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ARTICLE

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Renin-angiotensin system inhibitors in hypertensive adults with non-diabetic CKD with or without proteinuria: a systematic review and meta-analysis of randomized trials

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Abstract

The efficacy and safety of renin-angiotensin system inhibitors (RAS-I) in hypertensive adults with non-diabetic chronic kidney disease (CKD) differ depending on the presence or the absence of proteinuria. To estimate the effects of RAS-I in this population, we performed a systematic review and meta-analysis of randomized controlled trials where treatment with angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers were compared with placebo or active controls in adults with non-diabetic CKD. The treatment effects were separately reviewed in patients with and without proteinuria. Based on a search of Medline and the Cochrane Library up to September 2017, we identified 42 eligible trials (28, proteinuria-positive group; 6, proteinuria-negative group; 2, mixed-proteinuria group; and 6, proteinuria data-unavailable group). RAS-I reduced renal failure events in comparison to placebo or active agents in the proteinuria-positive group (relative risk [RR] 0.63, 95% confidence interval [CI] 0.52–0.75), but showed no significant effects on renal failure risk in the proteinuria-negative group (RR 0.64, 95% CI 0.18–2.30) although it reduced microalbuminuria. For cardiovascular events, RAS-I was not associated with a significantly reduced risk in both the proteinuria-positive and proteinuria-negative group (RR 0.77 and 1.06, 95% CI 0.51–1.16 and 0.85–1.32, respectively). In the mixed-proteinuria group and proteinuria data-unavailable group, RAS-I showed no significant effects on renal and cardiovascular events. Among adverse events, hyperkalemia increased with RAS-I administration in the proteinuria-positive group (RR 2.01, 95% CI 1.07–3.77). Our analysis showed the renoprotective effects of RAS-I treatment in patients with non-diabetic CKD having proteinuria, supporting its use as the first-line antihypertensive therapy in this population.

Keywords Angiotensin-converting enzyme inhibitors · Angiotensin II receptor blockers · Chronic kidney disease · Proteinuria · JSH 2019 guidelines

Introduction

Chronic kidney disease (CKD) is a long-term condition that occurs as a result of damage to the kidney, which leads to end-stage renal disease and a high risk of cardiovascular disease [1]. Hypertension is the most common comorbidity affecting patients with CKD and further accelerates the kidney function decline [2]. Blood pressure-lowering with pharmacological agents is central to the management strategies for slowing the progression of renal dysfunction, as well as for reducing the risk for cardiovascular disease in CKD patients.

Renin-angiotensin system inhibitors (RAS-I), including angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB), are antihypertensive drugs, which act to inhibit the renin-angiotensin system and

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are believed to have renoprotective and cardioprotective effects compared with other classes of antihypertensive agents. The beneficial effect in the reduction of the risk of end-stage renal disease and cardiovascular events has been established for patients with diabetic kidney disease [3, 4]. These benefits were also reported in CKD patients who do not have diabetes, particularly when overt proteinuria is present [5]. Due to these lines of evidence, clinical practice guidelines suggest the use of RAS-I as the first-line therapy for the patients with diabetic kidney disease or non-diabetic CKD with proteinuria [6–8].

However, the effectiveness in the subgroup of patients with non-diabetic CKD without proteinuria is less certain. In addition, the evidence for the cardioprotective effects is less consistent in patients with non-diabetic CKD [9, 10]. Therefore, we undertook a systematic review and meta-analysis aimed at evaluating the benefits and harms of RAS-I in the management of hypertensive adults with non-diabetic CKD separately for those with and without proteinuria.

Methods

Search strategy

We undertook a systematic review of the literature according to the approach recommended by the PRISMA statement for the conduct of meta-analysis of intervention studies [11]. We searched PubMed Medline database (from 1950 to 8 September 2017), Cochrane Library database, and the Japan Medical Abstracts Society (ICHUSHI) databases for relevant published RCTs based on the strategy reported in the Supplementary information. Reference lists of review articles and relevant studies were also checked.

Study selection

We included RCTs that compared ACE-I or ARB with other classes of antihypertensive agents or placebo in adult (18 years or over) hypertensive patients with CKD who did not have diabetes mellitus and did not on dialysis. CKD was defined as Kidney Disease Improving Global Outcomes (KDIGO) criteria [12]. Studies restricted to patients with a single specific renal diagnosis (such as IgA nephropathy and polycystic kidney disease) were included. Studies that included people with diabetes were kept in the review where the results were presented separately for those with and without diabetes. If the result were not presented separately, and less than 30% of the study population had diabetes mellitus, then the study was included. We excluded any studies of people with diabetes mellitus; studies of people undergoing hemodialysis, peritoneal dialysis or post-renal transplant patients; or studies examining the effect of combined therapy of ACE-I with ARB. Because our aim is to evaluate the antihypertensive treatment for hypertensive patients, we excluded studies in which less than 50% of the study population had hypertension at baseline. Two reviewers independently and in duplicate screened the titles and abstracts of all identified studies using a selection criteria. Subsequently, the same reviewers independently assessed eligibility of the full texts of potentially eligible studies. Reviewers resolved discrepancies through discussion or, if needed, by adjudication from a third reviewer.

Outcome measures

Outcomes of interest were (1) renal failure events that included end-stage renal disease (defined as the need for dialysis therapy or kidney transplantation), doubling of serum creatinine levels, and 50% reduction in glomerular filtration rate (GFR); (2) cardiovascular events: a composite of fatal or non-fetal myocardial infarction, fatal or non-fatal stroke, sudden death, hospitalization due to heart failure or angina; and (3) reduction of proteinuria or micro-albuminuria. For adverse outcomes, hyperkalemia and hypotensive events were examined. The definitions of hyperkalemia in the each studies were used for the data collection. Hypotensive events included hypotension, syncope, dizziness, vertigo, and lightheadedness.

