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ARTICLE

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The effects of renin–angiotensin system inhibitors on mortality, cardiovascular events, and renal events in hypertensive patients with diabetes: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Renin–angiotensin system (RAS) inhibitors are often used as a first-line treatment for hypertensive patients with diabetes because of purported benefits, such as reno-protection. However, there is no clear evidence for the superiority of RAS inhibitors to other classes of antihypertensives for clinically important outcomes in this population. We conducted a meta-analysis to assess whether RAS inhibitors are better than other classes of antihypertensives for reducing mortality, and cardiovascular and renal events in hypertensive patients with diabetes. From June to December 2017, we searched Medline, Cochrane Library, and the database of the Japan Medical Abstracts Society (ICHUSHI) for relevant published randomized controlled trials that directly compared the effects of RAS inhibitors to other classes of antihypertensives as first-line treatments for reducing adverse outcomes among hypertensive patients with diabetes. Our predetermined outcomes included all-cause death, cardiovascular death, incidence of cardiovascular disease, and renal dysfunction. We identified 16 trials, including a total of 35,052 patients. No significant benefits for RAS inhibitors were found compared to other classes of antihypertensives for all-cause death (relative risk (RR) 0.95, 95% confidence interval (CI) 0.85–1.05, $p = 0.29$), cardiovascular death (RR 0.84, 95% CI 0.68–1.04, $p = 0.11$), incidence of cardiovascular disease (RR 0.93, 95% CI 0.84–1.03, $p = 0.16$), and incidence of renal dysfunction (RR 0.91, 95% CI 0.77–1.06, $p = 0.22$). In conclusion, RAS inhibitors are not superior to other classes of antihypertensive drugs for reducing all-cause and cardiovascular mortalities, cardiovascular events, and renal events in hypertensive patients with diabetes.

Keywords Diabetes mellitus · Hypertension · Meta-analysis · Renin angiotensin system blockers · Systematic review

Introduction

Hypertension is common among patients with both type 1 and 2 diabetes [1, 2]. Controlling blood pressure has been demonstrated to be effective for lowering the risk of microvascular (renal, ocular, or neural) and macrovascular (atherosclerotic cardiovascular disease) complications in patients with diabetes [3–5]. Clinical guidelines in Europe and in the US [6–8] indicate that the degree of blood pressure reduction is considered the major determinant of reduction in cardiovascular risk rather than the choice of antihypertensive drug class. Consequently, those guidelines recommend any of the drug classes shown to reduce cardiovascular events for patients with diabetes, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), thiazide-like diuretics, or dihydropyridine calcium-channel blockers (CCBs),

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as a first-line treatment for hypertensive patients with diabetes.

Renin–angiotensin system (RAS) inhibitors, which are mainly ACE inhibitors and ARBs, have the best efficacy for decreasing urinary albumin excretion [9] among antihypertensives. Since albuminuria is a known risk factor for cardiovascular events, RAS inhibitors have a potential benefit over other antihypertensive classes as the first-line treatment of hypertensives with diabetes for reducing cardiovascular risk. In fact, the Guidelines for the Management of Hypertension 2014 by the Japanese Society of Hypertension [10] and the Japanese Clinical Practice Guideline for Diabetes 2016 by the Japanese Diabetes Society [11] recommend RAS inhibitors as a first-line treatment for hypertension in patients with diabetes primarily because of their renoprotective properties (i.e., reduction in intraglomerular pressure and albuminuria) in addition to their metabolically favorable effects (i.e., improved insulin resistance not affecting the lipid level) [12–16]. However, there is no clear evidence favoring RAS inhibitors over other classes of drugs for reducing clinically important adverse outcomes, such as cardiovascular events or all-cause death for hypertensive patients with diabetes.

Therefore, in this meta-analysis, we sought to assess whether RAS inhibitors are superior to other classes of antihypertensive drugs as first-line pharmacological blood pressure (BP) treatments for hypertensive patients with diabetes in terms of reducing the risk of all-cause mortality and cardiovascular or renal events.

Methods

We conducted a systematic review and meta-analysis of the literature following the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement for the conduct of meta-analyses of intervention studies [17]. We performed all the procedures from June 2017 to December 2017.

Data sources and search strategy

We searched Medline, the Cochrane Library database, and the database of Japan Medical Abstracts Society (Igaku Chuo Zasshi; ICHUSHI) for relevant published randomized controlled trials (RCTs). The search was limited to studies published in English or Japanese, but otherwise no restrictions, such as publication year, age, ethnicity/race, and countries/areas of study participants, were included. For the literature search, we used the key words including "diabetes mellitus", "angiotensin-converting enzyme inhibitor", "ACEI", "angiotensin receptor antagonists", "angiotensin receptor blocker", "receptor blocker", "ARB", "mineralocorticoid receptor antagonists", "renin inhibitor", "alpha blocker", "beta blocker", "calcium channel blocker", "CCB", "channel blocker", "diuretic", "thiazide", and specific names of each typical antihypertensive drug (Supplementary Table 1).

