAAS inhibition on all-cause mortality was limited to the class of ACEIs, and no mortality reduction could be demonstrated with ARBs. However, this meta-analysis was criticized, as positive effects of ACEIs on mortality could not be attributed only to ACEIs since the patients in the ACEI branches of the studies that contributed most to the overall effects of ACEIs had not been treated only with ACEI, but were treated with combination of ACEI and diuretics or amlodipine.[6]

The aim of the current study was to perform a meta-analysis to assess the effects of ACEI and ARB on major clinical outcomes, including all-cause death, CV death, and miscellaneous CV outcomes. Analysis was performed in 2 steps: (1) analysis of trials comparing RAAS blockers vs non-RAAS blockers and (2) analysis of randomized head-to-head trials of ARBs vs ACEIs.

Abbreviations:

ACEI	*Angiotensin-converting enzyme inhibitor*
ARB	*Angiotensin II receptor blocker*
CI	*Confidence interval*
CV	*Cardiovascular*
HR	*Hazard ratio*
OR	*Odds ratio*
RAAS	*Renin-angiotensin-aldosterone system*
RR	*Risk ratio*

METHODS

Data sources and searches

Ovid Medline, Embase, Cochrane Database of Systemic Reviews, Cochrane Central Register of Controlled Trials, and BIOSIS databases were systematically searched for articles published in English as of December 2014. Studies were identified using the phrase: ([angiotensin-receptor-antagonist OR angiotensin-receptor-blocker OR azilsartan OR candesartan OR eprosartan OR irbesartan OR losartan OR olmesartan OR telmisartan OR valsartan] OR [angiotensin-converting-enzyme-inhibitor OR benazepril OR captopril OR cilazapril OR enalapril OR fosinopril OR imidapril OR lisinopril OR moexipril OR perindopril OR quinapril OR ramipril OR trandolapril OR zofenopril]) AND (cardiovascular OR mortality OR death).

LIMIT TO "all adult (19 plus years)" AND LIMIT TO humans AND LIMIT TO English language AND remove duplicates.

Study selection

This study was designed according to the Preferred Reporting Items for Systemic reviews and Meta-Analyses (PRISMA) statement.[7,8] No initial criterion was established for blinding methodology or characteristics of the patients in the studies or the definition of hypertension. After assessment of full-text manuscripts, studies with suitable design and sufficient data were included in the analysis.

Two sets of studies were selected:

- One set included randomized clinical trials comparing a RAAS blocker (ARB or ACEI)

with placebo or active treatment. Studies conducted on hypertensive populations were included, but studies conducted on populations in which the patients have specific conditions that might interfere with the effect of a RAAS blocker on CV outcomes or death, and might thereby contaminate the conclusion reached with the analysis, were not included. These populations included:

- o Acute myocardial infarction
- o Heart failure
- o Normal blood pressure
- o Hemodialysis

- Second set included head-to-head randomized clinical trials comparing an ARB with an ACEI. The number of published studies comparing ARBs with ACEIs head-to-head is very scarce (Early versus Late Intervention Trial with Estradiol [ELITE]-I, ELITE-II, Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan [OPTIMAAL], Diabetics Exposed to Telmisartan and Enalapril [DETAIL], Valsartan in Acute Myocardial Infarction [VALIANT], Renoprotection of Optimal Antiproteinuric Doses [ROAD], Hong Kong Diastolic Heart Failure [DHF] Study, and the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial [ONTARGET]); therefore, variations in the study populations were intentionally ignored and all studies meeting this definition were included in the analysis.

The studies in both sets reported any CV outcome parameter or death, i.e., all-cause mortality, CV mortality, emergence of CV events, myocardial infarction, cerebrovascular event, stroke, heart failure, and hospitalization for heart failure.

Data extraction and quality assessment

Two independent reviewers performed article identification and screening phases. Results were reviewed by another investigator. Inconsistencies detected between the lists were discussed by 2 reviewers and a semifinal list was prepared. Two independent reviewers reviewed the full texts of the studies on the semifinal list. The reports were evaluated by 2 reviewers and then studies for analysis were selected.

During the full-text assessment, details of study design, including types of study drugs, dosages, and the duration of follow-up, as well as basic patient characteristics, including gender, age, and concomitant diseases were extracted. Risk ratios (RR) of selected outcomes (all-cause mortality, CV mortality, emergence of CV events, including or excluding death, fatal and non-fatal myocardial infarction, cerebrovascular event, stroke, heart failure, fatal heart failure, and hospitalization for heart failure) were abstracted or calculated.

Quality of the studies was assessed using Jadad scoring,[9] which uses 3 features to determine a score between 0 and 5. First item is related to randomization (0, non-randomized; 1, randomized but sequence of randomization was not reported; 2, randomized appropriately). Second item is related to double-blinding (0, not double-blinded; 1, double-blinded but details were not reported; 2, appropriate double-blinding techniques were performed). Third item is related to withdrawals and dropouts (0, number and reason for withdrawals were not stated; 1, number and reason for withdrawals were stated). A priori Jadad score cut-off value for study to be included was not set.

Data synthesis and analysis

The reported eligible results in the studies, not individual patient data, were used in this analysis, otherwise calculated manually based on the results provided.

All data presented in the publications were reviewed critically in order to validate accuracy and integrity. Percentages that were reported with rounding were re-calculated using number of patients. RR values of some outcomes were not given in some publications. Since RR and confidence intervals (CI) should be known to perform meta-analysis, these unknown values were calculated.

Data were initially entered in Excel (Microsoft Corp., Redmond, WA, USA) spreadsheets. Precise figures and unknown RRs and CIs were calculated in these Excel sheets. Then, these validated final data were transferred to software for meta-analysis.

The studies included in the analysis were performed both independently and in different populations in order to test absolutely different hypotheses; therefore, it is unlikely that the studies were function-

ally equivalent. Consequently, random effects model was used to estimate effect size, since this approach would be superior to fixed-effect model to extrapolate our results to entire population. Nevertheless, heterogeneity among studies was tested by using Q value and I2 statistics to evaluate inconsistency in the results of the studies.[10]

Publication bias was assessed using funnel plots and Begg and Mazumdar rank correlation test.[11] Funnel plot is a scatter-plot of standard error or precision of study parameter on vertical axis versus effect size on horizontal axis.[10] While larger studies tend to cluster toward the top of the graph near the mean effect size, smaller studies appear dispersed within a range of values toward the bottom of the graph. When there is no publication bias, studies analyzed are expected to be distributed symmetrically regarding effect size. On the other hand, in the presence of bias, studies are expected to be distributed asymmetrically across mean effect size. Another method used to evaluate presence of publication bias was Begg and Mazumdar rank correlation test.[10] This test is based on the concept underlying funnel plots. Since large studies can more easily be published regardless of the treatment effect and small studies are more likely to be published only if the treatment effect is large, an inverse correlation between study size and effect size might be expected. Therefore, if rank order correlation (Kendall's tau-b) between treatment effect and standard error (used as a summary measure of sample size) is significant, publication bias might exist.

Sensitivity of estimated effect size to possible excessive impact of individual studies was reviewed using repeated runs and omitting 1 study in each run. RR, confidence interval and p value calculated in each run were examined, and changes that made inferences drawn from analysis of all studies significantly different were noted.

All analyses were performed using Comprehensive Meta-Analysis Version 2 (Biostat, Englewood, NJ, USA) software.