Data abstraction and risk of bias assessment

Two reviewers extracted the following data, independently and in duplicate: general study information (authors and publication year); study population details (sample size, age, diagnosis, and percentage of participants with CKD, hypertension and diabetes); details on the intervention and comparison; and outcome as listed above. In RCTs with more than two arms, we extracted data from the arm that RAS-I treated groups and control groups. In the studies performed subgroup analysis, we extracted data from the eligible subgroups. When the data was described only in the graphs, we inquired the values to the authors or estimated them from the graphs. When the standard deviations of urinary protein or albumin were not described in the texts, the values were estimated by the calculation using available data. Two reviewers independently assessed risk of bias using the modified Cochrane risk of bias instrument. We resolved disagreements between reviewers in data extraction and assessments of risk of bias or quality of evidence by discussion and, if needed, by third party adjudication.

Classification by the presence of proteinuria

According to the baseline information on proteinuria in the study participants, we divided the eligible studies into four

groups: (1) proteinuria-positive group, (2) proteinuria-negative group, (3) a group in which proteinuria-positive and negative patients were mixed, and (4) proteinuria data-unavailable group. When the mean level in the participants was more than 0.5 g/day (or g/creatinine ratio) proteinuria or more than 300 mg/day (or g/creatinine ratio) albuminuria, which indicates macroproteinuria and corresponds to the KDIGO CKD classification of A3 category, the study was included in the proteinuria-positive group. When the mean level of proteinuria or albuminuria was less than the cut-off values, the study was included in the proteinuria-negative group. When proteinuria-positive participants and proteinuria-negative participants were greatly overlapped in the study, the study was included into the mixed-proteinuria group. The studies in which urinary protein levels were not examined were included in the proteinuria data-unavailable group.

Data synthesis and statistical methods

All data from each eligible study were extracted and entered into a standardized spreadsheet. For each trial, we analyzed the outcomes separately, and calculated the relative risks (RR) for dichotomous outcome or mean differences for continuous outcome with 95% confidence intervals (CI). We used random effects models to estimate summary RR and mean differences for all outcomes. Heterogeneity was analyzed using Q statistical score with an alpha of 0.05 used for statistical significance and with the I^2 test. We examined publication bias using funnel plots for each outcome. Data were analyzed using Revman 5 software (Cochrane Collaboration, Oxford, UK).

Results

Description of included studies

The literature search yielded 4390 articles, 58 of which were reviewed in full text. Among these, we identified 42 eligible RCTs reported in 45 publications (Fig. 1). The reasons for exclusion in the full text review are shown in Supplementary table 1. The details of the included studies are summarized in Table 1. According to the urinary protein levels in the study population, we classified the trials into the four groups: 28 were classified as the proteinuria-positive group; 6, the proteinuria-negative group; 2, the mixed-proteinuria group; and 6, the proteinuria data-unavailable group. The intervention drug was ACE-I in 30 trials, ARB in 10 trials, and ACE-I or ARB in 2 trials. The risk of bias is summarized in Supplementary Table 2. Quality assessment showed that inadequate random sequence generation and lack of blinding were the main causes of potential bias. Funnel plots for each outcome are shown in Fig. 2. There was no clear evidence of publication bias.

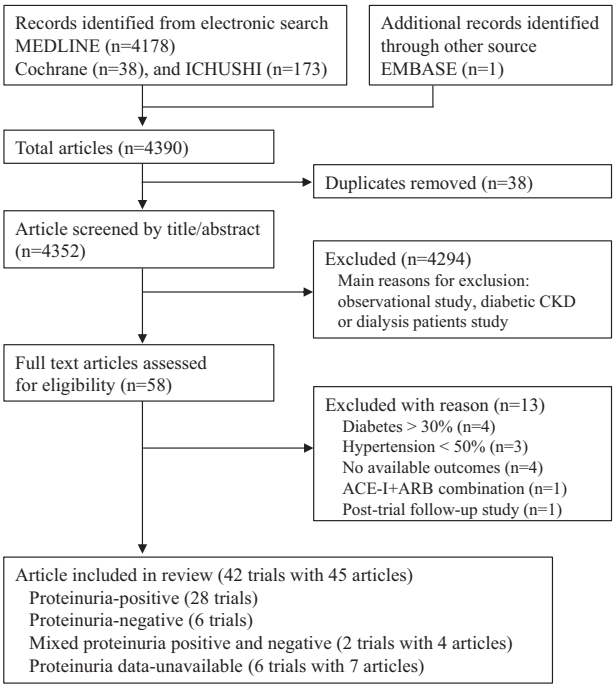

Fig. 1 Selection of studies in review

Renal outcome

Data regarding the effect of RAS-I on renal failure events were available from 18 studies in the proteinuria-positive groups [13–30], and four studies in the proteinuria-negative group [24, 31–33]. In the mixed-proteinuria group and proteinuria data-unavailable group, one study each was available, which were the AASK study [34] and a sub-analysis of the ALLHAT study [35], respectively. The results of the AASK study were also separately classified into proteinuria-positive group and proteinuria-negative group using the subgroup data [24]. The definition of outcomes in each study are listed in Supplementary Table 3. In the proteinuria-positive group, RAS-I significantly reduced the risk of renal failure events by 37% compared with placebo or active agents (RR 0.63, 95% CI 0.52–0.75, Fig. 3a). Whereas in the proteinuria-negative group, RAS-I showed no significant effects on the outcome of renal failure (RR 0.64, 95% CI 0.18-2.30, Fig. 3b). In the mixed-proteinuria group and the proteinuria data-unavailable group, RAS-I also did not show a significant impact on the risk of renal failure events (RR 0.89, 95% CI 0.74–1.08 and RR 1.01, 95% CI 1.30–0.90, respectively, Figs. 3c, d). There was no evidence of heterogeneity across the trials.

