IJKD KIDNEY DISEASES

Comparisons of Three Main Treatments on Renoprotective Effects in Diabetes mellitus

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Introduction. Antihypertension, intensive glucose control (IGC), and lipid lowering were the main therapeutic strategies in diabetes mellitus. However, the comparative effects of them on renoprotection remain unclear.

Materials and Methods. We searched the PubMed, EMBase, and Cochrane Library up to May 18, 2017, for studies with comparative interventions on regression, end-stage renal disease and all-cause death in diabetes mellitus. Statistical analysis was done using the Bayesian network meta-analysis (NMA). The surface under the cumulative ranking area and median rank were calculated to rank the interventions.

Results. A total of 73 randomized controlled trials with 13 3703 participants were included for the comparisons of 14 interventions. Angiotensin-converting enzyme inhibitor plus angiotensin receptor blocker (ACEI-ARB) ranked first in regression (odds ratio, 62; 95% confidence interval, 5.2 to > 999); ACEI-ARB also ranked first in end-stage renal disease decline (odds ratio, 0.58, 95% confidence interval, 0.39 - 0.85), followed by IGC hemoglobin A1c less than 6.5% (odds ratio, 0.58, 95% confidence interval, 0.36 - 0.90). The ACEI plus calcium channel blocker reduced all-cause death leaving other interventions insignificant (odds ratio, < 0.001; 95% confidence interval, < 0.001 to 0.30). The surface under the cumulative ranking area analyses also matched the result ranks.

Conclusions. Compared with antihypertension interventions, IGC including IGC hemoglobin A1c less than 6.5% and lipid lowering, ACEI-ARB showed the best renoprotective effects.

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INTRODUCTION

The burden of diabetes mellitus (DM) is rapidly rising and current projections estimate the global prevalence of diabetic individuals to rise from 6.4% (285 million) in 2010 to 7.7% (439 million) in 2030.[1] Diabetic kidney disease (DKD) is estimated to affect one-third of individuals with DM and is associated with considerable morbidity and mortality. It is the leading cause of end-stage renal disease (ESRD) worldwide, accounting for nearly half of all patients treated with dialysis.[2] The combination of diabetes and kidney disease is associated with a 4-fold increase in the prevalence of "all-cause death" of DKD.[3,4]

The main therapeutic strategies for DKD involve antihypertension, intensive glucose control (IGC) and lipid lowering. According to the pathogenesis development of DKD, the initial treatment should be IGC hemoglobin A1c less than 7.0%.[5] Blood pressure lowering interventions have been central to the treatment of DKD for decades and improved anti-hypertension, such as monotherapy and combination therapy of Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin

receptor blockers (ARBs), having been credited with decreased prevalence of ESRD over the past 10 years.[6] As for lipid-lowering, β-hydroxy β-methylglutaryl-CoA reductase inhibitors (statins) also inhibit the expression of monocyte chemotactic factor genes and reduce the production of fibrosis factors, thereby delaying the DKD process.[7]

However, the comparative effect of individual interventions on the renal protection of DKD under the three main therapeutic strategies is unclear. Such an important question made it necessary to compare the existing evidence by means of some statistical methods tightly based on renal outcomes (ie, ESRD and all-cause death). Indicators reflecting kidney function include urinary albumin excretion rate or proteinuria, urine albumin-creatinine ratio (ACR), and estimated glomerular filtration rate (GFR).[8-10]

There is an unavoidable constraint to pair-wise meta-analyses when available evidence are not all be used if all the studies included in the analysis do not provide a direct comparison.[11] Network meta-analysis (NMA), also known as mixed treatment comparison, has extended this concept by providing estimates for comparative effectiveness of all related treatments even when no head-to-head comparisons are available.[12] The synthesis of all available evidence (both direct and indirect) also generally improves the accuracy of estimates.[13] Then the NMA allows us to rank the interventions and improve the decision-making frameworks.[14]

In this study, a Bayesian model was used for the first time in NMA, and the comparative effects of antihypertension, IGC, and lipid-lowering were evaluated by combining direct and indirect evidence.

MATERIALS AND METHODS

Study Design

A total of 14 interventions (9 by antihypertension, 3 by IGC, and 1 by lipid-lowering and placebo) were compared. The antihypertensive interventions were made according to the type of drugs, monotherapy or combination, regardless of dose and anti-hypertensive targets. The IGC interventions were implemented based on different targets of glycosylated hemoglobin (HbA1C), grouped into IGC HbA1C less than 6.5%, 6.5% to 7.0%, and 7.0% to 7.5%. Standard glucose control was also regarded as "placebo." Statins are considered another lipid lowering intervention. The NMA integrated data from direct and indirect comparisons of treatment and interventions in trials, comparing commonly used comparators in different trials, to compare all treatment studies. Herein, we reported the meta-analysis according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses statement.[15]

Participants

We selected DM adults with or without kidney disease and were treated in clinical trials that compared any antihypertensive drug including ACEI, ARB, calcium-channel blocker (CCB), β-blocker, diuretic, or renin inhibitor (RI), alone or in combination, with a second antihypertensive drug or combination, placebo, or control. We also selected diabetic patients who were randomized to intensive or standard glucose-lowering regimens or statins. A single variable should be maintained as much as possible in each group. For example, patients with antihypertensive interventions might receive hypoglycemic agents or lipid-lowering drugs to keep blood glucose and lipid biochemistry in normal. Patients in other groups were the same. All the subjects were followed up at least for a median of 2 months. Participants with kidney transplantation or dialysis were excluded.