RESULTS

Characteristics of the studies and patients

The abstracts of 3092 articles included in the screened set of publications were reviewed. Total of 2835 were excluded (76 meta-analyses, 66 design papers, 300

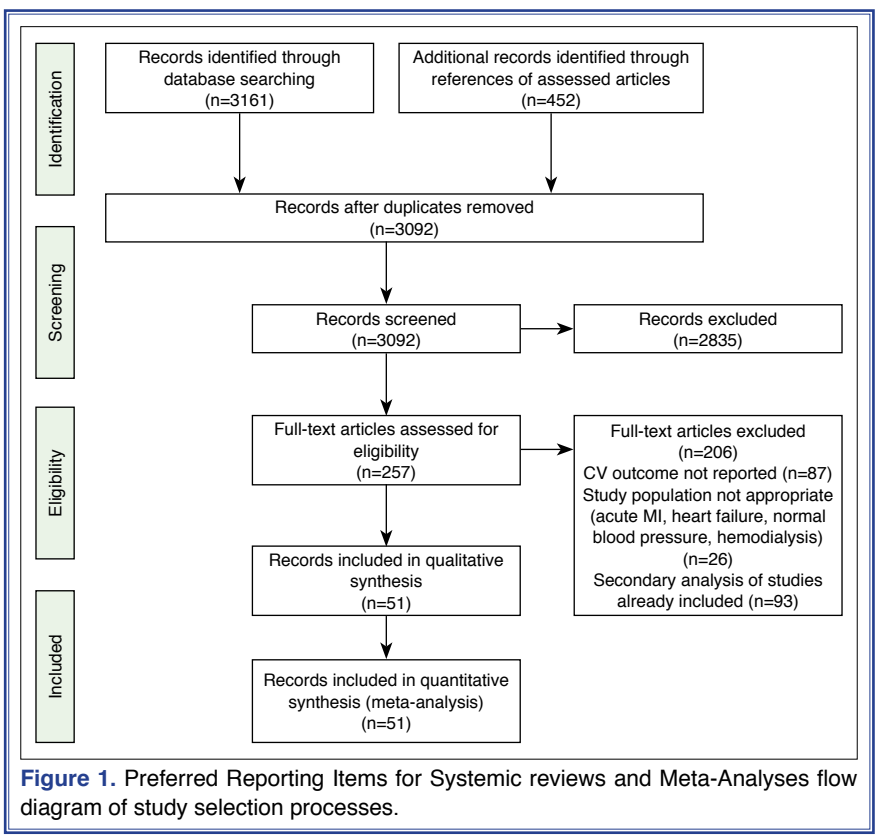

Figure 1. Preferred Reporting Items for Systemic reviews and Meta-Analyses flow diagram of study selection processes.

Table 1. List of studies included in the analysis

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secondary analyses of relevant trials, and 2393 unrelated to the study hypothesis), and full text of the remaining 257 articles was reviewed. After elimination of additional 206 articles due to inappropriate study design or irrelevant study population (i.e., subjects with acute myocardial infarction, heart failure, normal blood pressure, or on hemodialysis), 51 trials with 277,609 patients were included in the analysis. Figure 1 demonstrates the flow diagram of study selection processes.

Among 54 pairwise comparisons of 51 studies, 9 were ARB vs placebo studies with 57,031 patients, 7 were ARB vs non-RAAS blocker with 35,736 patients, 16 were ACEI vs placebo studies with 64,834 patients, and 14 were ACEI vs non-RAAS blocker studies with 84,321 patients. The remaining 8 were ARB vs ACEI studies with 36,998 patients. The list of 51 studies included in the analysis is provided in Table 1.

Table 2 summarizes the basic characteristics of the studies included in the analysis. Data from Irbesartan Type II Diabetic Nephropathy Trial (IDNT),[12] pilot-Hypertension in the Very Elderly Trial (HYVET),[13] and the Bergamo Nephrologic Diabetes Complications Trial Phase A (BENEDICT-A)[14] studies with more than 2 study arms were arranged to suit pairwise group comparison. Each pairwise comparison was assumed to be separate study.

Studies comparing RAAS blockers with non-RAAS blockers

In a total of 16 studies comparing ARB with non-RAAS blocker(s) or placebo, number of patients ranged from 203 to 10,146 in ARB arm, and from 203 to 10,186 in control arm. Average duration of follow-up was 2 to 6.4 years. Mean age was 58 to 76 years. Population was 18% to 65% female (Table 2).

In studies comparing ACEI with non-RAAS

Table 2. Basic characteristics of the studies included in the meta-analyses (sorted by publication year)

	Study population	Study medication and daily dose		n		Follow-up (years)		Female (%)		Mean age (years)		Jadad items and total score
		Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2	
RAAS BLOCKERS vs. NON-RAAS BLOCKERS												
ARB vs placebo				28491	28540							
RENAAL 2001	DM + RD	Losartan	Placebo	751	762	3.4	3.4	38.5	35.2	60.0	60.0	1+1+1=3
IDNT 2003	DM + HT + RD	Irbesartan	Placebo	579	569	2.6	2.5	35.0	29.0	59.3	58.3	2+2+1=5
Kondo 2003	CAD	Candesartan	Placebo	203	203	2.0	2.0	26.0	23.0	65.0	65.0	1+1+0=2
SCOPE 2003	HT	Candesartan	Placebo	2477	2460	3.7	3.7	64.8	64.2	76.4	76.4	2+2+1=5
PRoFESS 2008	Cerebrovascular disease (post-stroke)	Telmisartan	Placebo	10146	10186	2.5	2.5	35.7	36.2	66.1	66.2	2+1+1=4
TRANSCEND 2008	High CV risk	Telmisartan	Placebo	2954	2972	4.7	4.7	43.3	42.6	66.9	66.9	2+2+1=5
NAVIGATOR 2010	DM (Impaired glucose tolerance)	Valsartan	Placebo	4631	4675	6.4	6.4	50.0	51.3	63.7	63.8	2+2+1=5
ACTIVE I 2011	AF + High CV risk	Irbesartan	Placebo	4518	4498	4.1	4.1	39.2	39.3	69.5	69.6	2+1+1=4
ROADMAP 2011	DM	Olmesartan	Placebo	2232	2215	3.2	3.2	53.0	54.7	57.7	57.8	2+2+1=5
ARB vs non-RAAS blocker				17945	17791							
LIFE 2002	HT	Losartan + HCTZ	Atenolol + HCTZ	4605	4588	4.8	4.8	54.0	54.0	66.9	66.9	2+2+1=5
IDNT 2003	DM + HT + RD	Irbesartan	Amlodipine	579	567	2.6	2.5	35.0	37.0	59.3	59.1	2+2+1=5
VALUE 2004	HT + High CV risk	Valsartan +/- HCTZ	Amlodipine +/- HCTZ	7649	7596	4.2	4.2	42.4	42.5	67.3	67.2	2+2+1=5
E-COST 2005	HT	Candesartan	Conventional Rx	1053	995	3.1	3.1	55.5	48.2	NA	NA	1+0+1=2
MOSES 2005	Cerebrovascular disease + HT	Eprosartan	Nitrendipine	681	671	2.5	2.5	46.4	45.2	67.7	68.1	2+0+1=3
CASE-J 2008	HT	Candesartan + Diuretic/BB	Amlodipine + Diuretic/BB	2354	2349	3.2	3.2	46.4	43.2	63.8	63.9	2+0+1=3
HIJ-CREATE 2009	CAD + HT	Candesartan	Non-ARB	1024	1025	4.2	4.2	18.2	21.4	64.5	65.0	2+0+1=3
ACEI vs placebo				32415	322419							
Lewis 1993	DM	Captopril	Placebo	207	202	3.0	3.0	48.0	46.0	35.0	34.0	2+2+1=5
AIPRI 1996	RF	Benazepril	Placebo	300	283	3.0	2.9	26.7	29.0	51.0	51.0	2+2+1=5
REIN-2 1997	RD	Ramipril	Placebo	78	88	1.3	1.3	15.0	27.0	48.9	49.7	2+2+1=5
HOPE 2000	High CV risk	Ramipril	Placebo	4645	4652	5.0	5.0	27.5	25.8	66.0	66.0	2+2+1=5
SCAT 2000	CAD	Enalapril	Placebo	229	231	4.0	4.0	11.0	11.0	60.0	62.0	2+2+0=4
PROGRESS 2001	Cerebrovascular disease	Perindopril + Indapamide	Placebo	3051	3054	3.9	3.9	30.0	30.0	64.0	64.0	2+2+1=5
QUIET 2001	CAD	Quinapril	Placebo	878	872	2.2	2.2	18.0	19.0	58.0	58.0	1+1+1=3
EUROPA 2003	CAD	Perindopril	Placebo	6110	6108	4.2	4.2	14.5	14.7	60.0	60.0	2+2+1=5
Pilot-HYVET 2003	HT	Lisinopril	No Rx	431	426	1.1	1.1	64.0	63.4	83.7	83.8	2+0+1=3
BENEDICT-A 2004	DM + HT	Trandolapril	Placebo	301	300	3.6	3.6	47.8	50.3	61.6	62.6	2+2+1=5
DIABHYCAR 2004	DM + RD	Ramipril	Placebo	2443	2469	3.9	3.9	74.2	73.8	65.2	65.0	2+1+1=4
PEACE 2004	CAD	Trandolapril	Placebo	4158	4132	4.8	4.8	19.0	17.0	64.0	64.0	2+2+0=4
DREAM 2006	DM (Impaired fasting glucose / Impaired glucose tolerance)	Ramipril	Placebo	2623	2646	3.0	3.0	59.7	58.7	54.7	54.7	2+2+1=5