Table 1 Characteristics of studies included in systematic review

					Population setting		Baseline characters[a]					Intervention		Change in SBP (mmHg)	
UP(+)	Study/Author, year	Ref.	Follw-up (y)	*n*	Underlying condition	Inclusion criteria[a]	Comorbidity of diabetes	Mean age (y)	Mean sCr (mg/dL)[a]	Mean GFR (ml/min/1.73 m^2)	Mean UP (g/day or gCr)	RAS-I	Comparison	RAS-I	Comparison
	PUTS 1993	49	6 week	56	CKD of various causes	sCr < 2.5	18%	51.1	1.13	87.4	0.78	Perindopril	Placebo	−6.6	−2.4
	AIPRI 1996	13	3	583	CKD of various causes	sCr 1.5–4.0	3.6%	51.0	2.1	42.6	1.8	Benazepril	Placebo	−8	3.7
	REIN2 1997	15	3	166	Nondiabetic CKD	GFR 20–70 with UP > 3 g/d	0	49.3	2.4	38.7	5.3	Ramipril	Placebo	−5.4	−3.4
	REIN1 1999	14	2.8	186	Nondiabetic CKD	GFR 20–70 with UP 1–3 g/d	0	49.7	2.0	46.6	1.7	Ramipril	Placebo	NA	
	Ishimitsu 2005	55	1	22	Nondiabetic CKD	sCr 1.5–3.0	0	56.0	2.0	NA	1.03	Valsartan	Placebo	−1	0
	Hou 2006	16	3.4	224	Nondiabetic CKD	sCr 3.1–5.0 with UP > 0.3 g/d	0	44.7	4.0	26.6	1.65	Benazepril	Placebo	-28.2	-26.6
	HKVIN 2006	17	2	109	IgA nephropathy	sCr < 2.8 with UP > 1 g/d or sCr 1.4–2.8 regardless of UP	NA	40.5	1.2	82.5	2.05	Valsartan	Placebo	−6.3[e]	−0.1[e]
	Kampar 1992	18	2	70	CKD of various causes	sCr 1.7–10	19%	48.5	4.4	15.9	1.09[c]	Enarapril	Conventinal	−18	−4
	Woo 2000	19	1.1	41	IgA nephropathy	sCr > 1.4 and/or UP > 1 g	0	38.3	1.9	NA	2.15	Enalapril or Losartan	Conventinal	NA	
	Cinotti 2001	20	1.9	131	Nondiabetic CKD	GFR 20–50 with UP < 1.0 g/d	0	50.8	2.32	35.8	0.51	Lisinopril	Conventional	−3.2	−1.4
	Mimura 2008	21	4	102	Nondiabetic CKD		0	57.5	1.45	57.5	1.2	ACE-I or ARB	Conventional	2	1
	Zucchelli 1992	22	3	121	Nondiabetic CKD	sCr 1.8–5.0	0	55.0	2.95	30.5	1.78	Captopril	Nifedipine	−21[e]	−18[e]
	Holdaas 1998	50	4 week	15	Nondiabetic CKD	GFR 20-80 with U-Alb > 300 mg/d	0	45.0	3.2	37.0	4.0	Losartan	Amlodipine	−14	−8
	Kumagai 2000	51	1	49	CKD of various causes	sCr > 1.5	10%	58.6	2.1	NA	1.92	Enalapril or Captopril	Amlodipine	−21	−27
	ESPIRAL 2001	25	3	241	Nondiabetic CKD	sCr 1.5–5.0	0	54.4	2.85	35.6	1.75	Fosinopril	Nifedipine	−19.8	−14
	Nephros 2001	52	2	107[f]	Nondiabetic CKD	GFR below age adjusted nomal	0	53.5	1.74	42.5	0.43[c]	Ramipril	Felodipine	−14.3	−13.5
	Peterson 2001	23	1.8	40	CKD of various causes	sCr 1.7–6.8	20%	58.0	2.85	33.9	1.34[c]	Spirapril	Isradipine	1.2	2
	Park 2003	53	12 week	36	IgA nephropathy	sCr < 3.0 with UP > 1 g/d	0	41.5	1.5	63.0	2.2	Losartan	Amlodipine	−18	−17
	Praga 2003	36	20 week	97	Nondiabetic CKD	sCr < 2.5 with UP > 1.5 g/d	0	47.5	1.35	77.0	2.8	Losartan	Amlodipine	−18	−13
	JLIGHT 2003	37	0.5	117	CKD of various causes	sCr 1.5–3.0 with UP > 0.5 g/d	21%	56.6	2.0	NA	2.67	Losartan	Amlodipine	−17	−21.4
	Del Vecchio 2004	54	0.9	136	Nondiabetic CKD	GFR 20–60 and/or sCr 1.5–3.0	0	54.6	1.93	44.6	1.49	Enalapril	Manidipine	−23.1	−16.3
	MacGregor 2005	26	4	56[f]	Nondiabetic CKD	sCr 1.7–7.9	0	50.0	3.8	20.0	2.45	Quinapril	Amlodipine	−13	7
	AVER 2008	27	3	263	Nondiabetic CKD	GFR 20–60	0	58.0	2.0	46.2	1.27	Enalapril	Amlodipine	−24.7	−24.7

Table 1 (continued)

UP(+)	Study/Author, year	Ref.	Follw-up (y)	*n*	Population setting: Underlying condition	Population setting: Inclusion criteria[a]	Baseline characters[a]: Comorbidity of diabetes	Mean age (y)	Mean sCr (mg/dL)[a]	Mean GFR (ml/min/1.73 m^2)	Mean UP (g/day or gCr)	Intervention: RAS-I	Intervention: Comparison	Change in SBP (mmHg): RAS-I	Change in SBP (mmHg): Comparison
	Peng 2009	56	0.9	236	Hypertension with proteinuria	GFR 30–90 with UP 0.15–3 g	0	43.2	NA	51.0	1.31	Valsartan	Benidipine	−24.4	−22
	Hannedouche 1994	28	3	100	Nondiabetic CKD	sCr 2.3–4.5	0	51.0	3.0	NA	2.2	Enarapril	Acebutolol or Atenolol	−20	−13
	van Essen 1997	29	3.9	89	Nondiabetic CKD	GFR 30–90	0	49.5	1.8	53.0	3.4[d]	Enarapril	Atenolol	−14.3[e]	−12.5[e]
	Cheng 1998	30	3	28	IgA nephropathy	sCr 1.3–4.5	NA	36.4	1.58	94.6	2.2	Captopril	Nadolol	−14	−15
	PROCAPA 2002	38	0.5	90[f]	Nondiabetic CKD	GFR > 50 with UP > 1 g/d	0	43.5	1.23	87.3	5.24	Trandolapril	Atenolol or Verapamil	−12.4	−11.5