Study selection

In the primary screening, reviewers (AK, AF, HS, NH, and HO) screened the titles and abstracts of all identified studies independently and in duplicate. In the secondary screening, the same reviewers independently screened the full texts of possibly eligible studies and evaluated their eligibility. Disagreements in evaluations were resolved through adjudication among the reviewers.

We included only RCTs that directly compared the effects of RAS inhibitors (ACE inhibitors, ARBs, mineralocorticoid receptor antagonists, and renin inhibitors) and other classes of antihypertensive drugs as a first-line pharmacological treatment for lowering BP in hypertensive patients with diabetes. The exclusion criteria were the following: RAS inhibitor(s) were added to an existing pharmacological treatment; a combined regimen of RAS inhibitors was compared against other regimens of antihypertensives; no pharmacological treatment was given (i.e., placebo only) to a comparison group; and either nonhypertensive patients or nondiabetic patients were included (or did not have the measurements attributed only to hypertensive diabetics) in the study.

Our predetermined outcomes of interest were all-cause death, cardiovascular death, incidence of cardiovascular disease, and incidence of renal dysfunction. Cardiovascular disease was defined as a composite of myocardial infarction, cerebrovascular events, congestive heart failure, angina pectoris, coronary revascularization, arrhythmia (ventricular tachycardia, ventricular fibrillation, and atrial fibrillation), dissecting aortic aneurysm, peripheral artery disease, and sudden cardiac death. Renal dysfunction was defined as a composite of a doubling of serum creatinine concentration and development of end-stage renal disease requiring regular dialysis or renal transplantation. Additionally, we planned to conduct stratified analyses by renal impairment at baseline, repeating the comparison between RAS inhibitors versus other classes of antihypertensives according to the presence or absence of either a reduced estimated glomerular filtration rate or proteinuria/albuminuria at baseline.

Data extraction and risk of bias assessment

The data including general study information (authors, titles, publication year, sample size, and study design), study population details (age, gender, mean systolic and

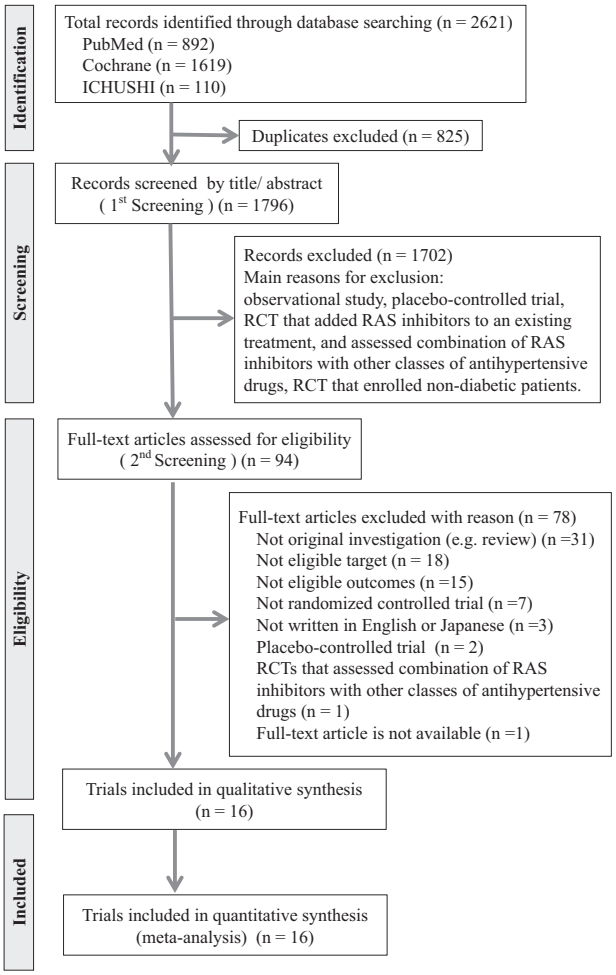

Fig. 1 Identification process for eligible trials. RAS, renin–angiotensin system; RCT, randomized controlled trial

diastolic BP levels at baseline and at the end of the trial as well as the follow-up duration), details on the intervention and comparison (the class of antihypertensive drug), and the outcome events were extracted.

Reviewers independently assessed the risk of the bias in each individual RCT by evaluating selection bias (randomization, concealment), performance bias (blinding), detection bias (blinding), and attrition bias (use of intention-to-treat analysis, incomplete outcome data) [18, 19].

Data synthesis and statistical analysis

In this analysis, tabular data were used because the individual patient data of each study were not available. Relative risk (RR) ratios and 95% confidence intervals (CIs) for each outcome of the individual studies were calculated before integration. We used a random effects model to obtain the summary estimates of RR ratios given that our included trials are likely heterogeneous because we set no restrictions for inclusion, except the language requirement. Statistical heterogeneity was determined with an I^2 statistic. We used an inverse-variance method for the meta-analysis of each outcome. We examined publication bias using funnel plots of the natural log of the RR vs its standard error for each outcome. In addition to producing a quantitative summary estimate (i.e., RR and 95% CI) for an outcome, we also assessed the quality of evidence for each summary estimate by considering the risk of bias, inconsistency, imprecision, indirectness, and publication bias. Then, we rated the quality of the evidence as "high", "moderate", "low", or "very low" [19]. Any disagreement in the rating among reviewers was adjudicated. A two-sided p value less than 0.05 was considered statistically significant. The data were analyzed with RevMan 5.3 (London, UK).