Table 2. Basic characteristics of the studies included in the meta-analyses (sorted by publication year) (cont.)

	Study population	Study medication and daily dose		n		Follow-up (years)		Female (%)		Mean age (years)		Jadad items and total score
		Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2	
RAAS BLOCKERS vs. NON-RAAS BLOCKERS												
ACEI vs placebo				32415	322419							
Hou 2006	RD	Benazepril	Placebo	112	112	3.4	3.4	50.0	51.0	44.4	45.0	2+2+1=5
ADVANCE 2007	DM + High CV risk	Perindopril + Indapamide	Placebo	5569	5571	4.3	4.3	42.5	42.5	66.0	66.0	2+2+1=5
IMAGINE 2008	CAD	Quinapril	Placebo	1280	1273	3.0	3.0	13.0	13.0	61.0	61.0	2+2+1=5
ACEI vs non-RAAS blocker			33327	50994								
GLANT 1995	HT	Delapril	CCB	980	956	1.0	1.0	44.4	44.4	60.0	60.0	1+0+1=2
ABCD 1998	DM + HT	Enalapril	Nisoldipine	235	325	5.0	5.0	33.2	31.9	57.7	57.2	2+2+1=5
FACET 1998	DM + HT	Fosinopril	Amlodipine	189	191	3.0	3.0	36.5	44.5	62.8	63.3	2+0+1=3
UKPDS 39 1998	DM + HT	Captopril	Atenolol	400	358	7.9	7.9	49.0	43.0	56.3	56.0	1+2+1=4
CAPPP 1999	HT	Captopril	Diuretics, BB or both	5492	5493	6.1	6.1	45.1	48.0	52.4	52.7	1+0+1=2
REIN 1999	RD	Ramipril	Conventional Rx	99	87	2.7	2.7	24.2	26.4	49.1	50.3	2+2+1=5
STOP-HT-2 1999	HT	Enalapril / Lisinopril	Felodipine / Isradipine or Conventional Rx	2205	4409	5.0	5.0	66.3	67.0	76.1	76.0	2+0+1=3
ALLHAT 2002	HT	Lisinopril	Amlodipine or Chlortalidone	9054	24303	6.0	6.0	46.2	47.1	66.9	66.9	2+2+1=5
ANBP-2 2003	HT	ACEI	Diuretic	3044	3039	4.1	4.1	50.0	52.0	72.0	71.9	1+0+1=2
Pilot-HYVET 2003	HT	Lisinopril	Bendrofluazide	431	426	1.1	1.1	64.0	62.9	83.7	83.8	2+0+1=3
BENEDICT-A 2004	DM + HT	Trandolapril	Verapamil	301	303	3.6	3.6	47.8	45.9	61.6	62.5	2+2+1=5
JMIC-B 2004	CAD + HT	ACEI	Nifedipine	822	828	3.0	3.0	30.0	32.4	64.9	65.8	2+0+1=3
ASCOT-BPLA 2005	HT	Amlodipine + Perindopril + Doxazosin	Atenolol + Bendroflumethiazide + Doxazosin	9639	9618	5.5	5.5	23.4	23.5	63.0	63.0	2+2+1=5
AASK 2006	HT + RD	Ramipril	Metoprolol or Amlodipine	436	658	4.1	4.1	38.8	40.1	54.2	54.4	2+2+0=4
ARB vs ACEI			18481	18517								
ELITE-I 1997	HF	Losartan	Captopril	352	370	0.9	0.9	33.5	33.0	74.0	73.0	2+1+1=4
ELITE-II 2000	HF	Losartan	Captopril	1578	1574	1.5	1.5	30.0	31.0	71.4	71.5	2+1+1=4
OPTIMAAL 2002	Acute MI + HF	Losartan	Captopril	2744	2733	2.7	2.7	28.2	29.3	67.6	67.2	2+2+1=5
DETAIL 2004	DM + HT + RD	Telmisartan	Enalapril	120	130	5.0	5.0	27.5	26.9	61.2	60.0	2+2+1=5
VALIANT 2006	Acute MI+ HF	Valsartan	Captopril	4909	4909	2.1	2.1	31.5	31.3	65.0	64.9	2+2+1=5
ROAD 2007	RD	Losartan	Benazepril	180	180	3.7	3.7	38.5	36.0	51.3	50.5	2+0+1=3
HONG KONG DHF Study 2008	HF	Irbesartan + Diuretic	Ramipril + Diuretic	56	45	1.0	1.0	66.0	60.0	75.0	74.0	2+0+1=3
ONTARGET 2008	High CV risk	Telmisartan	Ramipril	8542	8576	4.7	4.7	26.3	27.2	66.4	66.4	2+2+1=5

*Jadad scoring: Item 1 score + Item 2 score + Item 3 score = Total score. Full score 2+2+1=5.
ACEI: Angiotensin-converting enzyme inhibitor; AF: Atrial fibrillation; ARB: Angiotensin receptor blocker; BB: Beta-blocker; CAD: Coronary artery disease; CCB: Calcium channel blocker; CV: Cardiovascular; DM: Diabetes mellitus; HCTZ: Hydrochlorothiazide; HF: Heart failure; HT: Hypertension; MI: Myocardial infarction; RAAS: Renin-angiotensin-aldosterone system; RD: Renal disease; Rx: Treatment.