UP(-)												U-Alb (mg/day or gCr)			
	PREVEND IT 2004	39	3.8	864	Microalbuminuria	GFR > 60% of the normal value with U-Alb 15–300 mg/d	2.5%	51.3	1.02	NA	22.8	Fosinopril	Placebo	0	1
	PEACE 2007	40	4.8	642[g]	Coronary artery disease	U-Alb 17–125 mg/gCr	28%	66.2	1.05	77.7	NA	Trandopril	Placebo	NA	
	Ecder 2000	57	5	24	Polycystic kidney disease	GFR > 50	0	42.0	1.19	80.0	45.5	Enalapril	Amlodipine	−14	−13
	Nutahara 2003	31	3	49	Polycystic kidney disease	sCr < 2.0	0	NA	1.17	70.8	75.0	Candesartan	Amlodipine	−21	−21
	van Dijk 2003	32	3	28[h]	Polycystic kidney disease	sCr < 2.55	0	36.3	1.3	NA	42.2	Enalapril	Atenolol	−11	−3
	Zeltner 2008	33	3	37	Polycystic kidney disease	sCr < 4.0	0	40.3	1.22	87.6	70.1	Ramipril	Metoprolol	−13	−11

UP mixed											UP data				
	COPE 2013	41	3.6	834[i]	Hypertension patients	eGFR < 60 and/or UP positive	17%	66.4	NA	58.6	UP positive was 36%	ARB (+Benidipine)	BB or TD (+Benidipine)	−24.8	(BB)-24.6 (TD)-23.2
	AASK 2001, 2002, 2006	24, 34, 42	3	1094	Hypertensive renal disease	GFR 20-65	0	55.0	2.0	46.0	UP > 0.22 g/gCr was 33%	Ramipril	Amlodipine or Metoprolol	−16	(A)-17 (M)-15

UP NA												UP data			
	SAVE 2004	43	3.5	719[j]	postMI patients with LVEF < 40%	sCr < 2.5	29%	64.2	NA	41.8	NA	Captopril	Placebo	NA	
	PEACE 2006	44	4.8	1355[j]	Coronary artery disease	eGFR < 60 and sCr < 2.0	19%	68.2	1.33	NA	NA	Trandopril	Placebo	NA	
	PROGRESS 2007	45	4	1757[j]	Cerebrovascular disease	GFR < 60	11%	70.0	1.15	50.0	NA	Perindopril	Placebo	NA	
	SOLVD 2011	46	2.9	1036	CHF patients with LVEF < 35%	GFR < 60 and sCr < 2.5	29.7%	64.3	1.49	49.0	NA	Enarapril	Placebo	−7	0.1
	E-COST-R 2005	47	3.1	141	Nondiabetic CKD	sCr 1.2–2.0	0	66.9	1.47	44.2	NA	Candesartan	Conventional	−10.6	−11.6

Table 1 (continued)

UP NA					UP data						
					GFR < 60	0	70.7[l]	NA	50.2	NA	
ALLHAT 2005, 2006	35, 48	4.9	3774[k]	Nondiabetic subjects						Lisinopril	Chlorthalidone or Amlodipine	NA

UP (+) proteinuria-positive group, *UP (-)* proteinuria-negative group, *UP mixed* mixed-proteinuria group, *UP NA* urinary protein data-unavailable group, *sCr* serum creatinine (mg/dL), *GFR* glomerular filtration rate (ml/min/1.73 m^2), *UP* urinary protein, *U-Alb* urinary albumin group, *NA* no data available, *MI* myocardial infarction, *CHF* chronic heart failure, *SBP* systolic blood pressure, *BB* beta blockers, *TD* thiazide diuretics

[a]When the sCr was described as mol/L, the value is converted to mg/dL

[b]Overall mean of the both group was calculated

[c]The level of U-Alb

[d]Mean value for the patients with baseline UP > 1 g/day

[e]Mean BP data was used

[f]Exclued the combination group

[g]Used only the subgroup data of low-medium microalbuminuria group

[h]Used only the hypertensive group

[i]Used only the data of patients with CKD

[j]Used only the subgroup of GFR < 60

[k]Used only the group of GFR < 60 without diabetes. Outcome data was caluculated by subtracting event number in the total participants from those in the diabetic patients

[l]Mean age of the group contained diabetic patients

Cardiovascular events

A total of 27 studies evaluated the effects of RAS-I on the outcome of cardiovascular events, of which 15 were in the proteinuria-positive group [13–18, 20, 21, 25, 26, 28, 29, 36–38], four were in the proteinuria-negative group [32, 33, 39, 40], two were in the mixed-proteinuria group [41, 42], and six were in the proteinuria data-unavailable group [43–48]. The event details and their number in each studies are listed in Supplementary Table 4. In the proteinuria-positive group, RAS-I did not show significant differences in reducing the incidence of cardiovascular events compared to other class of agents (RR 0.77, 95% CI 0.51–1.16), although the ranges of CI in each study were wide due to the low event rates (Fig. 4a). In the proteinuria-negative group and the mixed-proteinuria group, RAS-I treatment also showed no significant impact on the outcome of cardiovascular events (RR 1.06, 95% CI 0.85–1.32 and RR 1.06, 95% CI 0.80–1.39, Figs. 4b, c). In the proteinuria data-unavailable group, the reducing effect of RAS-I on the cardiovascular events was not statistically significant (RR 0.89, 95% CI 0.77–1.03, $P = 0.09$, Fig. 4d); however, subgroup analysis omitting the ALLHAT study showed a significant decrease in cardiovascular outcome (RR 0.82, 95% CI 0.75–0.89, $P < 0.001$, Fig. 4d). There was no evidence of heterogeneity across the trials except for the proteinuria data-unavailable group that showed high heterogeneity ($I^2 = 76\%$)

Reduction of proteinuria or microalbuminuria

A total of 28 studies evaluated the effects of RAS-I on the outcome of reduction of proteinuria or microalbuminuria, of which 23 were in proteinuria-positive group [13, 15–17, 19, 20, 22, 23, 25, 27–29, 36–38, 49–56], five were in proteinuria-negative group [31–33, 39, 57]. In the proteinuria-positive group, RAS-I consistently reduced proteinuria (mean differences −0.42 g/day, 95% CI −0.58 to −0.26, Fig. 5a) compared with placebo or active agents. In the proteinuria-negative group, RAS-I also significantly reduced the microalbuminuria (−16.3 mg/g creatinine, 95% CI −30.1 to −2.6, Fig. 5b). There was moderate and high heterogeneity in treatment effects in the proteinuria-positive group (I2 = 50%) and in the proteinuria-negative group ($I^2 = 81\%$), respectively.

