Meta-Analysis of Randomized Trials on the Efficacy and Safety of Angiotensin-Converting Enzyme Inhibitors in Patients ≥65 Years of Age

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The comparative efficacy and safety of angiotensin-converting enzyme inhibitors (ACEIs) with other agents in patients ≥65 years of age with cardiovascular diseases or at-risk are unknown. Electronic databases were systematically searched to identify all randomized controlled trials that compared ACEIs with control (placebo or active) and reported long-term cardiovascular outcomes. We required the mean age of patients in the studies to be ≥65 years. Random-effects model was used to pool study results. Sixteen trials with 104,321 patients and a mean follow-up of 2.9 years were included. Compared with placebo, ACEIs significantly reduced all outcomes except stroke. Compared with active controls, ACEIs had similar effect on all-cause mortality (relative risk [RR] 0.99, 95% confidence interval [CI] 0.95 to 1.03), cardiovascular mortality (RR 0.99, 95% CI 0.93 to 1.04), heart failure (RR 0.97, 95% CI 0.91 to 1.03), myocardial infarction (RR 0.94, 95% CI 0.88 to 1.00), and stroke (RR 1.07, 95% CI 0.99 to 1.15). ACEIs were associated with an increased risk of angioedema (RR 2.79, 95% CI 1.05 to 7.42), whereas risk for hypotension and renal insufficiency was similar compared with active controls. Meta-regression analysis showed that the effect of ACEIs on outcomes remained consistent with age increasing ≥65 years. Sensitivity analysis excluding trials comparing ACEIs with angiotensin receptor blockers and heart failure trials yielded similar results, except for reduction in myocardial infarction. In conclusion, the efficacy of ACEIs was similar to active controls for mortality outcomes. Compared with placebo, there was evidence for reduction in cardiovascular outcomes; however, ACEIs failed to prevent stroke and increased the risk of angioedema, hypotension, and renal failure. **(Am J Cardiol 2016;118:1427−1436)**

In the United States, population aged ≥65 years is projected to nearly double to 84 million by 2050.[1] With a rapidly aging population, the prevalence of cardiovascular diseases such as hypertension, heart failure, and coronary artery disease is expected to increase in parallel. By blocking the renin-angiotensin-aldosterone system, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) decrease blood pressure, reduce afterload, and prevent ventricular remodeling. However, the comparative effectiveness of ACEIs in patients ≥65 years and cardiovascular diseases is not well studied. Patients ≥65 years have an increased burden of co-morbidities and therefore are often exposed to polypharmacy,[2] which may potentiate the risk of adverse effects. Despite these risks, there is a paucity of literature on adverse effects of ACEIs, particularly in patients ≥65 years of age.[3] We conducted a comprehensive meta-analysis to study the long-term efficacy and safety of ACEIs in patients ≥65 years and who either had cardiovascular diseases or were at high risk for cardiovascular diseases.

Methods

We performed a systematic search, without language restriction, using MEDLINE, Cochrane library, *ClinicalTrials.gov*, Embase, and Scopus databases from January 1, 1987, to March 1, 2016, for randomized controlled trials (RCTs) that compared ACEIs with placebo/active control and reported mortality and other cardiovascular outcomes. The search keywords included the following MeSH terms: (angiotensin-converting enzyme inhibitors OR ACEI OR benazepril OR captopril OR enalapril OR fosinopril OR lisinopril OR perindopril OR quinapril OR ramipril OR trandolapril) AND (randomized controlled trial or clinical trial) AND (mortality OR death OR cardiovascular events). Furthermore, we performed manual searches through the reference lists of studies, reviews, and meta-analyses on this topic to identify pertinent studies missed by the search strategy. When there were multiple reports from the same trial, we used the most complete and relevant reported data.

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Studies were included if they met the following inclusion criteria: (1) RCTs comparing ACEIs with placebo or active control; (2) trials providing data on all-cause mortality and other cardiovascular outcomes; and (3) mean age of the patients in the studies should be ≥65 years. Exclusion criteria were the following: (1) ACEIs not used as the first-line therapy; (2) ACEIs used in combination with other agents; and (3) study reported only noncardiovascular or renal outcomes.

Two reviewers (CB and MA) independently and in duplicate performed the literature search, reviewed the originally identified titles and abstracts, and selected studies for pooled analysis based on the inclusion and exclusion criteria. Any divergence was resolved with consensus. Quality of the included studies and assessment of trial bias risk were assessed for the domains suggested by the Cochrane Collaboration,[4] specifically emphasizing sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. The efficacy outcomes evaluated were all-cause mortality, cardiovascular mortality, myocardial infarction (MI), stroke, and hospitalization for heart failure, whereas angioedema, hypotension, and renal insufficiency were assessed as safety outcomes.