Table 3. Heterogeneity analysis for all parameters analyzed

Outcome parameter	Number of studies	Q	I^2	p^*	Fixed-effect		Random effects	
					Rate ratio	p^{**}	Rate ratio	p^{***}
All-cause mortality	42	46.330	11.505	0.262	0.972	0.036	0.967	0.034
Cardiovascular mortality	35	53.373	36.298	0.018	0.950	0.011	0.944	0.059
All cardiovascular events including death	30	64.552	55.075	0.000	0.960	0.002	0.932	0.003
All cardiovascular events excluding death	28	50.540	46.577	0.004	0.965	0.029	0.923	0.004
Myocardial infarction	28	63.674	57.596	0.000	0.932	0.002	0.915	0.044
Fatal myocardial infarction	11	6.389	0.000	0.782	0.805	0.029	0.805	0.029
Nonfatal myocardial infarction	18	26.750	36.448	0.062	0.861	0.000	0.859	0.014
Stroke	34	96.472	65.793	0.000	0.921	0.000	0.898	0.012
Stroke or cardiovascular event	37	97.967	63.253	0.000	0.921	0.000	0.899	0.007
Heart failure	20	31.387	39.465	0.037	0.910	0.000	0.893	0.006
Fatal heart failure	4	4.014	25.253	0.260	0.953	0.364	0.845	0.297
Hospitalization for heart failure	10	12.932	30.405	0.166	0.859	0.000	0.855	0.002

*P values for significance of I2. Studies included in the analysis are considered to be heterogeneous, when p value is less than 0.05.
**P values for significance of rate ratio calculated by fixed-effect model.
***P values for significance of rate ratio calculated by random effects model.

blocker(s) or placebo, number of patients was between 78 and 9,639 in ACEI arm, and 87 and 24,303 in control arm. Duration of follow-up period was 1 to 8 years. Mean age of study population ranged from 34 to 84 years (Table 2).

Random effects model was planned to estimate effect size and related statistics a priori. However, heterogeneity analysis was performed to check this assumption that studies analyzed were heterogeneous. As expected, I2 values were higher than 25 for most and even higher than 50 for some outcome parameters (Table 3). Seven of 12 outcome parameters to be analyzed had behaved heterogeneously (I2 values 36–66; p values <0.05). RR values and p values calculated with fixed-effect model for the 5 non-heterogeneous outcome parameters did not change enough to alter the conclusion. All analyses were done with random effects model in order to be consistent throughout the analysis.

Impact of possible publication bias was examined by reviewing funnel plots for all 12 parameters analyzed. All studies were represented by a dot on graph with log RR on horizontal axis and standard error of RR on vertical axis (Figure 2). For all parameters, studies tended to cluster symmetrically toward the top of the plot, near the intersection of the lines guiding the limits. Very small number of the studies was located outside the guidelines. Appearance of the funnel plots gave strong impression that publication bias did not have any considerable impact. In order to confirm this conclusion, Beg and Mazumdar rank correlation test was performed (Table 4). All correlation coefficients (tau-b) were quite small and mostly very close to 0. All p values were well over 0.05, denoting that there were not any significant correlations between RR and standard error of RR for any parameter. These results, along with the funnel plots, indicated that there was not a significant problem of publication bias.

Forest-plot for all-cause mortality demonstrating RR values and 95% CI of all individual studies comparing RAAS blockers with non-RAAS blockers along with Z and p values is presented in Figure 3. As seen, overall RR value is 0.967 with 95% CI of 0.937 and 0.997 (p=0.034). This might be translated to a statistically significant 3.3% decrease in all-cause mortality, when RAAS blocker is administered instead of non-RAAS blocker.

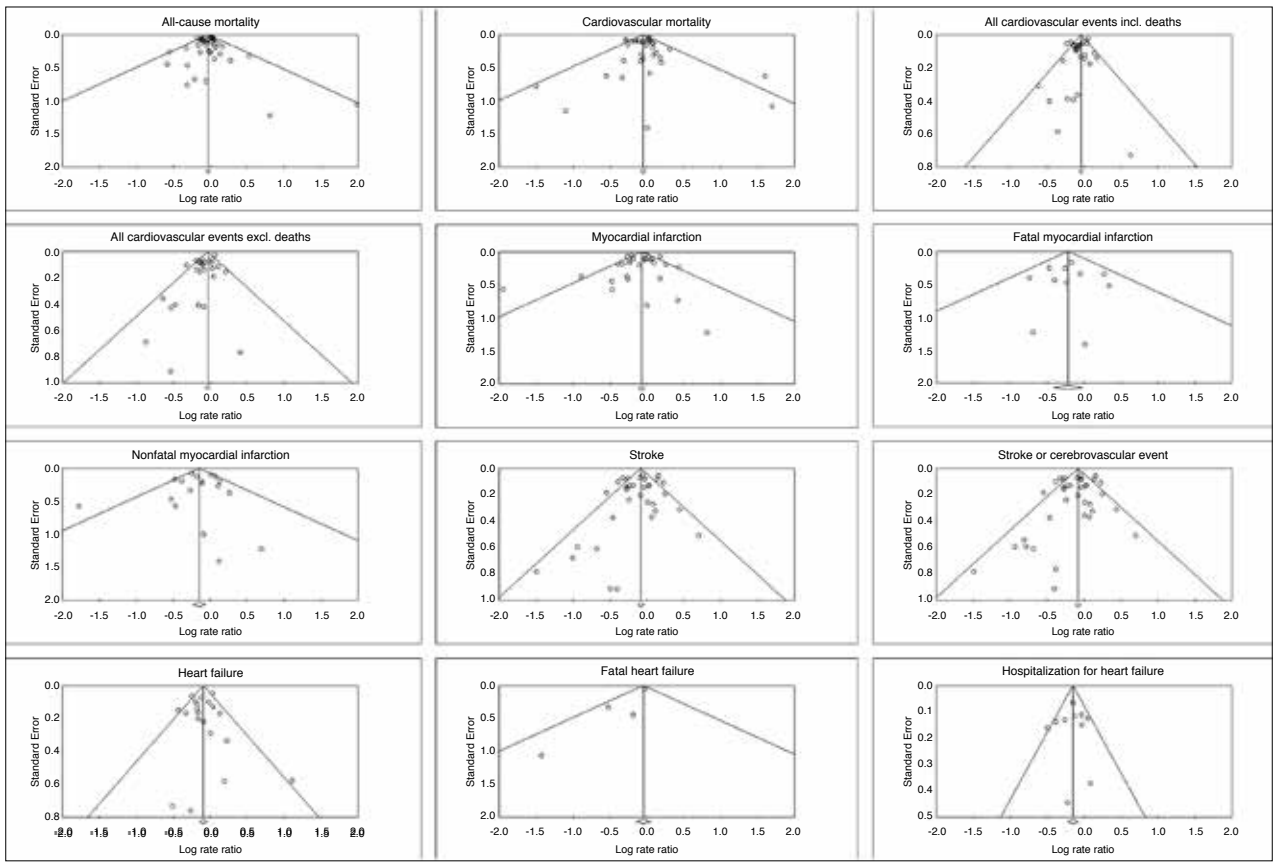

Figure 2. Funnel plots for all parameters analyzed.

The forest-plot for all CV events, including death, for studies comparing RAAS blockers with non-RAAS blockers is presented in Figure 4. Overall RR value is 0.932 (95% CI: 0.890-0.977; p=0.003). Therefore, it might be suggested that statistically significant 6.8% decrease in incidence of all CV events,

Table 4. Analysis regarding publication bias: Begg and Mazumdar rank correlation test

Outcome parameter	Number of studies	Kendall's tau b	*p**
All-cause mortality	42	0.028	0.397
Cardiovascular mortality	35	-0.020	0.432
All cardiovascular events including deaths	30	0.035	0.394
All cardiovascular events excluding deaths	28	0.058	0.332
Myocardial infarction	28	-0.061	0.325
Fatal myocardial infarction	11	0.073	0.378
Nonfatal myocardial infarction	18	-0.039	0.410
Stroke	34	-0.075	0.267
Stroke or cardiovascular event	37	-0.107	0.177
Heart failure	20	0.184	0.128
Fatal heart failure	4	-0.167	0.367
Hospitalization for heart failure	10	-0.222	0.185

*P values (one-tailed) for significance of Kendall's tau b. Publication bias is considered to be significant when p value is less than 0.05.