Results

Search results and characteristics of included trials

Through the literature search, we identified 1797 articles and reviewed 95 of them in full text. For qualitative synthesis, we included 16 RCTs (Fig. 1) [20–35].

Among the 16 RCTs, 8 trials were open-label RCTs [21, 26, 29–32, 34, 35] and the rest of the 8 trials were double-blinded RCTs [20, 22–25, 27, 28, 33]. Twelve trials compared RAS inhibitors with CCBs [21–26, 29, 31–35], four trials compared RAS inhibitors with beta-blockers [20, 26, 27, 30], and five trials compared RAS inhibitors with diuretics [26, 28, 30, 31, 33]. The mean duration of follow-up for each trial ranged from 1 to 9 years, but it was less than 5 years for most trials (Table 1). The risk of bias of the included trials varied substantially (Supplementary Table 2).

The mean baseline BP levels in the trials ranged between 137/76 and 196/97 (systolic/diastolic BP in mmHg). In most trials, no significant differences in achieved BP were found between RAS inhibitors and other classes of antihypertensive drugs during follow-up. However, in two trials, systolic BP during follow-up was significantly lower in individuals who were assigned diuretics [33] or CCB [32] compared to individuals who were assigned RAS inhibitors (Table 1).

Outcomes

All-cause death

Data on all-cause death (Figs. 2 and 3) were available from 12 trials that included 26,196 patients and 4106 events [20, 24–30, 32–35]. No significantly beneficial effect of RAS

Table 1 Characteristics of the included trials

Author and trial (publication year)	Design	Inclusion criteria	Pati ents (*n*)	Drugs		Duration of follow-up (years)	Mean age, intervention vs control (years)	Male, intervention vs control (%)	Mean blood pressure, baseline		Mean blood pressure, at the end of the trial		Endpoints
				Intervention	Control				Intervention	Control	Intervention	Control	
Tatti P et al., FACET (1998)[32]	Randomized, open-labeled	Patients with NIDDM and hypertension (sBP > 140 mmHg or dBP > 90 mmHg), no history of cardiovascular disease or stroke, sCr < 1.5 mg/dl or albuminuria < 40 μg/min	380	Fosinopril (189)	Amlodipine (191)	2.5	62.8 vs 63.3	63.5 vs 55.5	170/95	171/94	157/88	153/86	All-cause death, stroke, myocardial infarction, angina pectoris
Estacio RO et al., ABCD (1998)[24]	Randomized, double-blinded (subgroup analysis)	Patients with NIDDM, dBP > 100 mmHg	470	Enalapril (235)	Nisoldipine (235)	5.6	57.7 vs 57.2	66.8 vs 68.1	156/98	155/98	NA, no significant differences were seen between groups	NA, no significant differences were seen between groups	All-cause death, cardiovascular events (cardiovascular death, myocardial infarction, cerebrovascular events, heart failure)
UK Prospective Diabetes Study Group, UKPDS (1998)[20]	Randomized, double-blinded	Diabetic patients with hypertension	758	Captopril (400)	Atenolol (358)	9.0	56.3 vs 56.0	51 vs 57	159/94	159/93	144/83	143/81	All-cause death, myocardial infarction, stroke, amputation or death from peripheral vascular disease, heart failure, angina pectoris, renal failure, sudden death
Lindholm LH et al., STOP Hypertension-2 (2000)[26]	Randomized, open trial with blinded endpoint evaluation (subgroup analysis)	Elderly diabetic patients with hypertension (70–84 years)	719	ACEI # (enalapril or lisinopril)	Conventional drugs (atenolol, metoprolol, pindolol or hydrochloroth iazide + amiloride)	2.0	75.8 vs 76.0	39.1 vs 43.1	196/96	195/97	161/80	161/81	All-cause death, cardiovascular death, myocardial infarction, stroke, cardiovascular events, atrial fibrillation, heart failure
Lindholm LH et al., STOP Hypertension-2 (2000)[26]	Randomized, open trial with blinded endpoint evaluation (subgroup analysis)	Elderly diabetic patients with hypertension (70–85 years)	719	ACEI (enalapril or lisinopril)	Calcium antagonists (felodipine or isradipine)	2.0	75.8 vs 75.7	39.1 vs 36.8	196/96	196/97	161/80	162/79	All-cause death, cardiovascular death, myocardial infarction, stroke, cardiovascular events, atrial fibrillation, heart failure
Chan JC et al. (2000)[23]	Randomied, do uble-blinded	Type 2 diabetic patients with hypertension, sBP 150–220 mmHg and/or dBP > 100 mmHg, no history of cardiovascular disease, plasma Cr < 200 μmol/l	102	Enalapril (50)	Nifdepine (52)	5.5	60.0 vs 56.2	NA	172/93	167/93	137/72	132/73	24 h UAE, the regression coefficient of the yearly plasma Cr reciprocal, yearly change in 24 h CCr