The statistical analysis was performed in line with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We analyzed the efficacy and safety of ACEIs separately by placebo and active controls. Considering that the heterogeneity of the included trials might influence the treatment effects, we used the random-effects model to pool studies.[5] Analysis was performed on an intention-to-treat basis. Heterogeneity was assessed using Higgins and Thompson's I^2 statistic with I^2 values of <25%, 25% to 75%, and >75% corresponding to low, moderate, and high levels of heterogeneity, respectively.[6] We performed sensitivity analysis by excluding trials comparing ACEIs and ARBs and heart failure trials. Publication bias was estimated visually by funnel plots and Egger's regression test.[7] We also performed metaregression analysis to evaluate any association of age with ACEIs and outcomes. A 2-tailed p value <0.05 was considered statistically significant for all the analyses. All statistical analyses were performed using Stata 11 (Stata Corp., College Station, Texas) and RevMan v5.02 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014).

Results

Overall, 16 randomized trials[8–23] fulfilled all selection criteria for this meta-analysis (Supplementary Figure 1 available online only). The trials were either placebo controlled[8,11,12,15,19,22] or active comparator controlled.[9,10,13,14,16–18,21,23] The Pilot Hypertension in the Very Elderly Trial (HYVET) had both placebo and active controlled arms.[20] We excluded the combination arms (ACEIs plus ARBs) of the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET)[17] and the Valsartan in Acute Myocardial Infarction Trial.[23] Six ACEIs (captopril, enalapril, lisinopril, perindopril, ramipril, and trandolapril) were included in this meta-analysis. In total, 104,321 patients were randomized to either ACEIs or controls (placebo or active comparator). The average follow-up was 2.9 years (range 0.9 to 4.7 years), with a total follow-up across all trials of 302,531 patient-years. We included 1-year follow-up results from the Perindopril in Elderly People With Chronic Heart Failure trial[19] as a substantial number of patients ceased blinded treatment after 1 year. The characteristics of the included trials are listed in Table 1. The overall mean age of patients in ACEI and control arms was 69.7 years. The baseline characteristics of patients with mean blood pressure at baseline and at the end of the studies are listed in Table 1. Five trials (including Japan Multicenter Investigation for Cardiovascular Diseases-B [JMIC-B] trial with coronary artery disease and hypertension)[9,10,16,20,21] involved patients with hypertension, 3 trials involved patients with diabetes mellitus and high cardiovascular risk,[12,15,17] and the remaining trials involved patients with coronary artery disease, heart failure, or both. Most of the included studies were of low-bias risk, except for 4 studies[10,16,20,21] that were high-bias risk mainly for being open-label studies (Table 2).

ACEIs significantly reduced all-cause mortality compared with placebo (relative risk [RR] 0.86, 95% confidence interval [CI] 0.77 to 0.96). However, compared with active control, ACEIs had similar effect on all-cause mortality (RR 0.99, 95% CI 0.95 to 1.03, p = 0.02 for interaction; Figure 1). Similarly, the cardiovascular mortality benefit was demonstrated when ACEIs were compared with placebo (0.81, 95% CI 0.72 to 0.90) but not when compared with active controls (0.99, 95% CI 0.93 to 1.04, p = 0.01 for interaction; Figure 1). There was moderate heterogeneity and no evidence for publication bias.

Compared with placebo, ACEIs significantly reduced MI (RR 0.82, 95% CI 0.75 to 0.91) and heart failure (RR 0.76, 95% CI 0.70 to 0.83). However, no reduction in stroke was found (RR 0.88, 95% CI 0.65 to 1.19; Figure 2). Compared with active control, ACEIs were not associated with reduction in MI (RR 0.94, 95% CI 0.88 to 1.00), heart failure (RR 0.97, 95% CI 0.91 to 1.03), and stroke (RR 1.07, 95% CI 0.99 to 1.15; Figure 2 and Supplementary Figure 2 available online only). There was low to moderate heterogeneity and no evidence for publication bias for the outcomes.

Compared with placebo, ACEIs were associated with significant increased risk of angioedema (RR 2.29, 95% CI 1.02 to 5.15), hypotension (RR 1.40, 95% CI 1.22 to 1.62), and renal insufficiency (RR 1.29, 95% CI 1.02 to 1.63; Supplementary Figures 3–5 available online only). Compared with active controls, ACEIs were associated with significant increased risk of angioedema (RR 2.79, 95% CI 1.05 to 7.42, p = 0.04), whereas no increased risk of hypotension (RR 0.80, 95% CI 0.57 to 1.12, p = 0.19) and renal insufficiency (RR 0.87, 95% CI 0.70 to 1.07, p = 0.18) was observed (Table 3). The heterogeneity was low, and there was no evidence of publication bias for any outcomes.