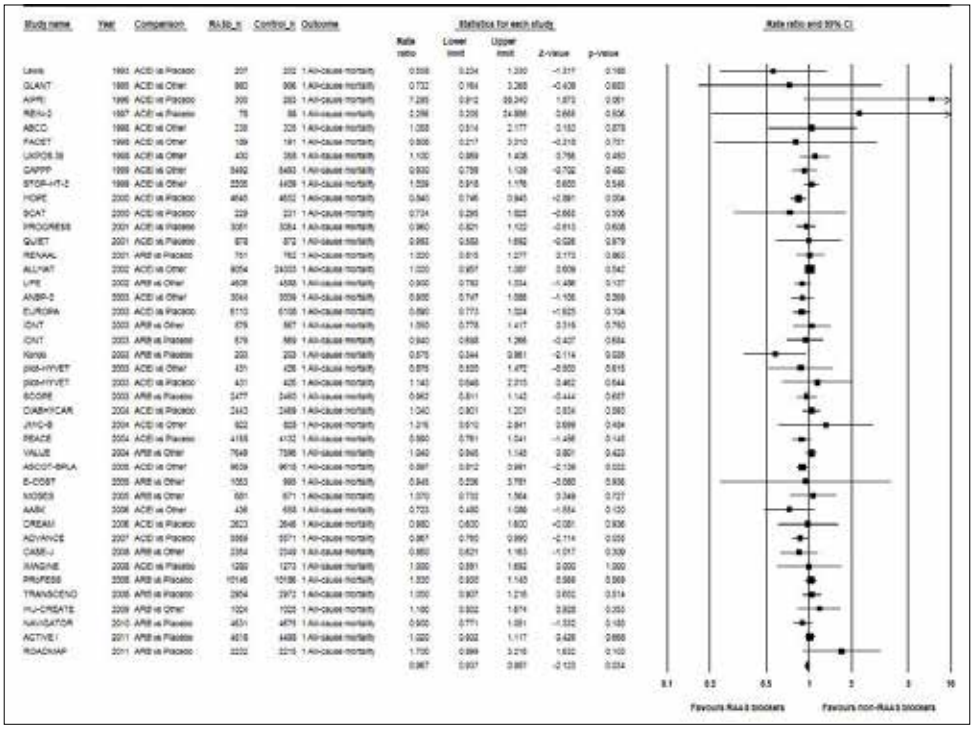

Figure 3. Forest plot of risk ratio for all-cause mortality: RAAS blockers vs non-RAAS blockers. ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; RAAS: Renin-angiotensin-aldosterone system.

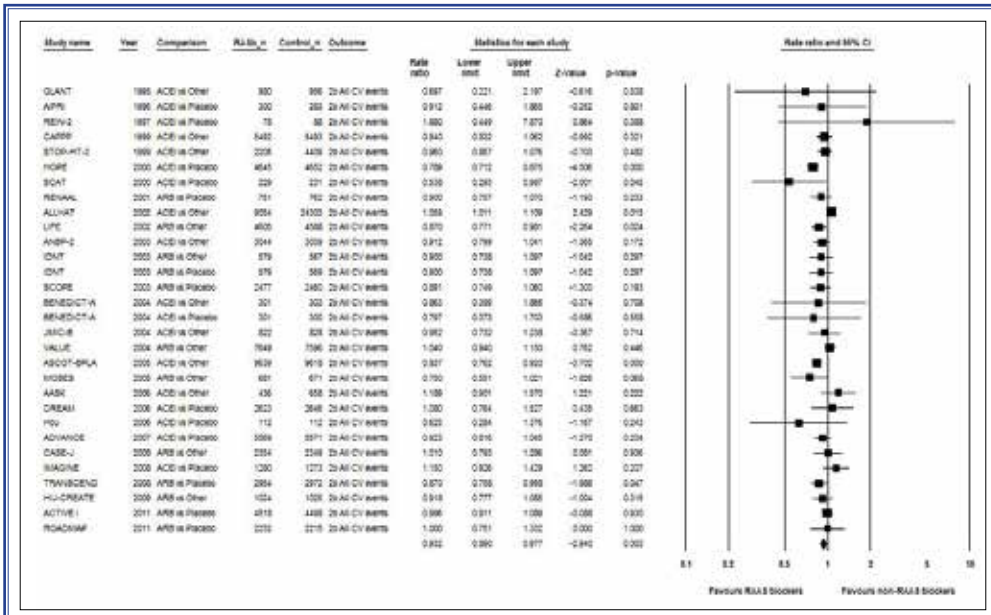

Figure 4. Forest plot of risk ratio for all cardiovascular events: RAAS blockers vs non-RAAS blockers. ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; RAAS: Renin-angiotensin-aldosterone system.

including death, occurs when RAAS blocker is administered rather than non-RAAS blocker. Forest-plots for myocardial infarction, stroke and heart failure for studies comparing RAAS blocker and non-RAAS blocker comparisons are presented in Figures 5 to 7). Overall RR values were 0.915 (95% CI: 0.840–0.997;

p=0.044), 0.898 (95% CI: 0.827–0.976; p=0.012), and 0.893 (95% CI: 0.825–0.967; p=0.006), respectively. These results should be read as statistically significant decreases of 8.5%, 10.2%, and 10.7% in incidence of myocardial infarction, stroke, and heart failure, respectively, when RAAS blocker is administered instead of non-RAAS blocker.

Overall RRs, confidence intervals and p values were summarized in a single forest-plot (Figure 8). As seen, RR values for all outcome parameters were

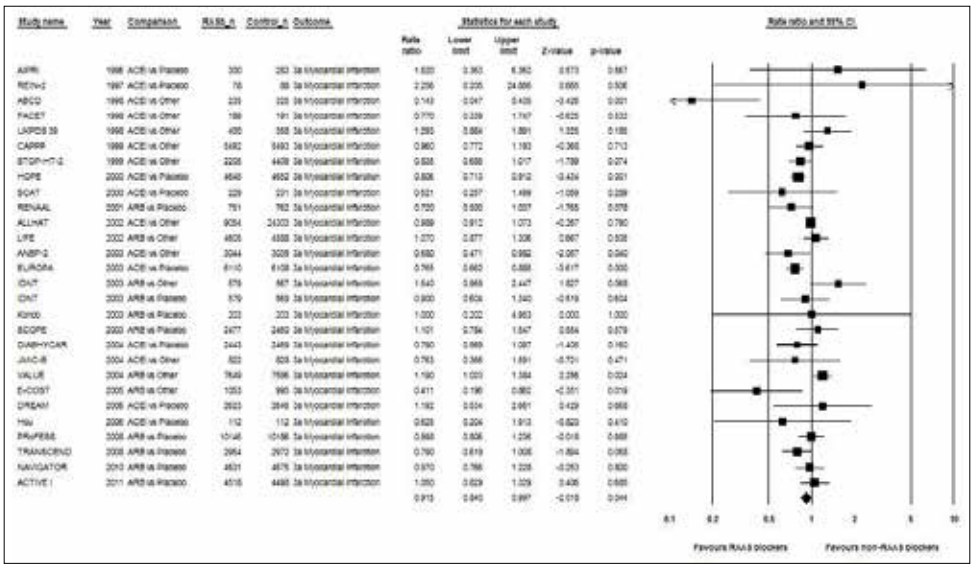

Figure 5. Forest plot of risk ratio for myocardial infarction: RAAS blockers vs non-RAAS blockers. ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; RAAS: Renin-angiotensin-aldosterone system.