Table 1 (continued)

Author and trial (publication year)	Design	Inclusion criteria	Pati ents (*n*)	Drugs		Duration of follow-up (years)	Mean age, intervention vs control (years)	Male, intervention vs control (%)	Mean blood pressure, baseline		Mean blood pressure, at the end of the trial		Endpoints
				Intervention	Control				Intervention	Control	Intervention	Control	
Lewis EJ et al. (2001)[25]	Randomized, double-blinded	Hypertensive patients with nephropathy due to type 2 diabetes, urinary protein excretion > 900 mg/24 h, 2.0 < sCr <3.0 mg/dl in women and 1.2 < sCr < 3.0 mg/dl in men	1715 (placebo 569)	Irbesartan (579)	Amlodipine (567)	2.6	59.3 vs 59.1	65 vs 63	160/87	159/87	140/77	141/77	Doubling of the base-line sCr, endstage renal disease, all-cause death, cardiovascular death, myocardial infarction, heart failure, cerebrovascular events, lower-limb amputation
Niskanen L et al., CAPPP (2001)[30]	Randomized, open trial with blinded endpoint evaluation (subgroup analysis)	Diabetic patients with hypertension, dBP > 100 mmHg	572	Captopril (309)	Conventional (diuretics and/or p-blockers) (263)	6.1	55.0 vs 55.7	63.4 vs 60.1	164/97	163/97	156/89	154/88	All-cause death, cardiovascular death, sudden death, myocardial infarction, stroke, ischemic heart disease, heart failure, atrial fibrillation, transient ischemic attacks
Baba S et al., J-MIND (2001)[21]	Randomized, open-labeled	Type 2 diabetic patients with hypertension, sCr ≤ 2.5 mg/dl or Ccr ≥ 30 ml/min, and AER consistent with normoalbuminuria (<30 mg/day) or microalbuminuria (<300 mg/day)	436	Enalapril (208)	Nifdepine (228)	2.0	59.9 vs 60.2	52.4 vs 48.7	161/90	162/90	NA	NA	Cardiovascular events (cerebral infarction, angina pectoris, myocardial infarction, heart failure, atrial fibrillation)
Lindholm LH et al., LIFE (2002)[27]	Randomized, double-blinded (subgroup analysis)	Diabetic patients with hypertension and signs of left ventricular hypertrophy on electrocardiograms, sBP 160–200 mmHg and/or dBP 95–115 mmHg	1195	Losartan (586)	Atenolol (609)	4.7	67.4 vs 67.4	48.4 vs 45.5	176/97	177/96	146/79	148/79	All-cause death, cardiovascular death, stroke, myocardial infarction, angina pectoris, heart failure, revascularization
Berl T et al., IDNT (2003)[22]	Randomized, double-blinded	Patients with type 2 diabetic nephropathy, BP > 135/85	1146	Irbesartan (579)	Amlodipine (567)	2.6	59.3 vs 59.1	65.2 vs 63.3	160/87	159/87	140/77	141/77	Cardiovascular death, myocardial infarction, heart failure, stroke, coronary revascularization
Yui Y et al., JMIC-B (2004)[35]	Randomized, open-labeled (subgroup analysis)	Hypertensive patients with coronary artery disease, sBP > 160 mmHg or dBP >95	372	ACEI (enalapril, imidapril,	Nifedipine (199)	3.0	64 vs 63	69.4 vs 68.8	146/81	147/82	140/78	138/76	All-cause death, cardiac death or sudden death, myocardial

Table 1 (continued)

