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Original Paper

Effects of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on All-Cause Mortality and Renal Outcomes in Patients with Diabetes and Albuminuria: a Systematic Review and Meta-Analysis

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Key Words
Albuminuria regression • All-cause mortality • Angiotensin II receptor blockers • Angiotensin-converting enzyme(ACE) inhibitors • Doubling of serum creatinine • End-stage renal disease • Macroalbuminuria • Meta-analysis • Microalbuminuria • Reno-protective effect • Diabetes

Abstract
Background/Aims: Whether angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB) could benefit patients with diabetes and albuminuria remains controversial. A systematic review and meta-analysis were conducted to answer this question by comparing ACE inhibitors or ARB with placebo among these patients. ***Methods:*** In this meta-analysis, electronic data sources (Medline, the Cochrane Collaboration, and EMBASE) were searched. Randomized controlled trials (RCTs) comparing ACE inhibitors or ARB with placebo in subjects with diabetes and albuminuria (defined as urinary albumin-to-creatinine ratio, UACR≥30mg/g Cr) were included. Outcomes parameters were all-cause mortality, end stage renal disease (ESRD), doubling of serum creatinine levels, and cardiovascular events (CV). ***Results:*** Twenty-six RCTs (including 20 for ACE inhibitors and 6 for ARB) were included, comprising 10378 participants with diabetes and albuminuria. Compared to placebo, treatment with ACE inhibitors or ARBs did not reduce all-cause mortality or CV. For renal outcomes, ARBs significantly reduced the risk of ESRD by 23% (odds ratio 0.77, 95%CI 0.65-0.92), while ACE inhibitors were not associated with a decreased risk of ESRD (0.69, 0.43-1.10). Both ACE

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inhibitors and ARBs reduced the risk of doubling of the serum creatinine level (0.60, 0.39-0.91 for ACE inhibitors; 0.75, 0.64-0.88 for ARBs), and subgroup analyses for patients with macroalbuminuria or microalbuminuria showed similar results. ***Conclusion:*** In patients with diabetes and albuminuria, ARBs reduced risks of ESRD and doubling of the serum creatinine level. ACE inhibitors and ARBs failed to reduce all-cause mortality and CV. Based on the renoprotective effects, ARBs may be preferred for diabetic patients with albuminuria.

Introduction

Albuminuria (urinary albumin-to-creatinine ratio, UACR ≥ 30 mg/g creatinine) affects about one-third of diabetic patients [1]. Subjects with diabetes and albuminuria are at high risks of all-cause mortality and end stage renal disease (ESRD)[2, 3]. Clinical trials demonstrated that renin angiotensin system (RAS) blockers (angiotensin-converting enzyme [ACE] inhibitors or angiotensin II receptor lockers [ARB]) reduced albuminuria and the risk of progressive decrease in glomerular filtration rate (GFR)[4, 5]. To clarify whether RAS blockers could reduce all-cause mortality or kidney events in patients with diabetes and albuminuria is an important issue.

In patients with diabetes, recent meta-analyses provided controversial results for the efficacy of RAS blockers. A meta-analysis indicated that RAS blockers were not superior to other antihypertensive drugs at reducing the risk of renal endpoints in people with diabetes [6]. However, other meta-analyses showed that compared to other blood pressure-lowering strategy, RAS blockers were the most effective strategies against renal diseases in adults with diabetes [7-9]. The selections of diabetic patients (eg. complicating with chronic kidney diseases, albuminuria or hypertension), time of follow-up (eg. RCTs less than six months), controls (placebo or other antihypertensive drugs) and outcomes (eg. changes of UACR, or incidence of ESRD) might account for the inconsistent results from these meta-analyses.

In diabetic patients with albuminuria, multi-center RCTs with large sample size such as DIABHYCAR, RENAAL and IDNT exhibited discordant results. The DIABHYCAR study indicated that an ACE inhibitor (ramipril) has no effect on ESRD or doubling of serum creatinine [10], while the RENAAL study suggested an ARB (losartan) conferred significant renal benefits such as reduction of ESRD incidence [11]. Furthermore, the IDNT study showed a trend of renal protection effect for irbesartan with no significant difference observed [12]. A meta-analysis might be helpful to explore whether RAS blockers could benefit diabetic patients with albuminuria.

We conducted this systematic review and meta-analysis to compare the effects of RAS blocker (ACE inhibitors or ARBs) with placebo on the risk of all-cause mortality, renal outcomes and cardiovascular events in diabetic patients with albuminuria.