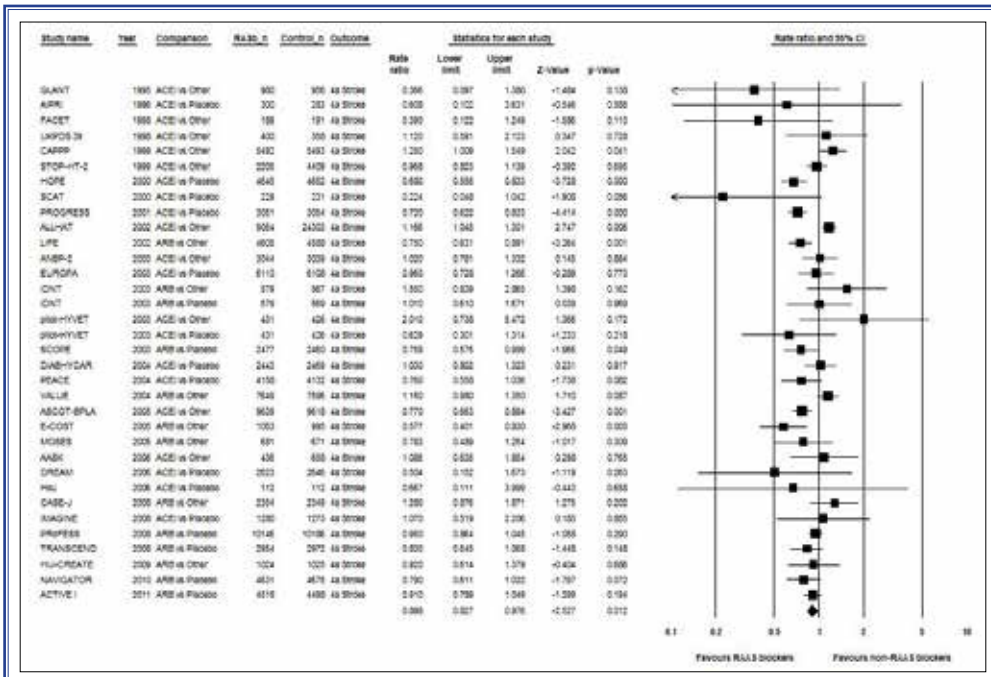

Figure 6. Forest plot of risk ratio for stroke: RAAS blockers vs non-RAAS blockers. ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; RAAS: Renin-angiotensin-aldosterone system.

found to be lower than unity, indicating that RAAS blockers have positive effects in terms of death and CV outcomes when compared to non-RAAS blockers or placebo. RR for 10 of 12 outcome parameters analyzed was significantly lower than unity; CV mortality (RR: 0.944; 95% CI: 0.889–1.002; p=0.059) and fatal heart failure (RR: 0.845; 95% CI: 0.617–1.159; p=0.297) were not. In addition to all-cause mortality mentioned in the above paragraph, percent reduction in emergence of events was 7.8% for CV events, 8.5% for myocardial infarction, 19.5% for fatal myocardial infarction, 10% for stroke, 11% for heart failure, and 14.5% for hospitalization for heart failure.

In order to test excessive impact of individual study, all analyses were run repeatedly, omitting 1 study in each run. For all-cause mortality, overall RR, which was 0.967 (p=0.034), increased slightly and p values exceeded significance limit of 0.05 when 7 of 42 studies (Heart Outcomes Prevention Evaluation [HOPE],[15] Losartan Intervention For Endpoint reduction in hypertension [LIFE],[16] Second Australian National Blood Pressure Study [ANBP-2],[17] Prevention of Events with Angiotensin-Converting Enzyme Inhibition [PEACE],[18] Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm [ASCOT-BPLA],[19] Action in Diabetes and Vascular disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE],[20] or Nateglinide and Valsartan

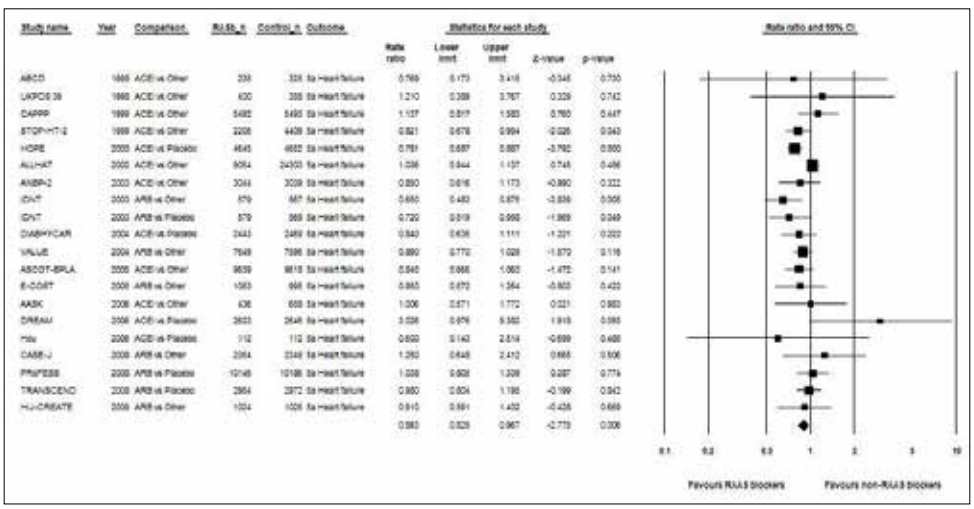

Figure 7. Forest plot of risk ratio for heart failure: RAAS blockers vs non-RAAS blockers. ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; RAAS: Renin-angiotensin-aldosterone system.

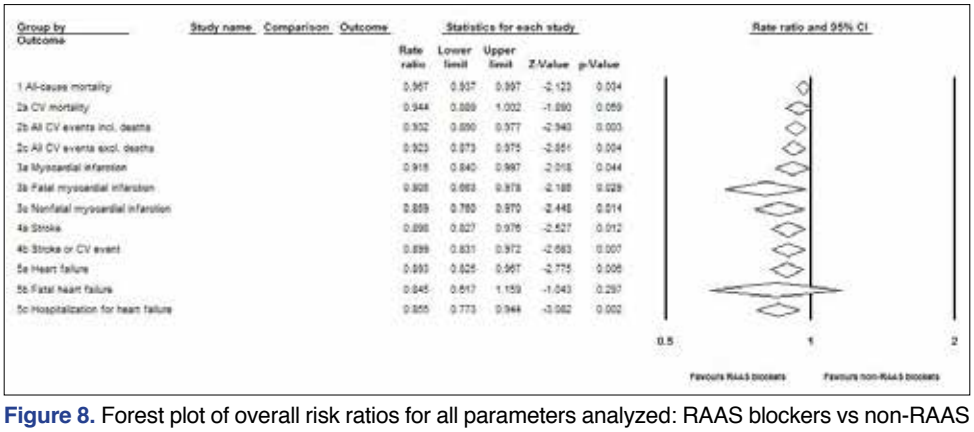

Figure 8. Forest plot of overall risk ratios for all parameters analyzed: RAAS blockers vs non-RAAS blockers. ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CV: Cardiovascular; RAAS: Renin-angiotensin-aldosterone system.