Author and trial (publication year)	Design	Inclusion criteria	Pati ents (*n*)	Drugs		Duration of follow-up (years)	Mean age, intervention vs control (years)	Male, intervention vs control (%)	Mean blood pressure, baseline		Mean blood pressure, at the end of the trial		Endpoints
				Intervention	Control				Intervention	Control	Intervention	Control	
		mmHg, sBP > 150 mmHg and dBP > 90 mmHg		lisinopril) (173)									infarction, angina pectoris, heart failure, ventricular tachycardia or ventricular fibrillation, coronary revascularization, cerebrovascular events, worsening of renal function
Marre M et al., NESTOR (2004)[28]	Randomized, double-blinded	Type 2 diabetic patients with hypertension, sBP 140–180, dBP < 110 mmHg, persistent microalbuminuria	570	Enalapril (286)	Indapamide (284)	1.0	59.2 vs 60.8	63 vs 66	160/94	161/94	139/81	137/81	ACR, AER, CCr, fractional albumin clearance
Whelton PK et al., ALLHAT (2005)[33]	Randomized, double-blinded (subgroup analysis)	Hypertension with at least one additional risk factor for coronary heart disease, no history of symptomatic heart failure, EF > 35%, sCr < 2 mg/dl	13101	Lisinopril (3510)	Chlorthalidone (5994)	4.9	NA	NA	147/83	146/84	138/75	135/74	Fatal coronary heart disease or nonfatal myocardial infarction, all-cause death, stroke, coronary revascularization, angina pectoris, heart failure, peripheral artery disease, end-stage renal disease
Whelton PK et al., ALLHAT (2005)[33]	Randomized, double-blinded (subgroup analysis)	Hypertension with at least one additional risk factor for coronary heart disease, no history of symptomatic heart failure, EF > 35%, sCr < 2 mg/dl	13101	Lisinopril (3510)	Amlodipine (3597)	4.9	NA	NA	147/83	146/83	138/75	136/74	Fatal coronary heart disease or nonfatal myocardial infarction, all-cause death, stroke, coronary revascularization, angina pectoris, heart failure, peripheral artery disease, end-stage renal disease
Rahman M et al., ALLHAT (2005)[31]	Randomized, double-blinded (subgroup analysis)	Hypertension with at least one additional risk factor for coronary heart disease, no history of symptomatic heart failure, EF > 35%, sCr < 2 mg/dl	12063	Lisinopril (3212)	Chlorthalidone (5528)	4.9	NA	NA	NA	NA	NA	NA	End-stage renal disease, a decrement in GFR of 50% or more from baseline
Rahman M et al., ALLHAT (2005)[31]	Randomized, double-blinded (subgroup analysis)	Hypertension with at least one additional risk factor for coronary heart disease, no history of symptomatic	12063	Lisinopril (3212)	Amlodipine (3323)	4.9	NA	NA	NA	NA	NA	NA	End-stage renal disease, a decrement in GFR of 50% or more from baseline

Table 1 (continued)

Author and trial (publication year)	Design	Inclusion criteria	Pati ents (*n*)	Drugs		Duration of follow-up (years)	Mean age, intervention vs control (years)	Male, intervention vs control (%)	Mean blood pressure, baseline		Mean blood pressure, at the end of the trial		Endpoints
				Intervention	Control				Intervention	Control	Intervention	Control	
		heart failure, EF > 35%, sCr < 2 mg/dl											
Nakao K et al., CASE-J (2010)[29]	Randomized, open trial with blinded endpoint evaluation (subgroup analysis)	Hypertension with at least one high-risk factor	2018	Candesartan (1011)	Amlodipine (1007)	3.3 M	63.9 vs 64.1	56.5 vs 55.6	160/88	160/88	NA	NA	All-cause death, cardiovascular death, cardiovascular events (sudden death, cerebrovascular events, heart failure, myocardial infarction, angina pectoris, sCr > 4.0 mg/dl, doubling of sCr, endstage renal disease, dissecting aortic aneurysm, arteriosclerotic occlusion of a peripheral artery)
Yamashita K et al., NHS (2013)[34]	Randomized, open trial with blinded endpoint evaluation (subgroup analysis)	Patients with type 2 diabetes or impaired glucose tolerance, hypertension, no history of cardiovascular disease within 6 months, EF > 40%, sCr < 221 mmol/l	1150	Valsartan (575)	Amlodipine (575)	3.2	NA	NA	NA	NA	NA	NA	Sudden cardiac death, myocardial infarction, stroke, coronary revascularization, heart failure

ACEI angiotensin-converting enzyme inhibitor, *AER* albumin excretion rate, *BP* blood pressure, *dBP* diastolic blood pressure, *EF* ejection fraction, *NA* not available, *NIDDM* noninsulin-dependent diabetes mellitus, *sBP* systolic blood pressure, *sCr* serum creatinine