Materials and Methods

Search strategy and selection criteria

We searched four electronic databases (Medline, PubMed, Scopus, and the Cochrane Library) between 1970 and 31 December 2016 for randomized clinical trials (RCTs) investigating ACE inhibitors and ARB treatment for patients with diabetes, with Medical Subject Headings (MeSH) and text words. We searched additional studies in the reference lists of all identified publications, including relevant meta-analyses and systematic reviews. The supplementary file provides a detailed study protocol and description of the search strategies.

We included randomized, parallel group design clinical trials comparing the effects of ACE inhibitors or ARB with placebo in patients with diabetes older than 18 years, with a follow-up of at least 12 months (as rapidly decreasing renal function suggests alternative or additional causes of kidney disease [1]). Both fixed-dose and flexible-dose studies that treating investigators could titrate drug doses were included. Included

studies had to report at least one of primary outcomes: Primary outcomes were all-cause mortality and renal outcome (End stage renal disease [ESRD] and doubling of serum creatinine), secondary cardiovascular outcomes were myocardial infarction, stroke, and cardiovascular mortality. ESRD was defined as the need for dialysis therapy or kidney transplantation. Doubling of serum creatinine was defined as an increase in serum creatinine level of at least two times compared with baseline level.

We included studies in patients with type 1 or type 2 diabetes and albuminuria. Microalbuminuria was defined as urine albumin excretion rate of 30–299mg/24h for 24 h urine collection, 30-299 mg/g creatinine for urinary albumin-to-creatinine ratio (UACR) from a spot urine collection, or 20–199μg/min for timed urine collection. Macroalbuminuria was defined as urine albumin excretion rate ≥300 mg/24 h, UACR≥300 mg/g creatinine or ≥200 μg/min for the same specimens. Eligible studies had to be published as full length articles or letters in peer reviewed journals. There was no restriction on language of publication.

Data analysis

Two investigators (Kanran Wang and Jinbo Hu) independently extracted the following information and entered it into a database: study design, patients characteristics, interventions, comparisons, primary and secondary outcomes, components for randomized trials are assessed by allocation concealment; intention-to-treat analysis; blinding of investigators, participants, and outcome assessors; and completeness of follow-up. In addition, we used the Jadad scale to determine the quality of the trials. We got in touch with the original authors for more information, if relevant information on design or outcomes was indistinct, or there is doubt on duplicate publications. Two investigators independently assessed risk of bias in contributing studies with standard criteria. Disagreements were resolved by discussion from study group.

All data from each eligible study were extracted and entered into a standardized spreadsheet. We analyzed three treatment outcomes separately (all-cause mortality, renal outcome, and cardiovascular outcome). We performed traditional pairwise meta-analyses for studies that directly compared RAS blockers treatment with placebo. Dichotomous outcome data from individual trials were analyzed using the odds ratio (OR) measure and its 95%CI.To determine the robustness of our pooled effects, we compared our primary analysis with random-effects models, since we were possible to find out the role of potential sources of heterogeneity with regard to the character of participants (numbers, location, age, type of diabetes, albuminuria), drugs, follow up (years) and quality assessment (Jadad score, intention to treat analysis [ITT], allocation concealment). These results were confirmed by the Mantel-Haenszel fixed-effect model to avoid small studies being overly weighted. Funnel plots was used to probe for publication bias. Heterogeneity was assessed among studies using the I^2 statistic, judging values of less than 25% to be minimal, 25% to 49% to be moderate, and 50% or greater to be substantial.

As results might be disparate based on the albuminuria (UACR>30mg/g), we performed the primary analyses after stratifying the studies based on albuminuria (microalbumunia and macroalbuminuria). We reckoned the difference between the estimates of the subgroups on the basis of tests for interaction. $P < 0.05$ indicates that the effects of treatment differed significantly between the tested subgroups. Two-sided P value <0.05 was considered statistically significant. All statistical analyses were implemented by using Review Manager, 5.30, statistical software (Cochrane Collaboration), for the meta-analysis.

Results

Trial Flow and Study Characteristics

We found 1797 articles from a combined search of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. Of these, 1492 were excluded on the basis of their title and abstract. Of the 305 that underwent full text evaluation, 25 met our inclusion criteria (Fig. 1). Our research included 25 randomized controlled trials, enrolling 10363 people with diabetes and albuminuria. The participants were followed for a mean of 2.3 years. Twenty trials compared ACE inhibitor with placebo, and 6 trials compared ARB with placebo. There were 15, 6 and 4 trials enrolled diabetic patients with microalbuminuria, macroalbuminuria, and albuminuria (microalbuminuria and macroalbuminuria) respectively. A total of 17 trials

enrolled people with diabetes and hypertension. The characteristics of participants included in our analysis were summarized in Table 1.