For the comparison between ACEIs and active controls, exclusion of studies comparing ACEIs with ARBs[13,14,17,18,23] or heart failure trials yielded largely similar results with

Table 1
Characteristics of included trials

Trials	Patients		Age (years)		Male		HTN		HF		DM		Baseline BP, mm Hg		BP end follow-up, mm Hg		Follow-up
	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control	
AIRE[8], 1993	1,004	982	65	65	73%	74%	29%	27%	8%	8%	12%	12%	NR	NR	NR	NR	15 months
ALLHAT[9], 2002	9,054	24,303	67	67	54%	53%	90%	90%	0	0	36%	36%	146/84	146/84	136/75	134/75	4.9 years
ANBP2[10], 2003	3,044	3,039	72	72	50%	48%	100%	100%	NR	NR	8%	7%	167/91	168/91	141/79	142/79	4.1 years
CONSENSUS[11], 1987	127	126	71	70	70%	71%	24%	19%	100%	100%	24%	21%	118/74	121/76	NR	NR	1 year
DIABHYCAR[12], 2004	2,443	2,469	65	65	70%	70%	56%	55%	0	0	100%	100%	146/82	145/82	142/80	143/80	4 years
ELITE[13], 1997	370	352	73	74	67%	65%	57%	57%	100%	100%	24%	27%	137/79	137/79	NR	NR	48 weeks
ELITE II[14], 2003	1,574	1,578	72	71	69%	70%	50%	48%	100%	100%	24%	24%	134/78	134/78	NR	NR	555 days
HOPE[15], 2000	4,645	4,652	66	66	73%	74%	48%	46%	0	0	39%	38%	139/79	139/79	136/76	139/77	5 years
JMIC-B[16], 2004	822	828	64	65	70%	68%	100%	100%	NR	NR	21%	24%	145/82	147/82	138/79	136/77	3 years
ONTARGET[17], 2008	8,576	8,542	66	66	73%	74%	69%	69%	0	0	37%	38%	142/82	142/82	NR	NR	56 months
OPTIMAAL[18], 2002	2,733	2,744	67	68	71%	72%	36%	36%	6.5%	5.9%	17%	18%	123/71	123/72	NR	NR	2.7 years
PEP-CHF[19], 2006	424	426	75	75	46%	43%	79%	79%	100%	100%	21%	20%	138/80	140/80	135	138	2.1 years
Pilot HYVET[20], 2003	431	852	84	84	36%	37%	100%	100%	NR	NR	NR	NR	182/100	182/100	151/84	163/90	13 months
STOP 2[21], 1999	2,205	4,409	76	76	34%	33%	100%	100%	2%	2%	11%	11%	194/98	194/98	159/81	159/80	4 years
TRACE[22], 1995	876	873	68	67	72%	71%	23%	23%	21%	23%	13%	14%	122/76	120/75	NR	NR	24-50 months
VALIANT[23], 2006	4,909	4,909	65	65	69%	69%	55%	56%	15%	16%	23%	23%	123/72	123/72	NR	NR	25 months

AIRE = Acute Infarction Ramipril Efficacy trial; ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ANBP2 = Second Australian National Blood Pressure trial; BP = blood pressure; CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study trial; DIABHYCAR = Non-Insulin-Dependent Diabetes, Hypertension, Microalbuminuria, Cardiovascular Events and Ramipril trial; DM = diabetes mellitus; ELITE = Evaluation of Losartan in the Elderly trial; HF = heart failure; HOPE = Heart Outcomes Prevention Evaluation trial; HTN = hypertension; HYVET = Hypertension in the Very Elderly Trial; JMIC-B = Japan Multicenter Investigation for Cardiovascular Diseases-B; ONTARGET = Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; OPTIMAAL = Optimal Trial in Myocardial Infarction With the Angiotensin II Antagonist Losartan; PEP-CHF = Perindopril in Elderly People With Chronic Heart Failure trial; STOP 2 = Swedish Trial in Old Patients With Hypertension-2; TRACE = Trandolapril Cardiac Evaluation trial; VALIANT = Valsartan in Acute Myocardial Infarction Trial.