Potential harms of treatment

Data on adverse outcome potentially associated with treatment were collected on hyperkalemia and hypotensive events. A total of 18 studies evaluated hyperkalemia, of which 14 were in proteinuria-positive group [13–17, 20, 22, 25–28, 37, 51, 55], one was in proteinuria-negative group

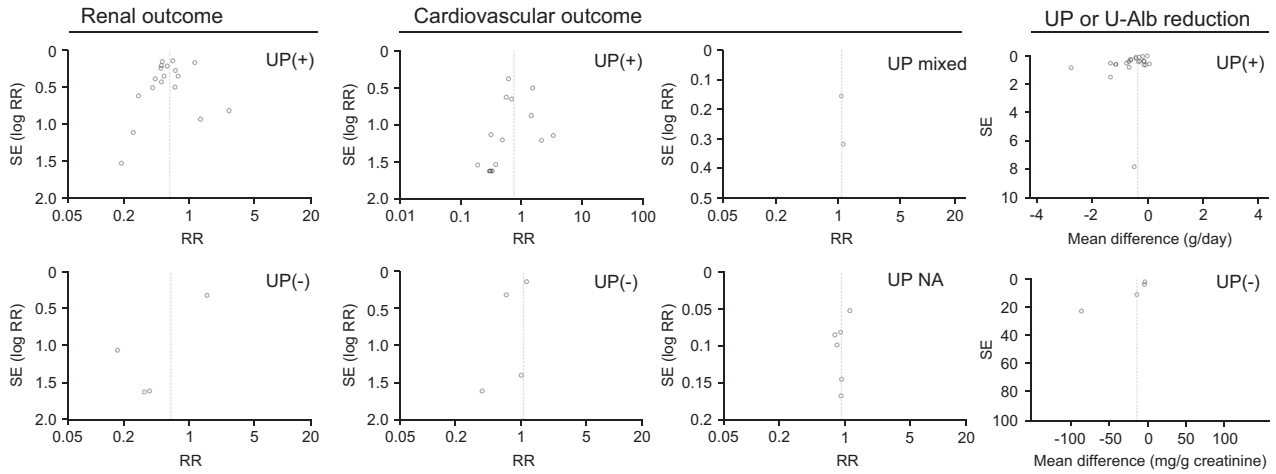

Fig. 2 Funnel plots for each outcomes. UP (+) proteinuria-positive group, UP (-) proteinuria-negative group, UP mixed, mixed-proteinuria group, UP NA urinary protein data-unavailable group

[31], two were in mixed-proteinuria group [34, 41], and one was in proteinuria data-unavailable group [46]. The risk of hyperkalemia significantly increased in RAS-I treatment for the proteinuria-positive group and mixed-proteinuria group (RR 2.01, 95% CI 1.07–3.77 and RR 6.45, 95% CI 1.80–23.07, respectively, Table 2), although the incidence rate was relatively low (2.9% and 1.5%, respectively). In the proteinuria-negative group by the available single study, no events of hyperkalemia were reported. Data about hypotensive adverse events were obtained from a total of ten studies, of which eight were in the proteinuria-positive group [13, 16, 17, 22, 26, 27, 36, 37] and two were in the mixed-proteinuria group [34, 41]. RAS-I did not increase the hypotensive events compared to placebo or active agents both in the groups (RR 1.21, 95% CI 0.64–2.28 and RR 0.48, 95% CI 0.03–6.58, respectively, Table 2). The proteinuria-negative group included no available studies for the outcome of hypotensive events.

Discussion

In this systematic review and meta-analysis reviewing the efficacy and safety of antihypertensive treatment by RAS-I in adults with non-diabetic CKD, we found that RAS-I treatment was effective for the prevention of renal failure progression in those with proteinuria. Whereas, the renoprotective effect was not found in those without proteinuria. The effects on cardiovascular events were not significant compared to other blood-pressure-lowering agents both in the proteinuria-positive and proteinuria-negative groups. The increased risk of hyperkalemia by RAS-I administration was found in the proteinuria-positive group.

On the basis of the present analysis, the Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2019) recommends RAS-I as first-line therapy for the hypertensive adults with non-diabetic CKD with proteinuria (defined as more than 0.15 g/day or /g creatinine) with attention to the increased risk of hyperkalemia. For those without proteinuria, other agents such as calcium-channel blockers and diuretics as well as RAS-I, are recommended for the first-line therapy.

The benefit of RAS-I for the renal outcome was found in non-diabetic CKD patients with proteinuria; however, it was not found in those without proteinuria. Our findings were consistent with the previous analysis that showed that the beneficial effect of RAS-I is stronger in patients with greater proteinuria [5]. Proteinuria, which reflects the glomerular hyperfiltration and/or glomerular injury, is a major determinant of renal disease progression and the reduction of proteinuria is renoprotective. Blockade of renin-angiotensin system by RAS-I decreases glomerular capillary pressure and thereby ameliorates glomerular hyperfiltration, reducing the level of proteinuria. The renoprotective effect of RAS-I increased in parallel with the severity of proteinuria and the degree of benefit of RAS-I is related to the antiproteinuric effect [58]. Thus, our analysis confirmed the renoprotective effect of RAS-I in non-diabetic CKD with proteinuria.