Quality Assessment

The quality of the included studies was assessed independently by 2 of the authors (Jinbo Hu and Qifu Li) using the Jadad score which ranges from 0 to 7 points. 14 studies (56.0%) had a Jadad score greater than 3. Participants and investigators were blinded in 26 trials, and 8 studies (32%) met allocation concealment criteria (Table 1).

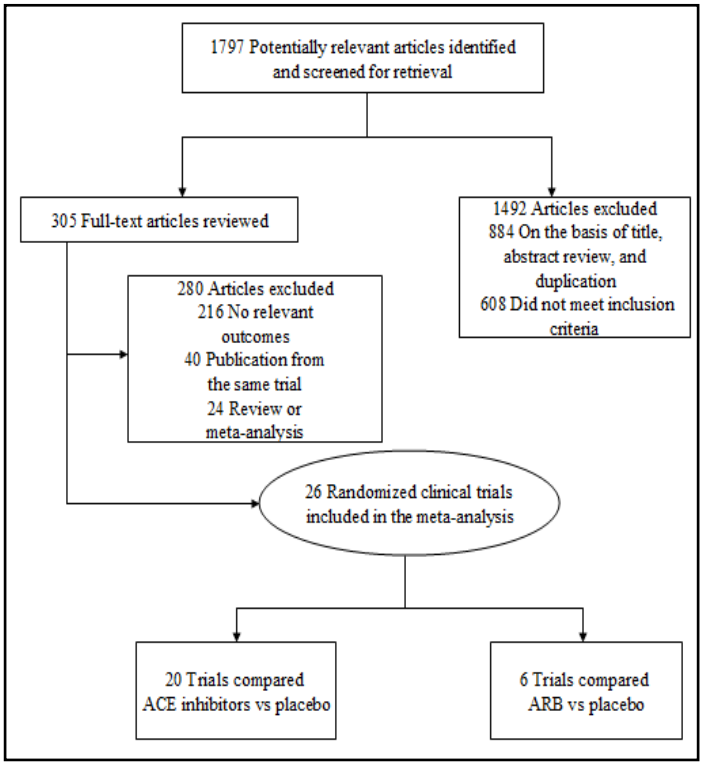

Fig. 1. Flowchart of Article Selection for Meta-analysis. ACE inhibitors: angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers. Muirhead et al 1999 which compares ACE inhibitors vs ARB vs placebo is divided into 2 trails.

Effects of RAS blockers on all-cause mortality

There were 26 RCTs (n=10378) evaluating the effects of RAS blockers on all-cause mortality, comprising 20 studies for ACE inhibitors (n= 6339) and 6 studies (n= 4039) for ARBs. Compared to placebo, RAS blockers treatment did not influence the risk of all-cause mortality (odds ratio 1.02, 95%CI 0.90-1.15, *P*=0.80). Neither ACE inhibitors nor ARBs were associated with the risk of all-cause mortality (for ACE inhibitors: 1.03, 0.88-1.21; for ARBs: 0.99, 0.82-1.20) (Fig. 2). The degree of heterogeneity in the treatment effect across all trials was low (I^2 = 0%; *P*= 0.80) and no evidence of publication bias was found.

Effects of RAS blockers on end stage renal disease (ESRD)

There were 26 RCTs (n=9484) evaluating the effects of RAS blockers on ESRD, comprising 20 studies for ACE inhibitors (n= 5668) and 6 studies (n= 3816) for ARBs. Compared to placebo, RAS blockers treatment significantly reduce the risk of ESRD (odds ratio 0.76, 95%CI 0.65-0.89, *P*=0.0009). Furthermore, ARBs leads to a significant reduction of ESRD risk (0.77, 0.65-0.92; *P*=0.003), while ACE inhibitors were not associated with risk of ESRD (0.69, 0.43-1.10; *P*=0.12) (Fig. 3). The degree of heterogeneity in the treatment effect across all trials was low (I^2 = 0%; *P*= 0.75) and there is no evidence of publication bias (Fig. 4).