Table 2
Baseline characteristics of study population in included trials

Trial	Patient characteristics	ACEIs	Controls	Primary outcome	Blinded outcome assessment	Generation of treatment assignment	Follow up %	Study Quality
AIRE[8]	CAD, HF	Ramipril	Placebo	All-cause mortality	Double blinded	Central randomization system	NR	Low-bias risk
ALLHAT[9]	HTN	Lisinopril	Chlorthalidone/Amlodipine	Fatal coronary heart disease or non-fatal MI	Double blinded	Central randomization system	97	Low-bias risk
ANBP2[10]	HTN, ≥65 years	ACEIs	Diuretic	All-cause mortality or cardiovascular events	Open label with blinded end points	Central randomization system	97	High-bias risk
CONSENSUS[11]	HF	Enalapril	Placebo	All-cause mortality	Double blinded	Computer generated	NR	Low-bias risk
DIABHYCAR[12]	DM II, proteinuria	Ramipril	Placebo	Cardiovascular death, non-fatal MI, stroke, HF, end-stage renal failure	Double blinded	Centralized randomization system	83	Low-bias risk
ELITE[13]	HF	Captopril	Losartan	Measure of renal dysfunction	Double blinded	NR	NR	Low-bias risk
ELITE II[14]	HF, ≥60 years	Captopril	Losartan	All-cause mortality	Double blinded	NR	89	Low-bias risk
HOPE[15]	DM, high risk patients	Ramipril	Placebo	MI, stroke, cardiovascular mortality	Double blinded	NR	NR	Low-bias risk
JMIC-B[16]	CAD, HTN	ACEIs	Nifedipine	Cardiac/sudden death, MI, angina, HF, arrhythmia, coronary interventions	Open label with blinded end points	Computer generated	79	High-bias risk
ONTARGET[17]	DM, high risk patients	Ramipril	Telmisartan	Cardiovascular death, MI, stroke, hospitalization for HF	Double blinded	Central randomization system	100	Low-bias risk
OPTIMAAL[18]	CAD, HF	Captopril	Losartan	All-cause mortality	Double blinded	Central randomization system	100	Low-bias risk
PEP-CHF[19]	HF, ≥70 years	Perindopril	Placebo	All-cause mortality, unplanned HF related hospitalization	Double blinded	Computer generated	100	Low-bias risk
Pilot HYVET[20]	HTN, ≥80 years	Lisinopril	Diuretic/placebo	Stroke events, total mortality, cardiovascular mortality	Open label	Computer generated	98	High-bias risk
STOP 2[21]	HTN, ≥70 years	Lisinopril/enalapril	Beta-blockers/diuretics/CCBs	Cardiovascular mortality	Open label with blinded end points	NR	100	High-bias risk
TRACE[22]	CAD, HF	Trandolapril	Placebo	All-cause mortality	Double blinded	Computer generated	63	Low-bias risk
VALIANT[23]	CAD, HF	Captopril	Valsartan	All-cause mortality	Double blinded	Interactive voice-response system	99	Low-bias risk

ACEI = angiotensin-converting enzyme inhibitor; CAD = coronary artery disease; CCB = calcium channel blocker; DM = diabetes mellitus; HF = heart failure; HTN = hypertension; MI = myocardial infarction; NR = not reported.