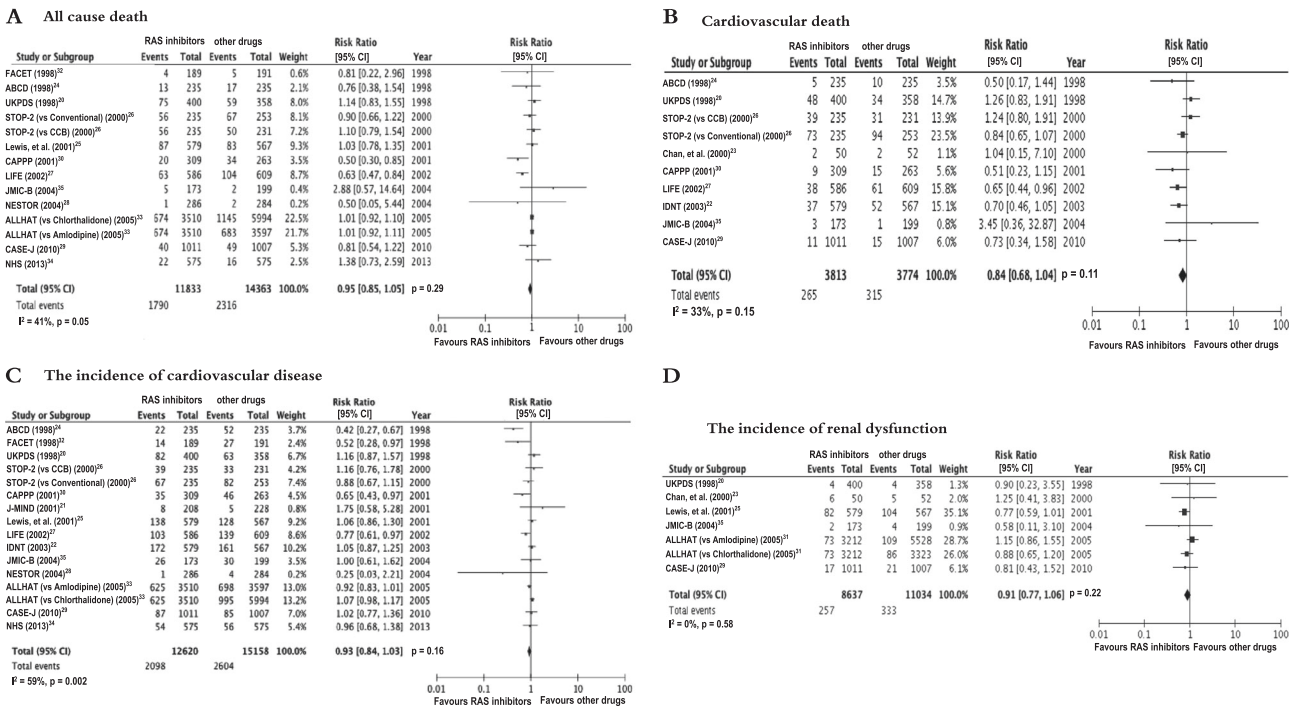

Fig. 2 Effects of renin–angiotensin system inhibitors on **a** all-cause death, **b** cardiovascular death, **c** the incidence of cardiovascular disease, and **d** the incidence of renal dysfunction. Boxes and horizontal lines represent the relative risk ratios and 95% CI for each trial. Diamonds represent the 95% CI for pooled estimates of the effect and are centered on the pooled relative risk ratio. CCB, calcium-channel blocker; CI, confidence interval; conventional, conventional drugs; RAS, renin–angiotensin system

inhibitors for all causes of death was observed (RR 0.95, 95% CI 0.85–1.05, $p = 0.29$), and there was relatively weak evidence of heterogeneity in the magnitude of the effects across the included trials ($I^2 = 41\%$, $p = 0.05$). A funnel plot revealed no publication bias among the included trials. The quality of evidence for the summary estimate was rated as "moderate" (Table 2).

Cardiovascular death

Data on cardiovascular death were available from nine trials that included 7587 patients and 580 events [20, 22–24, 26, 27, 29, 30, 35]. No significantly beneficial effect of RAS inhibitors on cardiovascular death was observed (RR 0.84, 95% CI 0.68–1.04, $p = 0.11$), and there was weak evidence of heterogeneity in the magnitude of the effect across the included trials ($I^2 = 33\%$, $p = 0.15$). A funnel plot revealed there was no publication bias among the included trials. The quality of evidence for the summary estimate was rated as "moderate" (Table 2).

Incidence of cardiovascular disease

Data on the incidence of cardiovascular disease were available from 14 trials that included 27,778 patients and 4702 events [20–22, 24–30, 32–35]. No significantly beneficial effect of RAS inhibitors on the incidence of cardiovascular disease was observed (RR 0.93, 95% CI 0.84–1.03, $p = 0.16$). However, substantial heterogeneity in the magnitude of the effect across included trials was found ($I^2 = 59\%$, $p = 0.002$). We performed a subgroup analysis to explore the sources of heterogeneity by excluding apparently heterogeneous trials in the estimates one by one (ABCD [24], FACET [32], J-MIND [21], and NESTOR [28]). However, these exclusions did not alter the overall results of our summary estimate (Table 2). A funnel plot revealed there was no publication bias among the included trials. The quality of evidence for the summary estimate was rated as "moderate" (Table 2).

Incidence of renal dysfunction

Data on the incidence of renal dysfunction were available from six trials that included 19,671 patients and 590 events [20, 23, 25, 29, 31, 35]. No significantly beneficial effect of RAS inhibitors on the incidence of renal dysfunction was observed (RR 0.91, 95% CI 0.77–1.06, $p = 0.22$), and there was no evidence of heterogeneity in the magnitude of the effect across the included trials ($I^2 = 0\%$, $p = 0.58$). A funnel plot revealed there was no publication bias among the included trials. The quality of evidence for the summary estimate was rated as "high" (Table 2).