In the subgroup of macroalbuminuria, there were 7 RCTs (n=3702) evaluating the effects of RAS blockers on ESRD, comprising 3 studies for ACE inhibitors (n= 474) and 4 studies (n= 3228) for ARBs. Compared to placebo, RAS blockers treatment significantly reduce the risk of ESRD (odds ratio 0.76, 95%CI 0.64-0.89, *P*=0.0008). Furthermore, ARBs leads to a significant reduction of ESRD risk (0.77, 0.65-0.92; *P*=0.003), while ACE inhibitors were not associated with risk of ESRD (0.60, 0.34-1.06; *P*=0.08). Data from subgroup of microalbuminuria which aimed at evaluating the effects of RAS blockers on ESRD were insufficient for meta-analysis.

Table 1. Summary of included clinical trials and patient characteristics. * Micro: microalbuminuria, defined as urine albumin excretion rate of 30–300mg/24h for 24 h urine collection, or 30-299 mg/g creatinine for urinary albumin-to-creatinine ratio (UACR) from a spot urine collection, or 20–199μg/min for timed urine collection. Macro: macroalbuminuria, defined as urine albumin excretion rate ≥300 mg/24 h, UACR≥300 mg/g creatinine or ≥200 μg/min for the same specimens. Micro/macro: microalbuminuria and macroalbuminuria. ITT: intention-to-treat

Study ID	Characteristics of Participants					Drugs	Follow Up Years	Quality Assessment		
	Number	Location	Age	Type Of Diabetes	Albuminuria*			Jadad Score	ITT#	Allocation Concealment
JAPAN-IDDM 2002[26]	79	Japan	33.5	1	Micro/macro	Captopril, Imidapril	1.5	5	Yes	NR
ABCD-2V 2006[27]	129	USA	56.1	2	Micro	Valsartan	1.9	5	Yes	Yes
ATLANTIS 2000[28]	140	UK, Ireland	40	1	Micro	Ramipril	2	3	Yes	NR
Bauer et al 1992[18]	33	USA	44.1	mixed	Macro	Enalapril	1.5	2	No	NR
Bojestig et al 2001[29]	55	Sweden	39.7	1	Micro	Ramipril	2	3	Yes	NR
Capek et al 1994[30]	20	Sweden	63.6	2	Micro	Captopril	1	3	No	NR
Chase et al 1993[31]	16	USA	22	1	Micro	Captopril	1	3	No	NR
Crepaldi et al 1998[32]	66	Italy	38	1	Micro	LÍSinopril	3	7	No	NR
DIABHYCAR 2004[10]	4912	Europe, North Africa	65.1	2	Micro /macro	Ramipril	3	5	Yes	Yes
ESPRIT 2001[33]	36	Europe	38.0	1	Micro/macro	Enalapril	3	4	Yes	NR
IDNT 2001[12]	1148	Multi-national	58.9	2	Macro	Irbesartan	2.5	5	Yes	Yes
IRMA-2 2001[25]	590	Multi-national	58	2	micro	Irbesartan	2	5	Yes	Yes
Jerums 2001[34]	29	Australia	30.8	1	micro	Perindopril	2	4	No	Yes
Laffel et al 1995[35]	143	North America	32.7	1	Micro	Captopril	2	3	No	NR
Lewis et al 1993[17]	409	USA	34.5	1	Macro	Captopril	3	4	Yes	NR
Mathiesen et al 1999[36]	44	Denmark	28.9	1	Micro	Captopril	4	3	Yes	NR
Muirhead et al 1999[37]	122	Canada	58.3	2	Micro	Captopril, Valsartan	1	4	Yes	Yes
Nankervis et al 1998[38]	40	Australia	46	mixed	Micro	Perindopril	3	3	No	NR
O'Donnell et al 1993[39]	32	the UK	48.3	mixed	Micro	Lisinopril	1	4	No	NR
ORIENT 2011[20]	577	Japan, China	59.1	2	Macro	Olmesartan	3.2	5	Yes	Yes
Parving et al 1989[19]	32	Denmark	30.9	1	Macro	Captopril	1	2	No	NR
Ravid et al 1993[40]	108	Israel	43.5	2	Micro	Enalapril	5	3	No	NR
RENAAL2001[11]	1513	Multi-national	60	2	Macro	Losartan	3.4	5	Yes	Yes
Sano et al 1994[41]	52	Japan	62	2	Micro	Enalapril	4	2	No	NR
Tong et al 2006[42]	38	China	65.8	2	Micro/macro	Fosinopril	2	4	Yes	NR

Effects of RAS blockers on doubling of the serum creatinine level

There were 26 RCTs (n= 9415) evaluating the effects of RAS blockers on doubling of the serum creatinine level, comprising 20 studies for ACE inhibitors (n= 5598) and 6 studies (n= 3817) for ARBs. Compared to placebo, RAS blockers treatment significantly reduce the risk of doubling of the serum creatinine level (odds ratio 0.72, 95%CI 0.62-0.84, P<0.0001). Furthermore, either ACE inhibitors or ARBs was associated with lower risks of doubling of the serum creatinine level (0.60, 0.39-0.91 for ACE inhibitors; 0.75, 0.64-0.88 for ARBs) (Fig. 3). The degree of heterogeneity in the treatment effect across all trials was low (I^2 = 7%; P= 0.38) and no evidence of publication bias (Fig. 4).