Although RAS-I treatment ameliorated microalbuminuria among the proteinuria-negative group, the effect was not associated with reducing renal failure events. The reason for this, the low risk for disease progression in the non-proteinuric CKD individuals may associated with the decreased benefits of RAS-I. Indeed, in our analysis, the total rate of renal failure events was lower in the proteinuria-negative group (11%) than in the proteinuria-positive group (24%) (Figs. 3a, b). In addition, considering the pathophysiology of non-proteinuric CKD with reduced GFR, the underlying factors for renal function deterioration

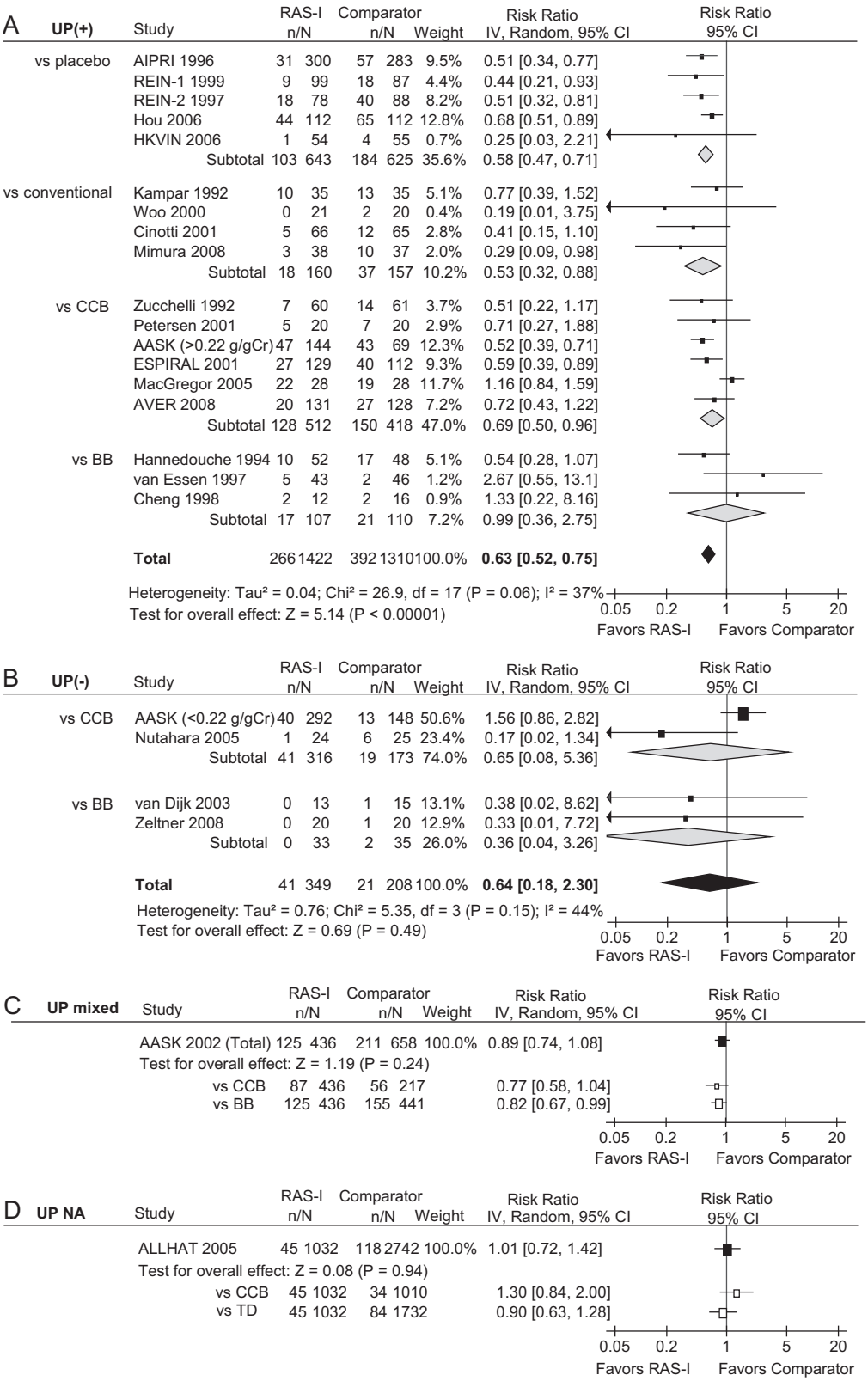

Fig. 3 Effects of RAS-I on the risk of renal events in non-diabetic CKD patients. UP (+) proteinuria-positive group, UP (−) proteinuria-negative group, UP mixed mixed-proteinuria group, UP NA urinary protein data-unavailable group, conventional, conventional antihypertensive therapy, CCB calcium-channel blockers, BB β-blockers, TD thiazide diuretics. Data from AASK trial was used as the subgroup of proteinuria positive (>0.22 g/g creatinine) and that of non-proteinuria (<0.22 g/g creatinine) in addition to the total data