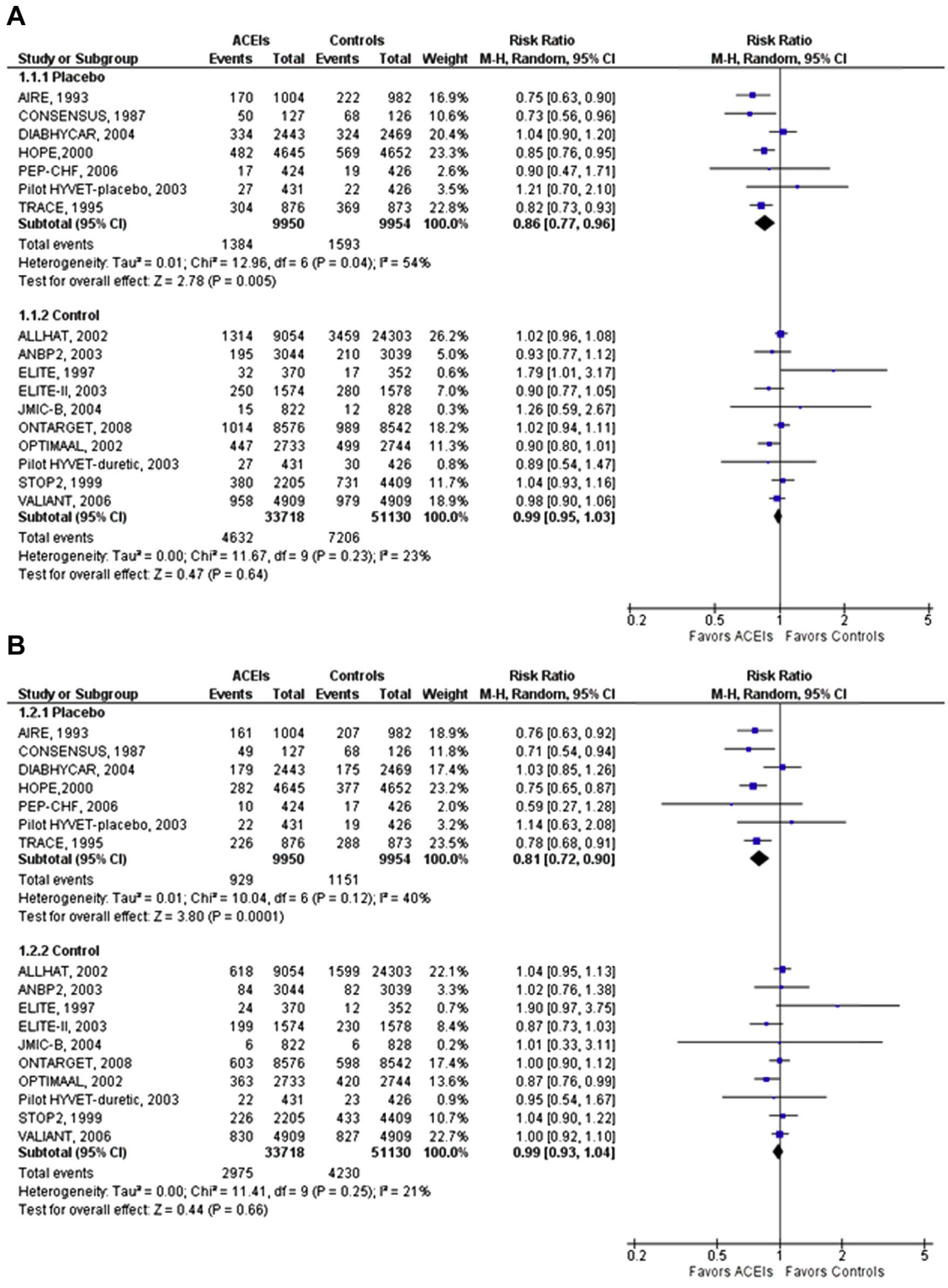

Figure 1. Forest plot of comparison of ACEIs and controls for *(A)* all-cause mortality and *(B)* cardiovascular mortality in patients with age ≥65 years. *Squares* represent the risk ratio of the individual studies; *horizontal lines* represent the 95% CIs of the risk ratio. The size of the square reflects the weight that the corresponding study exerts in the meta-analysis. The *diamond* represents the pooled risk ratio or the overall effect.

ACEIs having no significant effect on outcomes, except for a reduction in MI (Supplementary Tables 1 and 2 available online only). Subgroup analyses of trials with mean age >70 years and ≤70 years (i.e., 65 to 70 years) were in line with the primary results with ACEIs comparable to other agents for all outcomes including stroke and protective for MI in the >70 years subgroup (Supplementary Table 3 available online only). To further evaluate the effect of age on ACEIs

