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

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Abstract

Background/Aim: Whether 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 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 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) and cardiovascular events(CV).

Results: RCTs (with ARB) were included, comprising participants with diabetes and albuminuria. Compared to placebo, treatment with 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).

Conclusion: In patients with diabetes and albuminuria, ARBs reduced risks of end stage renal disease (ESRD) ARBs failed to reduce all-cause mortality and cardiovascular events . Based on the renoprotective effects, ARBs may be preferred for diabetic patients with albuminuria.

Keywords: • All-cause mortality • Angiotensin II receptor blockers • End-stage renal disease •Microalbuminuria • Reno-protective effect • Diabetes

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). 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 [4]. 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 [5-7]. 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.

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 electronic databases (Medline, Scopus, and the Cochrane Library)

for randomized clinical trials (RCTs) investigating 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 ARB with placebo in patients with diabetes older than 20 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. 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.

Data analysis

The following information entered 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.

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 pair wise 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. 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 statistical software (Cochrane Collaboration), for the meta-analysis.

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

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), The degree of heterogeneity in the treatment effect across

all trials was low. In the subgroup of macroalbuminuria, Compared to placebo, RAS

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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), Data from subgroup of microalbuminuria which aimed at evaluating the effects of RAS blockers on ESRD were insufficient for meta-analysis.

Effects of RAS blockers on cardiovascular events (CV)

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), The degree of heterogeneity in the treatment effect across all trials was low .

Discussion:

This meta-analysis showed that in patients with diabetes and albuminuria, ARBs

significantly reduced the risks of ESRD by approximately 26%.However, ARBs failed to reduce all-cause mortality and CV. RAS blockers had similar renoprotective effects both in subgroups of macroalbuminuria and microalbuminuria. In our study, even though 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].

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 [8] . 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 . 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.

Our meta-analysis was conducted to evaluate the effects of ARBs in diabetic patients with albuminuria. In accordance with previous studies , ARBs were not found to prolong survival or reduce CV. Interestingly, ARBs significantly reduced the risk of ESRD . 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])[9] , and the IDNT study showed that irbesartan also tend to protect patients from ESRD (OR 0.77[0.56, 1.05])[10] . Although the ORIENT study suggested a negative result [11], 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 .Furthermore, experimental studies suggested that ARBs could slow the progression of diabetic nephropathy by reducing podocyte injury and glomerulosclerosis [12-14] , which might be potential mechanisms against ESRD in diabetes.

Our study has potential limitations. First, it was confirmed that RAS blockers reduced progressive albuminuria and decrease eGFR in a dosage dependent manner [15] , while the effect of RAS blockers with various doses was not analyzed in our meta-analyses. Second, the participants included were followed for a mean of two years, which may not be long enough to observe all-cause mortality and CV. Third, few data were available from countries of low-to middle income .Thus, some bias may be incurred.

Conclusion:

In patients with diabetes and albuminuria, ARBs significantly reduced the risks of end stage renal disease (ESRD) . ARBs failed to reduce all-cause mortality and cardiovascular events .Based on the renoprotective effects, ARBs might be the first choice for diabetic patients with albuminuria.

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