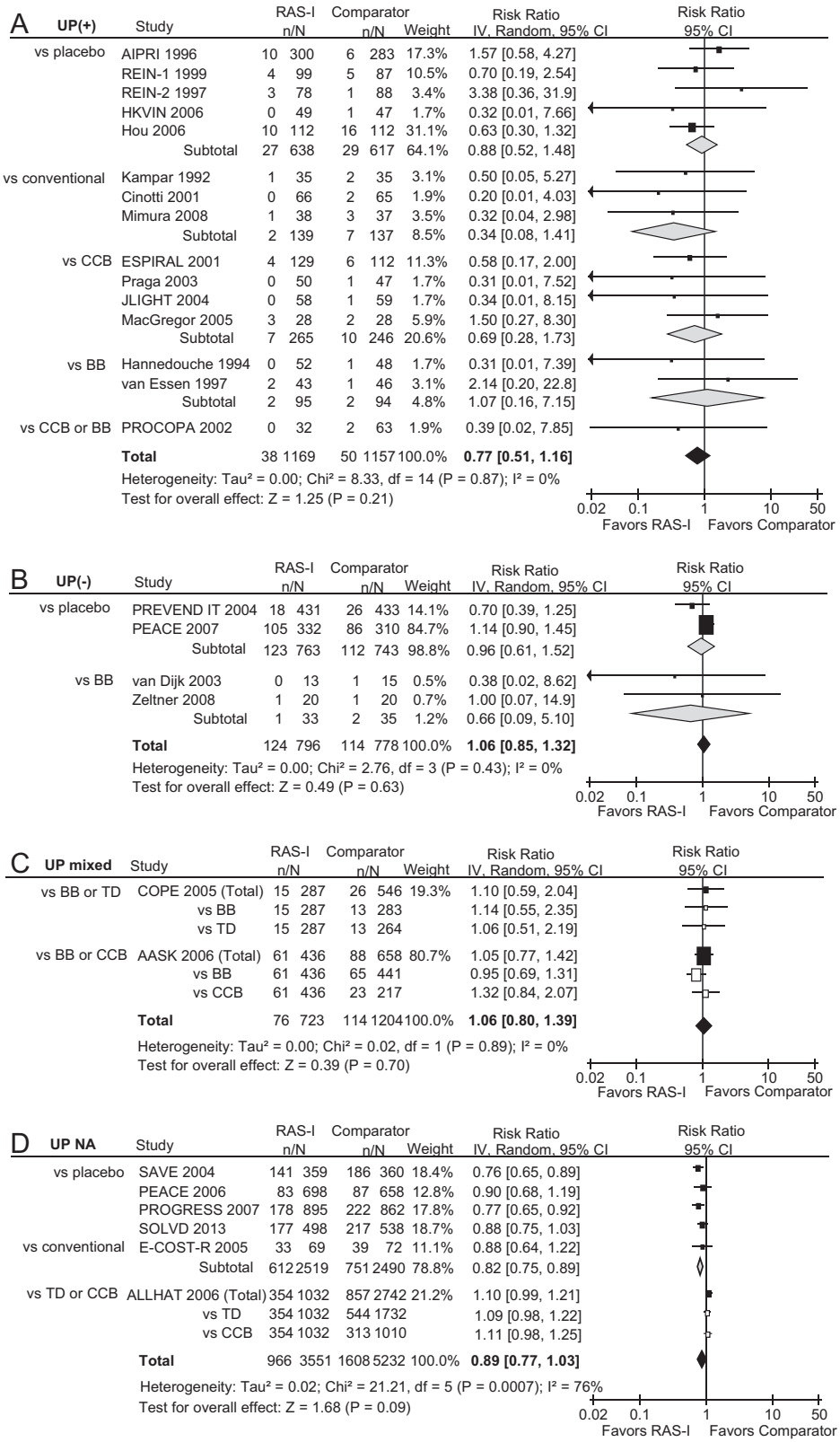

Fig. 4 Effects of RAS-I on the risk of cardiovascular events in non-diabetic CKD patients. UP (+) proteinuria-positive group, UP (−) proteinuria-negative group, UP mixed, mixed-proteinuria group, UP NA urinary protein data-unavailable group, conventional, conventional antihypertensive therapy, CCB calcium-channel blockers, BB β-blockers, TD thiazide diuretics

would differ from the glomerular hyperfiltration. When other mechanisms such as glomerular ischemia are predominant for the renal function declines, RAS-I would not ameliorate the factor and then not exert more beneficial effects on the disease progression compared with other antihypertensive agents.

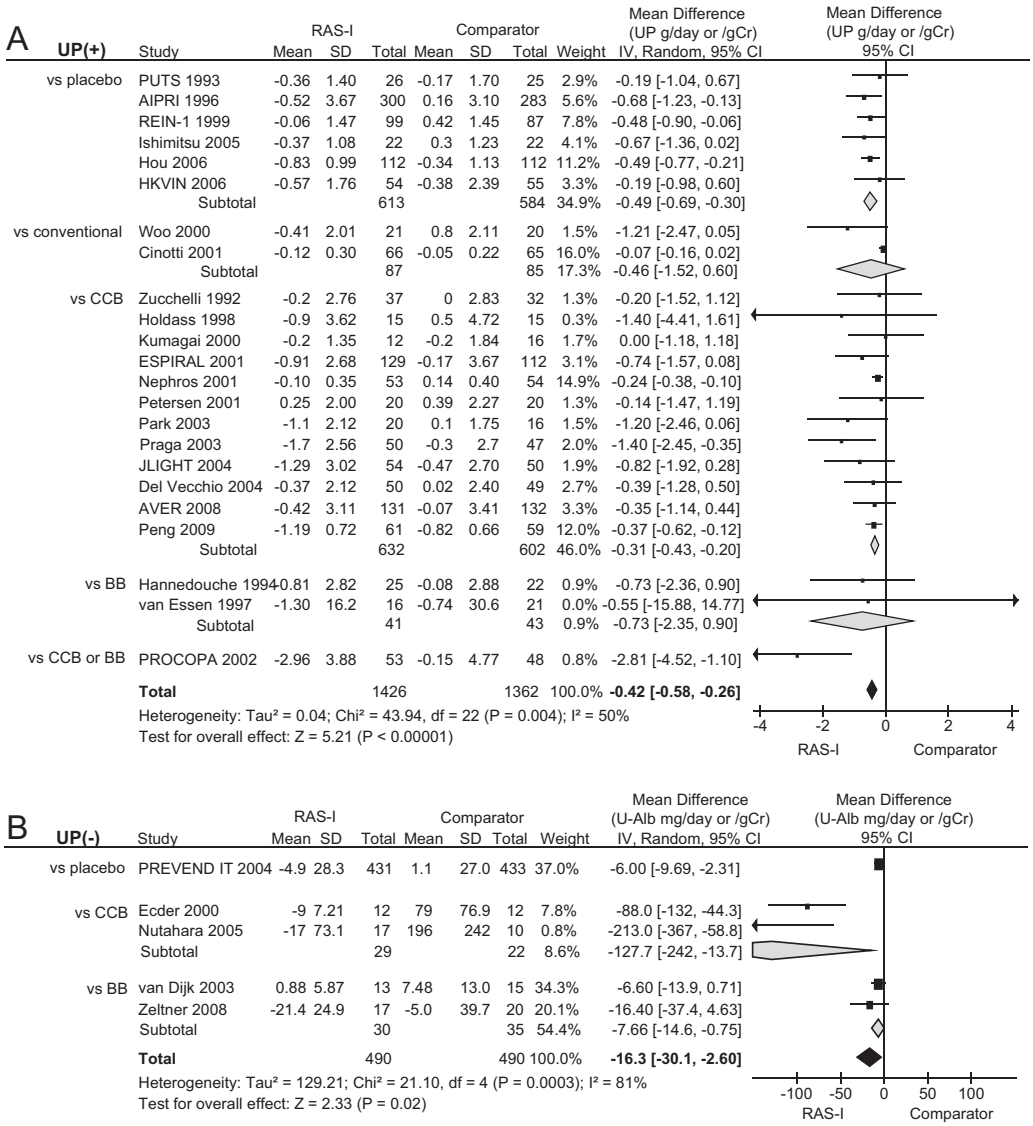

Fig. 5 Effects of RAS-I on the reduction of proteinuria or microalbuminuria in non-diabetic CKD patients. UP (+) proteinuria positive group, UP (−) proteinuria-negative group, UP urinary protein, U-Alb urinary albumin