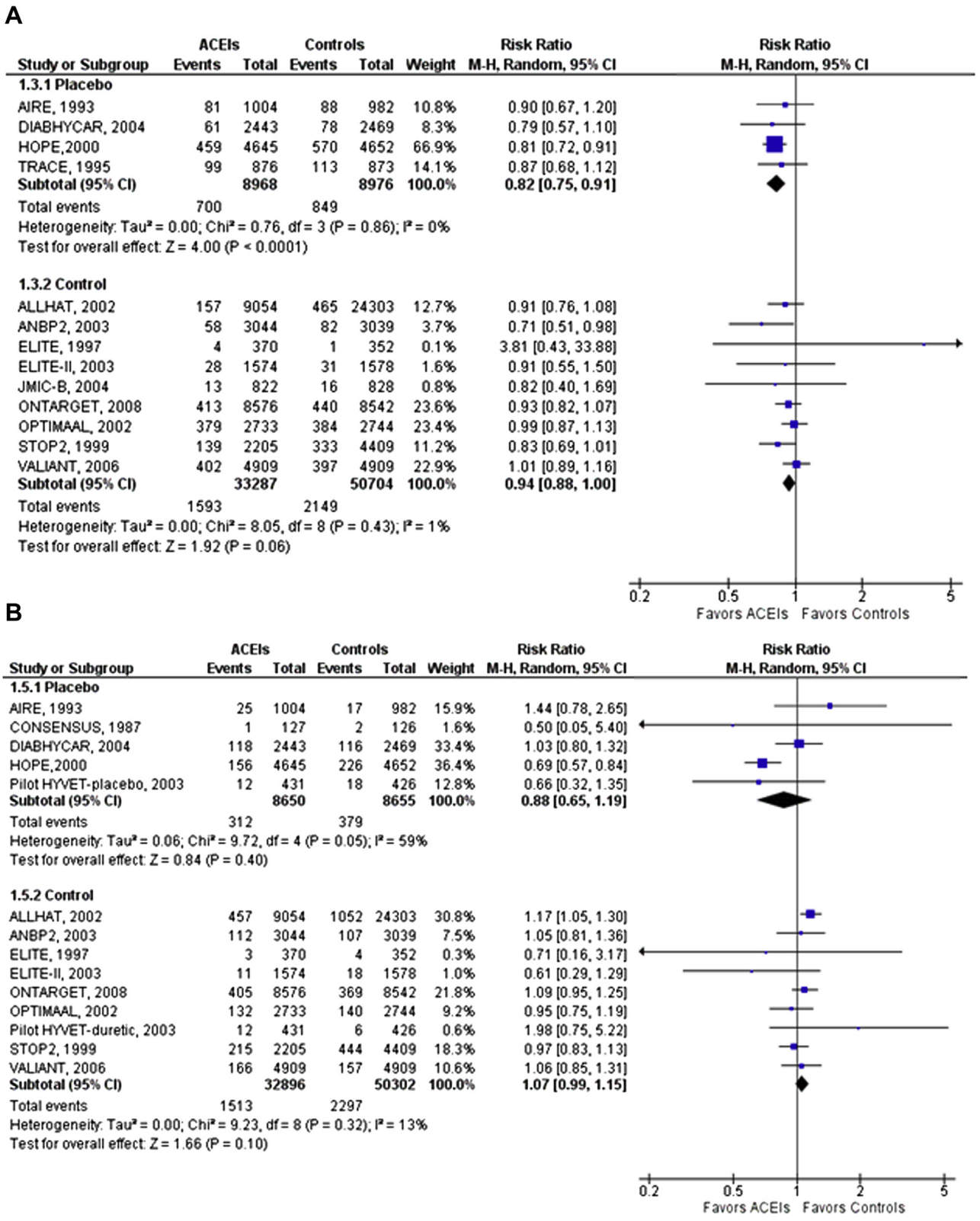

Figure 2. Forest plot of comparison of ACEIs and controls for *(A)* myocardial infarction and *(B)* stroke in patients with age ≥65 years. *Squares* represent the risk ratio of the individual studies; *horizontal lines* represent the 95% CIs of the risk ratio. The size of the square reflects the weight that the corresponding study exerts in the meta-analysis. The *diamond* represents the pooled risk ratio or the overall effect.

Table 3
Efficacy and safety outcomes of ACEIs compared to placebo and active controlled trials

Outcomes	ACEIs vs Placebo			ACEIs vs Active controls		
	Studies*	Patients	RR (95% CI)	Studies*	Patients	RR (95% CI)
Efficacy						
All-cause mortality	7	19,904	0.86 (0.77 -0.96)	10	84,848	0.99 (0.95 -1.03)
Cardiovascular mortality	7	19,904	0.81 (0.72 -0.90)	10	84,848	0.99 (0.93 -1.04)
Myocardial Infarction	4	17,944	0.82 (0.75 -0.91)	9	83,991	0.94 (0.88 -1.00)
Heart Failure	6	19,047	0.76 (0.70 -0.83)	9	83,991	0.97 (0.91 -1.03)
Stroke	5	17,305	0.88 (0.65-1.19)	9	84,126	1.07 (0.99-1.15)
Safety						
Angioedema	3	15,059	2.29 (1.02 -5.15)	5	66,492	2.79 (1.05 -7.42)
Hypotension	5	14,135	1.40 (1.22 -1.62)	5	34,785	0.80 (0.57 -1.12)
Renal insufficiency	4	4,838	1.29 (1.02 -1.63)	5	62,665	0.87 (0.70 -1.07)

ACEI = angiotensin-converting enzyme inhibitors; CI = confidence interval; RR = relative risk.
* Pilot-HYVET has 2 comparison arms (placebo and diuretic) which were considered separately for the analysis.