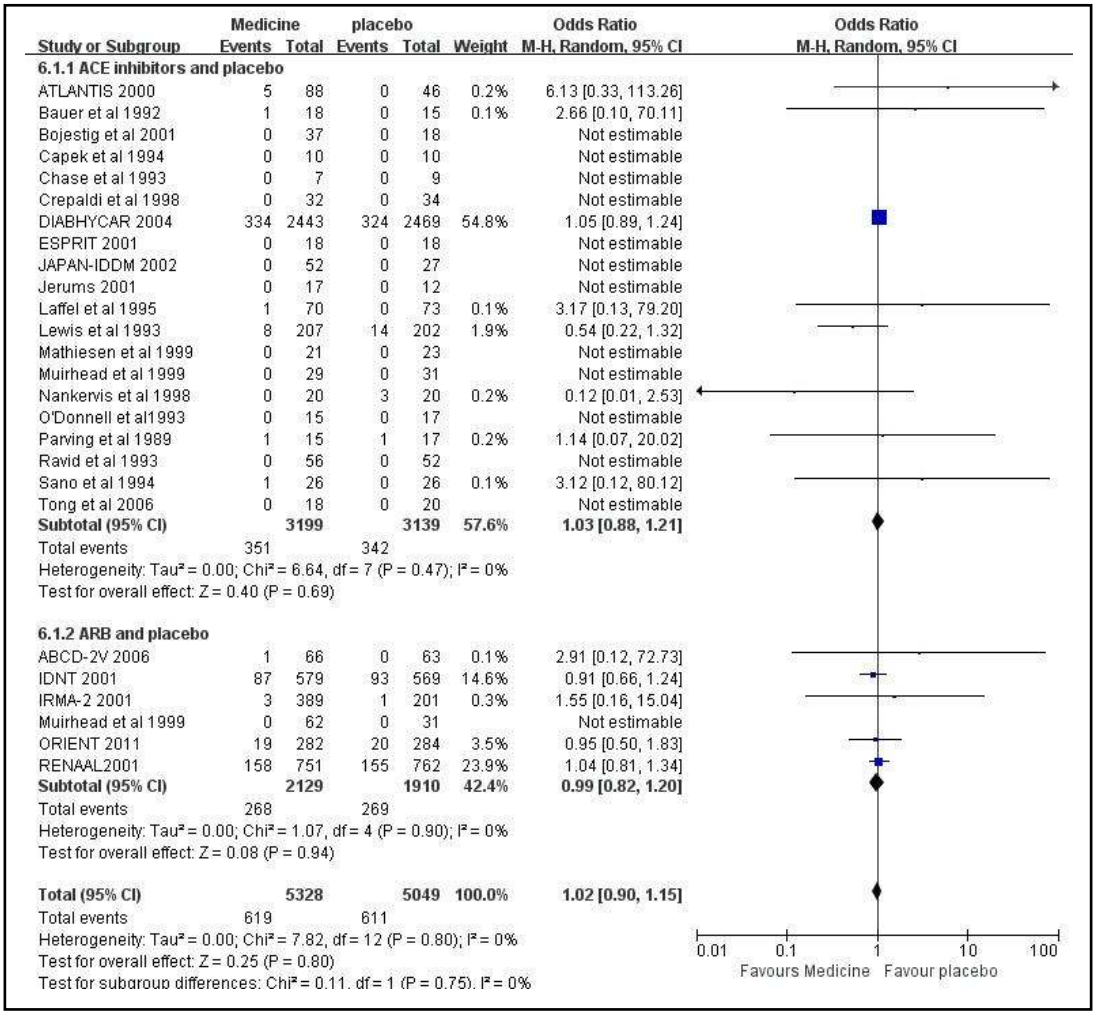

Fig. 2. Outcome of all-cause mortality with renin angiotensin system (RAS) blockers compared with placebo in patients with diabetes and albuminuria. Diamond indicates the overall summary estimate for the analysis (width of the diamond represents the 95%CI); boxes, the weight of individual studies in the pooled analysis. Trials to the left of the vertical line showed a reduction in risk with the experimental intervention; those to the right showed an increase in risk with the experimental intervention. M-H indicates Mantel-Haenszel.