There have been only a few studies examining the effects of RAS-I limited for non-diabetic CKD without proteinuria. In addition, among the enrolled studies in the proteinuria-negative group, four trials examined patients with polycystic kidney disease [31–33, 57]. If the studies are excluded, the remaining available studies are only a subgroup analysis of AASK trial for the renal outcome [24], and two studies for the cardiovascular outcome [39, 40]. In the general population, the most frequent cause of non-diabetic, non-proteinuric CKD are nephrosclerosis by hypertension and by aging [59, 60]. Since the pathophysiology and event risks are greatly different depending on the etiology of CKD [61], it would be difficult to extrapolate the result from specific renal diagnosis group such as polycystic kidney disease to the wider population with CKD. However, in the subgroup analysis of ALLHAT, RAS-I also showed no significant benefit on renal failure events and cardiovascular events in non-diabetic hypertensive patients with GFR less than 60 ml/min per 1.73 m^2 (Figs. 3d and 4d). Although the urinary protein level was not measured in the ALLHAT trials, most participants in the study would not have proteinuria, given their population characteristics. Therefore, the result of ALLHAT supports the decreased benefits of RAS-I in the non-diabetic CKD population without proteinuria.

The question of the cut-off level of proteinuria for the renoprotective properties of RAS-I still remains. A study by Cinotti et al. [20] showed the reduction in renal events by RAS-I in the non-diabetic CKD patients with mild proteinuria whose mean proteinuria was 0.51 g/day. The previous

Table2 Effects of RAS-I on the adverse events in non-diabetic CKD patients

Adverse events	study (*n*)	RAS-I			Comparator			Relative risk [95% CI]	*p*-Value
		Events/ total (*n*)		Rate	Events/ Total (*n*)		Rate		
Hyperkalemia									
UP(+)	14	35	1200	2.9%	14	1156	1.2%	2.01 [1.07, 3.77]	0.03
UP(-)	1	0	22	0%	0	22	0%	Not estimatable	
UP mixed	2	11	723	1.5%	3	1204	0.2%	6.45 [1.80, 23.07]	0.004
UP NA	1	9	498	1.8%	9	538	1.7%	1.62 [0.58, 4.52]	0.36
Hypotensive events									
UP(+)	8	20	788	2.5%	16	769	2.1%	1.21 [0.64, 2.28]	0.55
UP(-)	0		0			0		Not estimatable	
UP mixed	2	29	723	4.0%	44	1204	3.7%	0.48 [0.03, 6.58]	0.58
UP NA	0		0			0		Not estimatable	

UP (+) proteinuria positive group, *UP (-)* proteinuria-negative group, *UP mixed* mixed-proteinruia group, *UP NA* urinary protein data-unavailable group

pooled analysis also showed that ACE-I is beneficial among the subgroup of the patients with >0.5 g/day compared to other antihypertensive agents [5]. Thus, the current guidelines, the 2017 American College of Cardiology/American Heart Association high blood pressure (AHA/ACC) guideline [6] and Canada's 2018 Guidelines [7], adopts the cutoff values of albuminuria > 300 mg/day or proteinuria > 0.5 g/day for recommendation of RAS-I in patients with non-diabetic CKD. In contrast, JSH 2019 uses the presence of >0.15 g/day (or g/g creatinine ratio) of proteinuria for the recommendation of RAS-I in non-diabetic CKD patients because the guideline defines the value as positive for proteinuria in Japanese population. However, there is no conclusive evidence to support the renoprotective effect of RAS-I for non-diabetic patients with 0.15 to 0.5 g/day of proteinuria, which corresponds to the KDIGO CKD classification of A2 category in non-diabetic CKD.

In our analysis, RAS-I treatment showed no significant impact on cardiovascular events in people with non-diabetic CKD even with proteinuria. The benefit of RAS-I to cardiovascular outcome in the non-diabetic CKD population has been controversial. A meta-analysis showed that RAS-I were associated with a reduction in the risk of cardiovascular event and mortality in CKD patients [10]; however, the analysis included patients with diabetic kidney disease. A systematic review targeting to early stage of non-diabetic CKD showed that ACE-I had no significant impact on cardiovascular events with insufficient evidence [9]. In our analysis, because most of the studies among the proteinuria-positive group did not set cardiovascular events as the primary or secondary endpoint, we collected the data of cardiovascular events mainly from the list of treatment withdrawal reasons. Thus, the numbers of cardiovascular events that occurred in each study might not be precise, which may weaken the strength of the evidence. Indeed, the total rate of cardiovascular events were low (=3.8%) in the proteinuria-positive group (Fig. 4a). By contrast, the risk of cardiovascular outcomes was significantly reduced in the proteinuria data-unavailable group except in the ALLHAT study (Fig. 4d). However, almost all the studies among the group were sub-analyses of randomized trials examining the patients with cardiac dysfunction or cardiovascular diseases (Table 1) [43–46]. Thus, these data suggest the cardioprotective effect of RAS-I for the non-diabetic CKD patients with comorbidity of cardiovascular diseases. Therefore, cardioprotective benefit of RAS-I has been not conclusive for the non-diabetic CKD without comorbidity of cardiovascular diseases.

As a limitation, our analysis did not distinguish ACE-I and ARB. Some of the guidelines prefer ACE-I as the first-line therapy for CKD patients on the grounds of cost. However, whether ACE-I and ARB have different effects in prevention of clinically important outcomes in patients with non-diabetic CKD remain inconclusive, because clinical trials designed to compare ACE-I directly with ARB are rare.

In conclusion, our analysis shows that RAS-I treatment is an effective strategy for the prevention of renal failure progression in non-diabetic CKD patients with proteinuria. For the patients without proteinuria, the benefit of RAS-I is not apparent compared to that of other classes of antihypertensive agents, supporting the use of other drugs such as calcium-channel blockers and diuretics in those without proteinuria if adequate blood pressure control is achieved. These findings can inform clinical decision making on the management for these population.

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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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