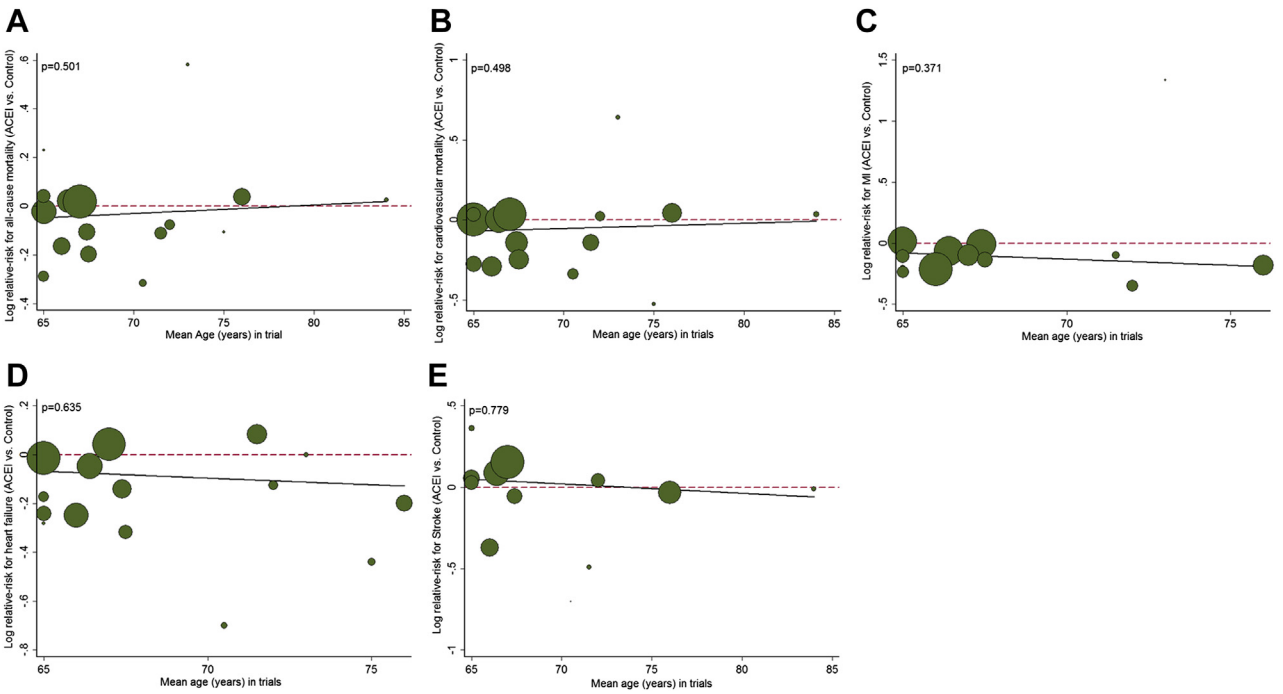

Figure 3. Univariate metaregression analysis exploring the effect of age ≥65 years on the effect size of ACEIs and outcomes (*A*, all-cause mortality; *B*, cardiovascular mortality; *C*, myocardial infarction; *D*, heart failure; and *E*, stroke). The size of the data marker *(green circles)* represents the weight of each trial. The regression fit *(solid line)* is shown.

and outcomes, we performed meta-regression analysis of ACEIs versus controls (placebo or active comparator) by age. Meta-regression analysis revealed that with age increasing ≥65 years, the effect of ACEIs remained consistent (Figure 3).

Discussion

In our meta-analysis of randomized trials predominantly involving patients ≥65 years of age, ACEIs significantly reduced all outcomes except stroke compared with placebo. However, compared with active controls, ACEIs had comparable results for all outcomes. When trials comparing ACEIs versus ARBs were excluded, ACEIs showed reduction in MI but still failed to reduce stroke. For safety outcomes, ACEIs were associated with increased risk for angioedema, hypotension, and renal insufficiency, although the risk for hypotension and renal insufficiency was similar compared with active controls.

Previous meta-analyses have consistently demonstrated the beneficial effects of ACEIs in different patient populations such as coronary artery disease, chronic heart failure,[24] hypertension,[25] and diabetes.[26] Accordingly, several sets of guidelines have endorsed ACEIs as a first-line therapy in treatment of these conditions. Not surprisingly, ACEIs have become one of the best selling drug classes in the United States.[27] Their superiority to placebo is obvious although most of the placebo-controlled trials were