In the subgroup of macroalbuminuria or microalbuminuria, RAS blockers treatment significantly reduced the risk of doubling of the serum creatinine level (0.73, 0.62-0.85 for macroalbuminuria subgroup; 0.21, 0.06-0.82 for microalbuminuria subgroup). Further analysis of ACE inhibitors and ARBs for each subgroup showed similar results with whole group (ACE inhibitors: 0.52, 0.31-0.87 for macroalbuminuria subgroup; 0.21, 0.06-0.82 for microalbuminuria subgroup. ARBs: 0.52, 0.31-0.87 for macroalbuminuria subgroup; none for microalbuminuria subgroup).

Effects of RAS blockers on cardiovascular events (CV)

There were 8 RCTs (n=8390) evaluating the effects of RAS blockers on CV, comprising 20 studies for ACE inhibitors (n= 5166) and 6 studies (n= 3224) for ARBs. Compared to placebo, RAS blockers treatment were not associated with risk of CV (odds ratio 0.94, 95%CI 0.83-1.06, *P*=0.33), Furthermore, neither ACE inhibitors nor ARBs were associated with risk of CV (0.98, 0.84-1.14 for ACE inhibitors; 0.87, 0.71-1.07 for ARBs). The degree of heterogeneity in the treatment effect across all trials was low (I^2 = 0%; *P*= 0.87) and no evidence of publication bias (Fig. 4).