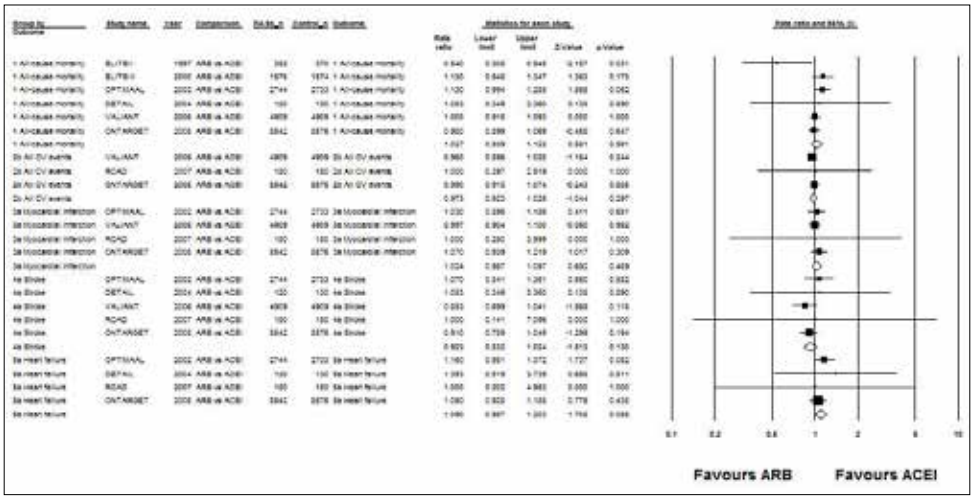

Figure 9. Forest plot of risk ratios for major parameters analyzed: ARBs vs ACEIs. ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CV: Cardiovascular; RAAS: Renin-angiotensin-aldosterone system.

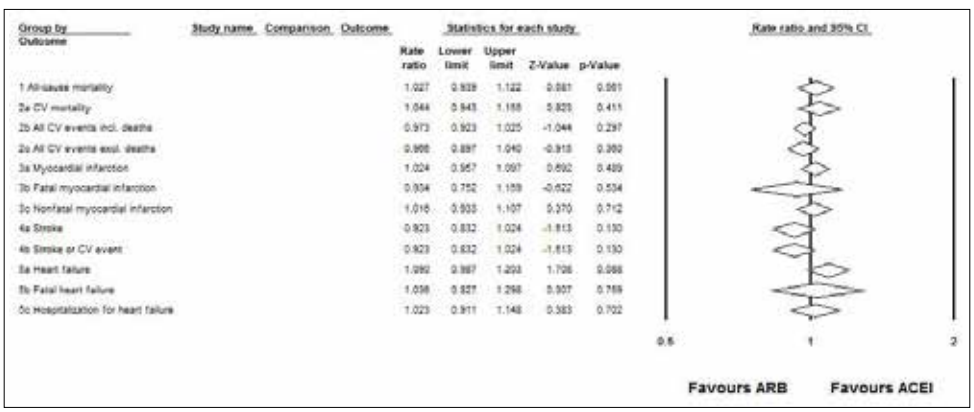

Figure 10. Forest plot of overall risk ratios for all parameters analyzed: ARBs vs ACEIs. ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CV: Cardiovascular; RAAS: Renin-angiotensin-aldosterone system.

Impaired Glucose Tolerance Outcomes Research [NAVIGATOR][21]) were omitted individually in each run (RR range: 0.969–0.979; p values: 0.054–0.136).

Significant RR values corresponding to all CV events, including death, all CV events excluding death, stroke, stroke or CV event, heart failure, and hospitalization for heart failure were insensitive to omission of any studies analyzed. On the other hand, overall RR for fatal myocardial infarction, 0.805 (p=0.029), became non-significant when 3 of 11 studies (Captopril Prevention Project [CAPPP],[22] European Trial on Reduction of Cardiac Events with Perindopril in Patients with Stable Coronary Artery Disease [EUROPA],[23] and the Non-insulin-dependent Diabetes, Hypertension, Microalbuminuria or Proteinuria, Cardiovascular Events, and Ramipril [DIABHYCAR] study[24]) were omitted individually at each run (RR range: 0.812–0.843; p value: 0.052–0.110). For myocardial infarction, overall RR, which was 0.915 (p=0.044), became non-significant when 14 of 28 studies were omitted 1 at each run (RR range: 0.916–0.929; p value: 0.050-0.098). For nonfatal myocardial infarction, overall RR of 0.859 (p=0.014) became non-significant when 1 of 18 studies (EUROPA) was omitted (RR=0.872; p=0.051).

Studies with head-to-head comparison of ARB and ACEI

Among 8 head-to-head ARB vs ACEI studies, the number of patients ranged from 56 to 8,542 in ARB

arm and from 45 to 8,576 in ACEI arm. Average duration of follow-up was 1 to 5 years. Mean age of population was between 51 and 75 years. Except for Hong Kong DHF[25] study, which included 66% females in ARB arm and 60% females in ACEI arm, study populations had more male patients than female patients (61%–74% male). Among these 8 studies, the patients had heart failure in 5 studies, renal failure in 2 studies and high CV risk in 1 study.

Separate forest-plots are provided in Figure 9 for major outcome parameters. Although these studies had differences in terms of study populations, results of CV outcome analysis were mostly consistent. RR for all-cause mortality was significantly different from unity in just 1 study (ELITE-I study), which was reported to be 0.540 with p value of 0.031. RR for all other CV outcome parameters in ELITE-I study and RR for all CV outcome parameters (including all-cause mortality) in other 7 studies ranged from 0.85 to 1.39, with no statistically significant difference from unity. Overall RRs, CIs and p values are summarized in a single forest-plot (Figure 10). As seen, RR values for all outcome parameters were found to be within narrow range around unity, with all p values higher than 0.05, even higher than 0.10, except for heart failure. These findings indicate that ARBs and ACEIs do not differentiate from each other in terms of all-cause mortality, CV mortality, CV events, myocardial infarction, stroke, or heart failure, and effects of treatment with ARBs or ACEIs are likely to be comparable with no statistically significant RR.

DISCUSSION

The effects of a treatment on a specific clinical outcome cannot be proven easily with a single randomized clinical trial. This is due to low statistical power of analysis for non-primary parameters due to a sample size that is too small. Meta-analysis is a useful way to overcome this problem, because when the data from many randomized clinical studies are pooled in a single population, the sample size and, hence, statistical power increases.[10] The pooled samples, however, should be as homogeneous as possible in order to make valid inferences. The main approach to avoid this very common problem is to build a fair and objective strategy to select studies with comparable study designs and populations. However, comparison of incomparable studies in meta-analysis, which leads to invalid results, is a common problem in the literature. Incorrectly designed meta-analyses cause misleading conclusions to be drawn, not only as result of original invalid results, but also because they form the basis for further studies or papers.

In our meta-analysis, we did not include clinical trials that had been conducted on patient populations with acute myocardial infarction, heart failure, or those undergoing hemodialysis, as these conditions might interfere with the effect of RAAS blockers on CV outcomes. Although studies of patients with acute myocardial infarction were not included, effects of RAAS blockers on prevention of acute myocardial infarction have been studied in other patient populations. Studies of normotensive populations were also excluded, as normal blood pressure levels would also influence effect of RAAS blockers on CV outcomes. Thus, efforts were made to avoid heterogeneity problem in pooling the samples.