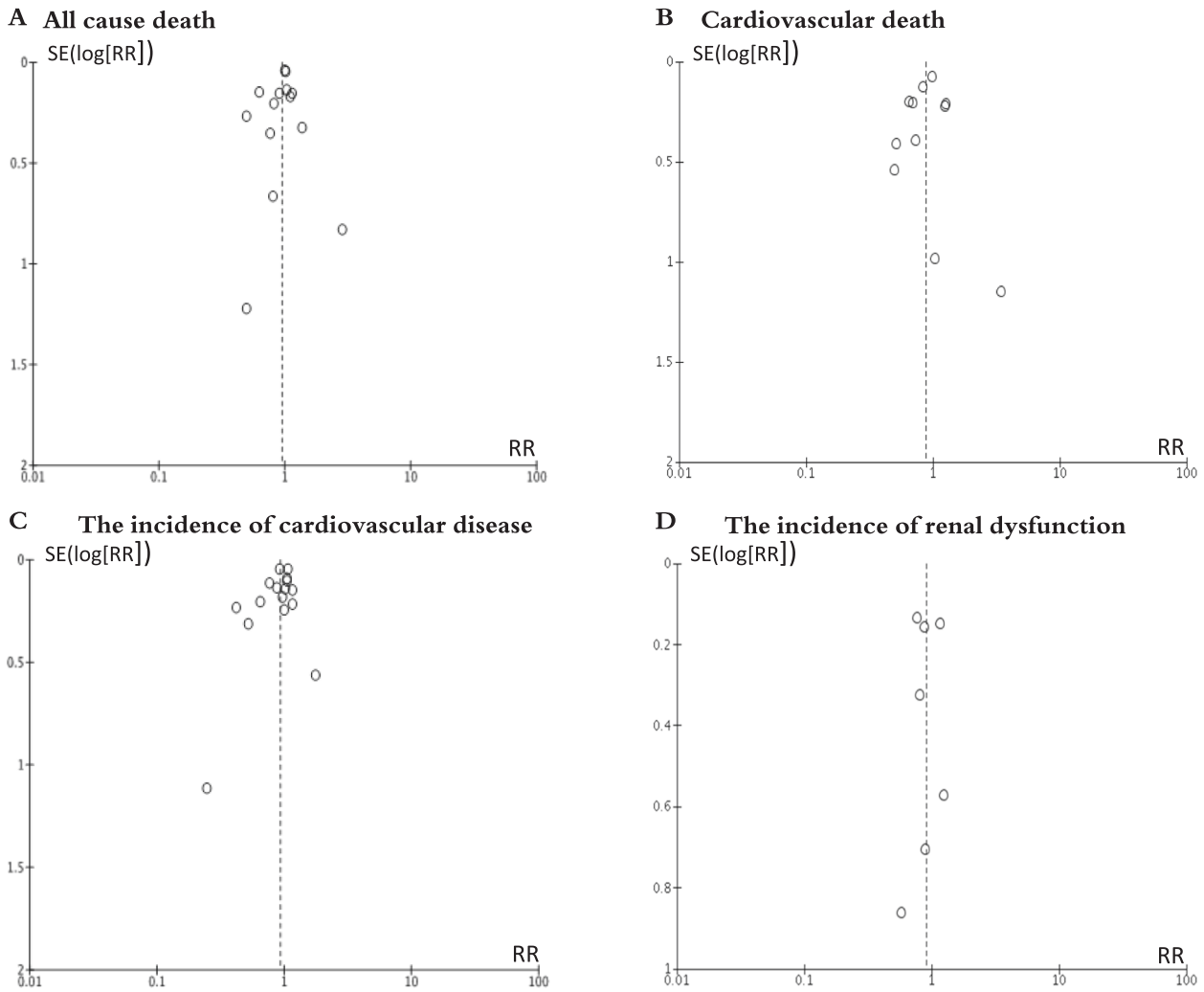

Fig. 3 Funnel plots of the natural log of the relative risk ratio vs its standard error for **a** all-cause death, **b** cardiovascular death, **c** the incidence of cardiovascular disease, and **d** the incidence of renal dysfunction. The funnel plots revealed no publication bias among the included trials. RR, relative risk; SE, standard error

Table 2 Summary of the quality of evidence assessments among the included trials

Outcomes	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Absolute effect estimates		Study results (95% CI) and measurements	Quality of evidence
						RAS inhibitors	Other drugs		
All cause death	-1	-1	-1	-1	0	1790/ 11833	2316/ 14363	RR: 0.95 (0.85-1.05) 26196 patients in 12 trials	Moderate
Cardiovascular death	-1	-1	-1	-1	0	265/ 3813	315/ 3774	RR: 0.84 (0.68-1.04) 7587 patients in 9 trials	Moderate
The incidence of cardiovascular disease	-1	-2	-1	-1	0	2098/ 12620	2604/ 15158	RR: 0.93 (0.84-1.03) 27778 patients in 14 trials	Moderate
The incidence of renal dysfunction	0	0	0	-1	0	257/ 8637	333/ 11034	RR: 0.91 (0.77-1.06) 19671 patients in 6 trials	High

High: -2; moderate/unclear: -1; low: 0. *CI* confidence interval, *RAS* renin–angiotensin system, *RR* relative risk

Outcomes in patients with or without renal dysfunction at baseline

We were unable to perform stratified analyses for the presence/absence of renal impairment, which was defined as either reduced estimated glomerular filtration rate or albuminuria/proteinuria, at baseline, because of the following reasons: (1) many trials excluded patients with serum creatinine concentrations ≥ 1.7 mg/dl at baseline and (2) many trials did not perform analyses that were stratified for renal impairment.