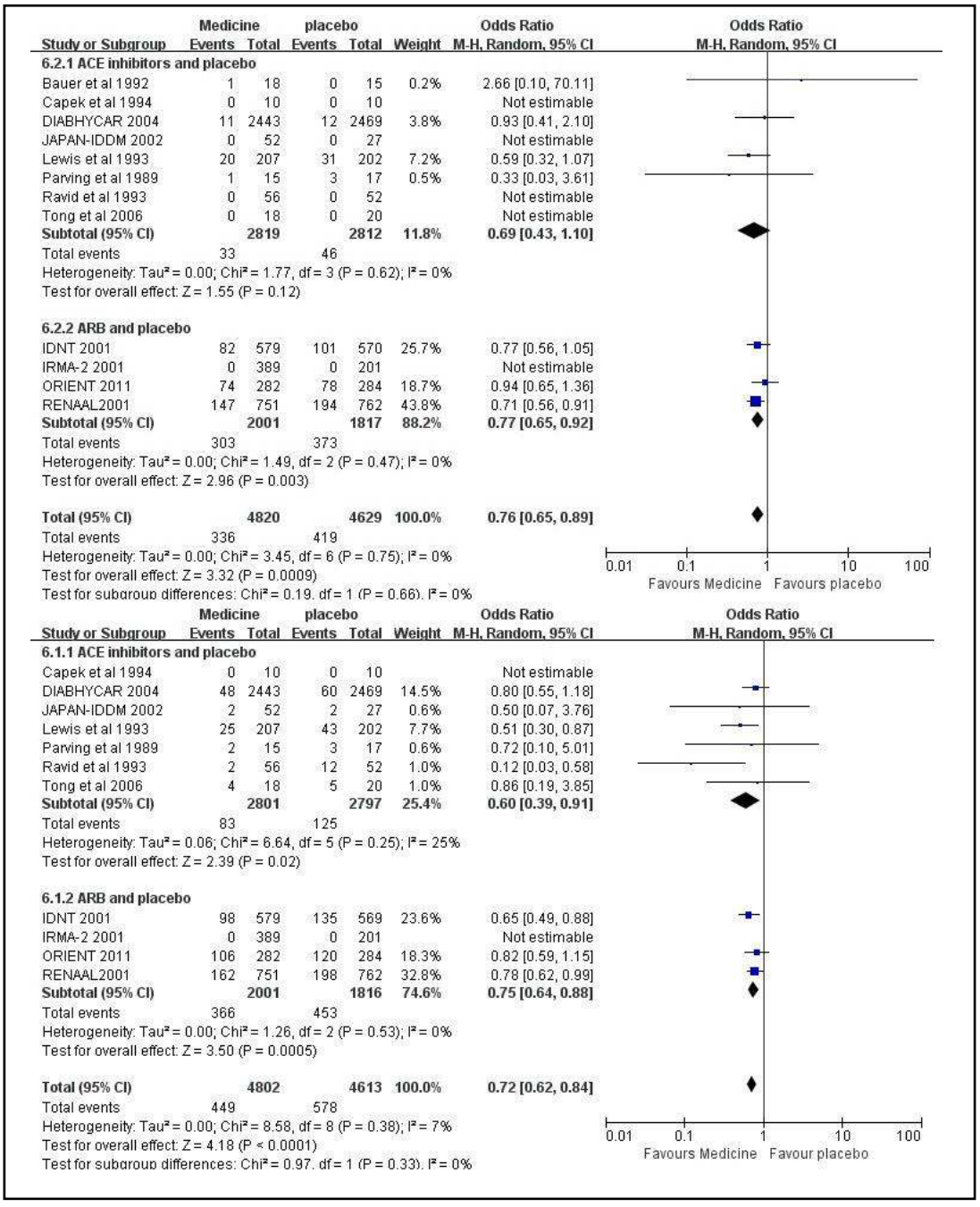

Fig. 3. Outcome of end stage renal disease (ESRD) (the first chart) and doubling of the serum creatinine level (the second chart) with renin angiotensin system (RAS) blockers compared with placebo in patients with diabetes and albuminuria. Diamond indicates the overall summary estimate for the analysis (width of the diamond represents the 95%CI); boxes, the weight of individual studies in the pooled analysis. Trials to the left of the vertical line showed a reduction in risk with the experimental intervention; those to the right showed an increase in risk with the experimental intervention. M-H indicates Mantel-Haenszel.

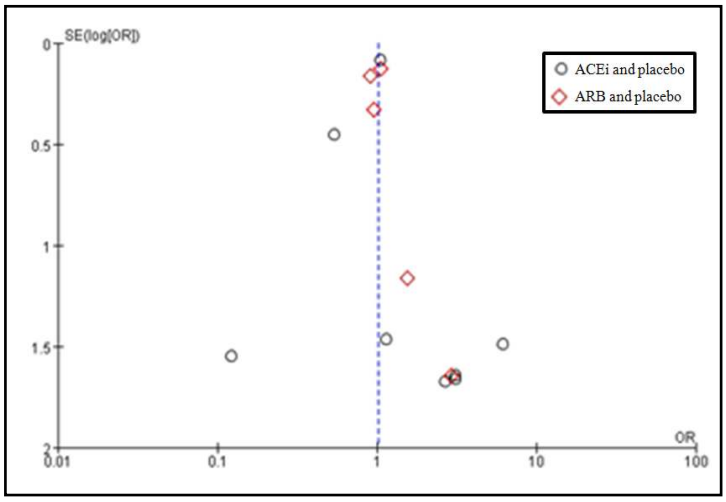

Fig. 4. Funnel Plot: RAS blockers versus placebo for the outcome of all-cause mortality.

Discussion

Including 26 RCTs, this meta-analysis showed that in patients with diabetes and albuminuria, ARBs significantly reduced the risks of ESRD by approximately 26% and doubling of the serum creatinine level by approximately 25%. However, ACE inhibitors and ARBs failed to reduce all-cause mortality and CV, and there was no significant change in the risk of ESRD when ACE inhibitors therapy was compared with placebo. RAS blockers had similer renoprotective effects both in subgroups of macroalbuminuria and microalbuminuria.

Guidelines from National Institute for Health and Care Excellence (NICE) 2014 and Kidney Disease Outcomes Quality Initiative (KDOQI) 2012 recommended the use of an ACE inhibitors or a ARB in patients with diabetes and albuminuria, even for subjects with microalbuminuria (UACR 30–299 mg/g Cr) and normal blood pressure [13, 14]. However, the use of RAS blockers in diabetic patients with microalbuminuria or normal blood pressure was not recommended by American Diabetes Association (ADA) 2017 guideline [1]. And some basic researches showed that some new drugs on RAS such as renin receptor blocker may do not have additively renoprotective effects over ACE inhibitors (Quinapril) monotherapy [15]. In our study, even though ACE inhibitors and ARBs failed to prolong survival or reduce CV, the renoprotetion of RAS blockers (especially for ARBs) may provide a reference for clinical practice guidelines,