There have been numerous clinical trials focusing on effects of ACEIs and ARBs in hypertensive patients who are at high risk for CV or cardiometabolic abnormalities. In some clinical trials, it has been claimed that ACEIs have beneficiary effect on reducing mortality, myocardial infarction, stroke, and new-onset congestive heart failure. Meanwhile, ARBs offer more improved blockade of the RAAS system than ACEIs, thus they are expected to have positive effects on CV outcomes in populations with heart failure or other comorbid CV conditions. Current meta-analyses comparing ARBs and ACEIs present varying results, depending on the clinical trials they include. ARBs and ACEIs were reported to be equally effective in reducing risk of myocardial infarction, CV mortality, and total mortality,[4,26,27] in the prevention of atrial fibrillation[28] and in the reduction of newly diagnosed type 2 diabetes incidence;[29] ARBs were found to be more effective than ACEIs in stroke prevention.[4]

A meta-analysis of nine randomized trials comparing treatments in 62,605 hypertensive patients also did not show beyond-blood pressure-lowering benefits of ACEIs.[30] In a recent meta-analysis, it was suggested that risk of emergence of major CV outcome parameters (mainly heart failure, but also stroke, coronary heart disease, and CV all-cause mortality) was significantly reduced with 10/5 mmHg reduction in systolic and diastolic blood pressures, regardless of class of

antihypertensive treatment.[31] In a Cochrane Library review conducted by Xue et al.,[32] benefits and harms of first-line RAAS inhibitors were compared to other first-line antihypertensive drugs in patients with hypertension and it was reported that they are comparable in terms of all-cause of mortality. In the review, the authors emphasized that first-line thiazides caused less heart failure than first-line RAAS inhibitors and that RAAS inhibitors reduced heart failure but increased stroke when compared with first-line calcium channel blockers.

In a meta-analysis of randomized clinical trials of RAAS inhibitors involving 158,998 patients reported by van Vark et al.,[5] effects of ACEIs and ARBs on all-cause mortality were evaluated. Findings of the study demonstrated that RAAS inhibition was associated with 5% reduction in all-cause mortality and 7% reduction in CV mortality resulted entirely from ACEIs, which were associated with a significant 10% reduction in all-cause mortality, whereas no mortality reduction could be demonstrated with ARB treatment. Thus, it was concluded that in patients with hypertension, treatment with an ACEI results in significant further reduction in all-cause mortality[6] and the conclusion about ARBs was found to be consistent with another large recent meta-analysis of 37 ARB trials,[27] which also failed to detect any reduction in all-cause or CV mortality. Additionally, Donzelli[6] also commented in a letter-to-the-journal published electronically on the website of the journal, that the conclusion about ACEIs was strongly biased, as the trials that showed the largest benefit for ACEIs in the meta-analysis conducted by van Vark et al.[5] (ASCOT-BPLA,[19] HYVET[33] and ADVANCE[20]) used treatment protocols in which ACEI was second-line.

In a recent report, when Kizilirmak et al.[34] re-analyzed the van Vark data, HRs for all-cause mortality and CV mortality were found to be 1.00 (95% CI: 0.96–1.05; p=0.86) for ACEI vs control group, and 0.98 (%95 CI: 0.94-1.03; p=0.47) for ARB vs control group, indicating that there were not any significant differences between effects of ARBs and ACEIs on all-cause and CV mortality.

A meta-analysis performed by Reboldi et al.[4] compared effects of ARBs and ACEIs on risk of myocardial infarction, stroke, CV mortality, and total mortality using the data of 6 trials on total of 49,924 patients. Results of the analysis revealed no significant differences between ARBs and ACEIs on risk of myocardial infarction (odds ratio [OR]: 1.01; 95% CI: 0.95–1.07; p=0.75), CV mortality (OR: 1.03; 95% CI: 0.98–1.08; p=0.23), and total mortality (OR: 1.03; 95% CI: 0.97–1.10; p=0.20). Risk of stroke was slightly lower with ARBs than ACEIs (OR: 0.92; 95% CI: 0.85–0.99; p=0.037). Thus, it was concluded that ARB and ACEI-based treatments provide similar protective effect on risk of fatal CV events and all-cause mortality, but that blockade of RAAS by antagonizing AT1 receptor stimulation by angiotensin II may be associated with slightly superior protective effect than blockade provided by ACEI.[4]

Findings of the meta-analysis conducted by Reboldi et al.[4] are consistent with 2 large observational studies.[35] The first study, which compared rates of hospitalization for acute coronary syndromes of ARB and ACEI users concluded that ARBs offered approximately 11% greater relative risk reduction compared to ACEIs.[35] The second study, evaluating 29,357 hypertensive patients using ARB or ACEI, found that patients receiving ARB had an 11% lower risk of major CV or renal event than those receiving an ACEI.[36]

In the present meta-analysis, our aim was to re-evaluate the data of trials included in the analysis by Reboldi et al.[4] along with those of recent trials to examine whether ARBs and ACEIs provide similar protective effects on risk of all-cause mortality and CV events. Our data revealed that ARBs and ACEIs have comparable benefits for patients with hypertension considering all-cause mortality, CV mortality, CV events, myocardial infarction, heart failure, and stroke. In our study, the HRs for all-cause mortality and CV mortality were 1.03 (95% CI: 0.94–1.12; p=0.561) and 1.04 (95% CI: 0.94–1.16; p=0.411), respectively. In the Reboldi et al. meta-analysis (4), OR for all-cause mortality was reported as 1.03 (95% CI, 0.98–1.08; p=0.178) and that of CV mortality as 1.03 (95% CI, 0.98–1.08; p=0.227). Thus, our results seem to be in accordance with those reported by Reboldi et al.[4] The second major finding of our analysis is that blockade of the RAAS (by use of either ARBs or ACEIs) is significantly superior to other treatments in terms of effects on risk of all-cause mortality, CV mortality, CV events, myocardial infarction, heart failure, and stroke. According to our results, comparison of ARBs/ACEIs with non-ARB and non-ACEI

leads to HR of 0.94 (95% CI: 0.91–0.97; p=0.000) for all-cause mortality, and 0.91 (95% CI: 0.87–0.96; p=0.000) for CV mortality.

In conclusion, the current meta-analysis implies that ARBs and ACEIs have similar benefit for CV outcomes in patients with hypertension and are superior to treatments other than ARBs and ACEIs.

Limitations

The present study has the limitations that apply to all meta-analyses. Although meta-analysis is the best way of summarizing vast amount of randomized clinical trials in literature to produce a single estimate of the effect of a treatment, the disadvantages of meta-analyses should always be considered. The main limitation is the heterogeneity of the studies included. Other limitations common to all meta-analyses are publication bias and lack of patient-based data. In order to overcome heterogeneity, we applied random effects model for all analysis.

A further limitation of this manuscript is the lack of studies published after the search of the literature had been completed. This is also a common problem experienced with this kind of meta-analysis with a large volume of data, because data synthesis, analysis, and reporting stages take considerable time and studies may be published in the interim before the manuscript is ready to be published.

Conflict-of-interest issues regarding the authorship or article:

Pınar Kızılırmak: Pharmaceutical employee.

Oktay Özdemir: Consultant, worked for several pharmaceutical companies.

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Keywords: ACE inhibitors; angiotensin receptor blocker; antihypertensive therapy; hypertension-vascular disease; outcomes of care.

Anahtar sözcükler: ACE İnhibitörleri; anjiyotensin reseptör blokeri; antihipertansif tedavi; hipertansiyon-vasküler hastalık; bakım sonuçları.