conducted before the year 2000, limiting its applicability to the current medical practice. Controversy still exists in selection of first-line therapy for hypertension in patients ≥65 years of age. The American College of Cardiology and the American Heart Association consensus statement, Joint National Committee-8, and European Society of Cardiology guidelines recommend ACEIs, ARBs, calcium channel blockers, or thiazide-like diuretics as the first-line treatment for hypertension.[28−30] Conversely, the National Institute for Health and Care Excellence (NICE) guidelines[31] recommend calcium channel blockers as the first-line therapy for hypertension in patients >55 years of age. We found no significant difference in risk of all-cause or cardiovascular mortality, heart failure, and stroke for ACEIs compared with active controls indicating ACEIs to be equally effective as calcium channel blockers and thiazide diuretics in patients ≥65 years of age. In our analysis, compared with other agents, ACEIs showed a trend in reduction of MI ($p = 0.06$), which became significant when trials comparing ACEIs versus ARBs were excluded. In separate large meta-analyses, ARBs[32,33] and calcium channel blockers[34] have not been shown to reduce the risk for MI compared with active controls.

Interestingly, we did not find any reduction in stroke-risk with ACEIs compared with either placebo or active control. ACEIs are efficacious blood pressure−lowering agents in older patients and the reduction in stroke is generally related to reduction in blood pressure. However, treatment of hypertension in such patients is often complicated by increased susceptibility to cerebral hypoperfusion with orthostatic hypotension[35,36] and blood pressure variability.[37,38] Moreover, the cardioprotective benefits of ACEIs might have been mitigated by a reduction in circulating angiotensin II levels and thereby decreased angiotensin receptor−dependent cerebroprotection.[39] These factors could have counteracted the positive effects of blood pressure reduction, resulting in an overall neutral effect of ACEIs for stroke reduction. Of note, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), lisinopril was associated with an increased risk of stroke compared to chlorthalidone. This was initially attributed to the reduced efficacy of ACEIs in controlling blood pressure, specifically in blacks as compared with nonblacks. However, when the analysis was controlled for blood pressure, similar results were obtained.[40] In contrast to ACEIs, ARBs have shown significant reduction in stroke risk, both in at-risk and age ≥65 years populations.[32,33] These observations suggest a mechanism other than renin-angiotensin-aldosterone system inhibition for the lack of benefit of ACEIs for stroke prevention. Importantly, the difference in outcome, if any, between ACEI and ARB trials seems to be mostly related to the fact that ARB trials were done a decade later. Consequently, patients were exposed to more aggressive concomitant therapy, giving rise to significantly lower placebo event rates.[41]

Our analysis documented a 2.8-fold increase in risk of angioedema by ACEIs compared with active controls; however, the actual incidence was very low (<0.5% from all trials). Angioedema is a known side effect of ACEIs mediated by bradykinin-induced increased vascular permeability and interstitial fluid accumulation.[42] Importantly, no increased risk in hypotension and renal insufficiency was observed compared with active controls. The lack of increased risk for renal insufficiency should be interpreted with caution as most of the trials excluded patients with moderate-to-severe renal dysfunction. Moreover, hypotension, early decrease in renal function and renal insufficiency, and hyperkalemia are dose-related adverse effects of ACEIs that need further scrutiny. Particularly in older population, concurrent use of other medications such as nonsteroidal anti-inflammatory drugs and diuretics could possibly increase the risk for renal injury.[43]

Our study has several limitations. First, we required a mean age of ≥65 years in a study to be included in the meta-analysis. Although not ideal, given the paucity of studies in this specific population and in the absence of patient-level data, this is probably acceptable. Our findings are hypothesis generating and should be confirmed in future clinical trials. Second, we observed low to moderate heterogeneity in some of the analysis. This could be due to several methodological differences in the included RCTs such as the type of ACEIs used, variation in dosages and duration of treatment, and difference in the type of controls and patient population. The inclusion of trials with different cardiovascular diseases such as hypertension, coronary artery disease, heart failure, and diabetes and high cardiovascular risk may introduce heterogeneity. However, these cardiovascular conditions are not mutually exclusive; several trials included patients with combination of these diseases, and ACEIs have shown survival benefit, albeit of different magnitude, in all these indications. Third, in the absence of patient-level data, we were unable to evaluate the dose−response relation and effect of ACEIs by ethnicity (blacks vs nonblacks). Finally, this meta-analysis assumed a class effect among the different ACEIs, but pharmacological differences exist among various ACEIs. However, there is little evidence that these differences influence clinical outcomes.[44]

Disclosures

Dr. Bangalore is a consultant or has advisory relationships with the following companies: Daiichi-Sankyo, Pfizer, Abbott, and Boehringer Ingelheim. Dr. Messerli is a consultant or has advisory relationships with the following companies: Daiichi-Sankyo, Pfizer, Abbott, Servier, Medtronic, WebMD, Ipca, and Menarini. The other authors have no conflicts of interest to disclose.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.amjcard.2016.07.074.

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