As far as we know, no meta-analysis was performed to evaluate the effects of RAS blockers in people with diabetes and albuminuria, but there are some meta-analyses performed in diabetic patients. A network meta-analysis included 28 RCTs (134 912 participants), comparing the renal outcomes between RAS blockers and other antihypertensive drugs or placebo in type 2 diabetes, and a consistent renoprotective effect of RAS blockers (ACE inhibitors and ARBs) over other antihypertensive drugs was observed [8]. Another Bayesian network meta-analysis identifying 63 trials (36 917 participants with diabetes) suggested that ACE inhibitors, not ARBs had renoprotective effects in patients with diabetes [9]. Similarly, a meta-analysis identified 35 RCTs, comparing ACE inhibitors and ARBs with other antihypertensive drugs or placebo, and the results showed that ACE inhibitors reduced all-cause mortality and CV events in patients with diabetes, but not ARBs [16]. Furthermore, a meta-analysis yielding 19 RCTs (25 414 participants with diabetes) indicated that RAS blockers (ACE inhibitors and ARBs) were not superior to other antihypertensive drugs at reducing the risk of death, CV events and renal endpoints [6]. With the huge heterogeneity of diabetes, subgroup analyses with more specific grouping criteria in RCTs are needed to identify the effects of RAS blockers clinically.

Recently, a network meta-analysis included 157 RCTs comprising adults with diabetes and kidney disease (defined as albuminuria, decreased glomerular filtration rate [below 60 ml/minute per 1.73 m^2] or investigator-defined chronic kidney disease). The results showed that compared to other blood pressure-lowering strategy, ACE inhibitors and ARBs were the most effective strategies against ESRD, and no antihypertensive drugs reduce all-cause mortality [7]. In this network meta-analysis, some trials (about 15%) did not specify

albuminuria or recruited subjects without albuminuria. More importantly, about half of the included studies followed up ≤ 6 months, while the decreased eGFR or increased albuminuria in a short time frame may suggest alternative or additional causes of kidney disease in some cases [1]. Therefore, although the meta-analysis provided a comprehensive understanding as regards the efficacy and safety of ACE inhibitors and ARBs in diabetes and kidney disease, whether RAS blockers should be recommended for diabetic patients with albuminuria is still controversial.

Our meta-analysis was conducted to evaluate the effects of ACE inhibitors and ARBs in diabetic patients with albuminuria. In accordance with previous studies [6, 7], ACE inhibitors and ARBs were not found to prolong survival or reduce CV. Interestingly, ARBs significantly reduced the risk of ESRD and doubling of the serum creatinine level, while ACE inhibitors failed to reduce the risk of ESRD. Among four RCTs evaluating the efficacy of ACE inhibitor on ESRD, only Lewis et al. reported that captopril tend to protect patients from ESRD compared to placebo (OR 0.59[0.32, 1.07] with no significant difference observed) [17], and the other three RCTs did not show any benefit of ACE inhibitor on ESRD[10, 18, 19]. Among three RCTs evaluating the efficacy of ARBs on ESRD, the RENAAL study exhibited that losartan significantly reduced the incidence of ESRD compared to placebo (OR 0.71[0.56, 0.91])[11], and the IDNT study showed that irbesartan also tend to protect patients from ESRD (OR 0.77[0.56, 1.05])[12]. Although the ORIENT study suggested a negative result [20], the RENAAL and IDNT studies accounted for 70% weight of all included studies and further confirmed the renoprotection of RAS blocker in diabetic patients with albuminuria. And the renoprotection may seem to be related to inhibition of podocyte apoptosis [21]. Furthermore, experimental studies suggested that ARBs could slow the progression of diabetic nephropathy by reducing podocyte injury and glomerulosclerosis [22-24], which might be potential mechanisms against ESRD in diabetes.

Our study has potential limitations. First, the number of studies as regards ACE inhibitors is more than that as regards ARBs (20 vs 6), with different number of participants included (ACE inhibitors vs ARB: 6339 vs 4039). Second, it was confirmed that RAS blockers reduced progressive albuminuria and decrease eGFR in a dosage dependent manner [25], while the effect of RAS blockers with various doses was not analyzed in our meta-analyses. Third, the participants included were followed for a mean of 2.3 years, which may not be long enough to observe all-cause mortality and CV. Fourth, few data were available from countries of low-to-middle income. Fifth, we included both type 1 and type 2 diabetic patients with albuminuria, but the pathogenesis of albuminuria could be different for type 1 or type 2 diabetes. Thus, some bias may be incurred.

Conclusion

In patients with diabetes and albuminuria, ARBs significantly reduced the risks of ESRD and doubling of the serum creatinine level, and ACE inhibitors reduced doubling of the serum creatinine level. ACE inhibitors and ARBs failed to reduce all-cause mortality and CV. Based on the renoprotective effects, ARBs might be the first choice for diabetic patients with albuminuria.

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Kanran Wang and Jinbo Hu are co-first authors of this article.

Disclosure Statement

The Authors have no conflicts of interest to disclose.

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