We performed subgroup analyses that excluded four trials that were rated as having a higher risk of bias (STOP-2 [26], J-MIND [21], JMIC-B [35], and CASE-J [29]) than other trials. The exclusions resulted in similar estimates to the main analyses (data not shown).

Discussion

In this meta-analysis of trials directly comparing RAS inhibitors and other drug class(es), we found that RAS inhibitors were no better than other classes of drugs as a first-line antihypertensive treatment for reducing all-cause death, cardiovascular death, the incidence of cardiovascular disease, and the incidence of renal dysfunction in hypertensive patients with diabetes. The summary point estimates of each outcome suggested that there was a reduced risk overall, but all the estimates were statistically non-significant. The results were consistent with recent meta-analyses [36, 37] and the recommendations from relevant major guidelines [6–8].

Apparent differences between our results and recommendation statements made by some guidelines are likely due, in part, to our strict inclusion criteria for trials (i.e., head-to-head comparison of RAS inhibitors vs other antihypertensives), and our predetermined outcomes included only clinically important adverse outcomes for hypertensive patients with diabetes [38]. For example, the 2014 guidelines by the Japanese Society of Hypertension [10] and 2016 guidelines by the Japanese Diabetes Society [11] recommended RAS inhibitors as a first-line treatment. However, these recommendations were not necessarily based on a systematic assessment of available trials that made a direct comparison between RAS inhibitors and other antihypertensive class(es) of drugs on the effects of death and cardiovascular events. Rather, the recommendation was largely based on the protective effect of RAS inhibitors over placebo from diabetic nephropathy. Another possible reason for the discrepancy is that we did not include the reduction of albuminuria/proteinuria as an outcome of our interest. It is noteworthy, however, that the 2014 Guidelines by the Japanese Society of Hypertension acknowledged the need for further studies to examine the purported superiority of ACEI over CCBs in preventing macrovascular complications in hypertensive patients with diabetes. Likewise, the 2016 Guidelines by the Japanese Diabetes Society stated that both ACEI and CCBs were shown to be effective in reducing macrovascular events. Putting all these conclusions together, our results are consistent with the detailed descriptions and understanding of the relevant literature from those guidelines. The results of our study imply that not only RAS inhibitors but also other classes of antihypertensive drugs that are proven to be effective in reducing important adverse outcomes in relevant patient groups should be recommended as a first-line antihypertensive treatment in diabetic patients as long as their blood pressure-lowering effects are equivalent. In cases in which a multidrug regimen is required to achieve a target BP, including an RAS inhibitor in that regimen may be reasonable given its protective effect against nephropathy [9, 37]. Such clinical judgments are endorsed by the recently updated guidelines by European Society of Cardiology and European Society of Hypertension 2018 [39].

For patients with diabetes and albuminuria, the guidelines and statements mentioned above recommend including an ACE inhibitor or ARB in the initial treatment with the primary reason being the risk reduction of kidney disease progression. The recommendations were based on a few trials in relevant patients [40]. Unfortunately, in our meta-analysis, we were unable to assess the question of whether this trend is also true with regard to reductions in total death and/or cardiovascular events, although we had initially planned to investigate the trend in the stratified analyses by the presence/absence of renal impairment at baseline. Nevertheless, even for this subgroup of patients (i.e., hypertensive patients with diabetic nephropathy), the supporting evidence for the superiority of RAS inhibitors in reducing total death and cardiovascular events remains relatively weak. The paucity of strong evidence is manifested in the 2017 American Hospital Association/American College of Cardiology Guidelines because they categorized their relevant recommendation as Class IIb (“weak”) [7]. Further studies are clearly needed to explore this question.

Study limitations

Several limitations of our study should be mentioned. First, most trials included in our meta-analysis compared RAS inhibitors with CCBs. Therefore, the results of this meta-analysis were mainly determined from comparisons of RAS inhibitors with CCBs rather than with β-blockers or diuretics. Second, many trials allowed multiple classes of blood pressure-lowering medication to achieve the target blood pressure when the effects of the assigned drugs (RAS inhibitors vs CCBs, β-blockers, and diuretics) were not

enough. Therefore, differences in class-specific effects on outcomes may have been obscured. Third, the relatively short follow-up period of included trials (an average of < 5 years in most studies) may have prevented us from detecting a smaller but true difference between the effects of RAS inhibitors and other classes on the outcomes that would require a longer duration to emerge. Fourth, many trials included in this meta-analysis excluded patients with elevated serum creatinine at baseline. Fifth, we did not perform stratified analyses for the presence/absence of history of cardiovascular disease at baseline because many trials did not make this distinction. Thus, we could not discuss the primary and secondary prevention against each outcome separately. Finally, we have not assessed the potential harms associated with each treatment. We have to take these limitations into consideration when we generalize the results of this meta-analysis.

Conclusion

In this meta-analysis of head-to-head comparison RCTs, RAS inhibitors were not superior to other classes of antihypertensive drugs in reducing mortality, cardiovascular events, and renal events in hypertensive patients with diabetes. However, for diabetic patients with proteinuria, we were unable to conduct an assessment due to the lack of available data.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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