End Points

Many indicators were related to kidney function (urinary albumin excretion rate or proteinuria, ACR, serum creatinine, etc.). Different indicators recorded in different studies are not the same, some reported the number of patients with regression of urinary albumin excretion rate (reduction of albuminuria by > 30% or > 20% of their baseline or regress to normal),[16] and others might record the dichotomous outcomes about ACR (reduction > 30% or > 20% of their baseline).[17] As long as the article reported the number of improved patients by any indicator, those patients would be summarized to get a total "regression" as the primary end point. The secondary end points were "ESRD" and "all-cause death."

Procedures

The selection criteria were: (a) the original research, (b) articles described the occurrence of

renal function indicators, ESRD or all-cause death, (c) articles provided exact value of events with odds ratio (OR) and 95% confidence interval (CI). The exclusion criteria were: (a) studies comparing different dosages of drugs, (b) systemic review or meta-analysis, (c) studies without exact values or with continuous data. We searched the PubMed, EMBase, and Cochrane Library for articles with comparative interventions on regression, ESRD, and all-cause death in DM. The predefined searching key words were ["diabetes" or "diabetic"] and ["anti-hypertensive" or "blood pressure-lowing" or "blood pressure-reduc*"] and ["glucose control" or "glycemic control"] and ["statin" or "HMGCo-Areductase inhibitor" or "lipid-lowering"] and ["renal" or "kidney" or "nephropathy" or "renoprotection" or "proteinuria" or "albuminuria" or "ESRD" or "end-stage renal kidney"] and "death."

Two reviewers selected studies and extracted data independently. The risk of bias assessment tool created by RevMan 5.2 was conducted mainly according to the following bias: selection, performance, detection, attrition and reporting bias. In case some important studies missed, the authors also searched the references in systemic reviews or meta-analysis articles related to this topic. Data extracted from each article includes: the first author's name, year of publication, baseline condition of subjects, follow-up duration, number of patients, number of regression, number of ESRD, number of all-cause death, types of diabetes, etc.

Statistical Analysis

The data were abstracted and analyzed by STATA (version 14.0, Stata MP), R software using "gemtc" package and WinBUGS (version 1.4.3, MRC Biostatistics Unit, Cambridge, UK). The occurrence of end points was extracted from the selected researches and used to measure the relative effect of various treatments with OR and 95% CI. We conducted traditional pair-wise meta-analyses making direct comparison in randomized controlled trials (RCTs) before the NMA. Calculations in conventional meta-analyses were performed by R software using relative forest plots. NMA was conducted in a Bayesian random-effects model assuming a binomial likelihood and executed using "gemtc" R package which recalls JAGS in R for Markov chain Monte Carlo (MCMC) sampling. Three parallel chains and 50000 samples were obtained after a 50000-sample burn in each chain.[18] Convergence was checked using the Brooks-Gelman-Rubin diagnostic and trace plots.[19,20]

The stability of the results was estimated by sensitivity analyses with discarding each study sequentially. We used surface under the cumulative ranking area (SUCRA) and median rank (MR) to rank the interventions, expressed as a percentage of the efficacies or safety of every intervention relative to an imaginary intervention that is always the best without uncertainty.[21] Thus, larger SUCRA scores might indicate a more effective or safer intervention. We also used Loop-specific inconsistency (used in STATA) and node-splitting approach (used in R with "gemtc" package) to assess the inconsistency that is the actual differences between direct and indirect compassions.[22]

The publication bias assessment was performed via Deek funnel plot asymmetry, Egger test, and Bgger test. Sensitivity analysis was conducted in R.

RESULTS

Characteristics of Included Studies

We identified 7280 unique records from our searches, and 56 RCTs were eligible to be included in our NMA; the selection process details are showed in the Figure 1. Trials included were published between 1988 and 2017, with more than half published after 2000 (Appendix: Table 1). Because we did not compare the dose of the drug, studies comparing different doses of homologues with placebo would be split into 2 arms trials. So the actual number of RCTs was 73. These trials randomized a total of 133703 participants with a sample size ranging from 21 to 11140. Sixteen RCTs (21.9%) were multicenter trials. Of the 57 trials reporting the region(s) in which participants were recruited, 22 (38.6%) recruited participants from North and South America, 21 (36.8%) from Europe, 12 (21.1%) from Asia, 1 (1.8%) from Oceania, and 1 (1.8%) from Africa.

Of the 14 interventions, the number of trials for each direct comparison is from 1 to 26. The direct comparison between ARB and placebo was the most pair appearing in current trials. And placebo was the most often used comparator and was studied in 54 trials (74.0%). Sixty-six trials (90.4%) had 2 treatment arms, 7 (9.6%) had 3 arms. More details are showed in Table 1 (Appendix).

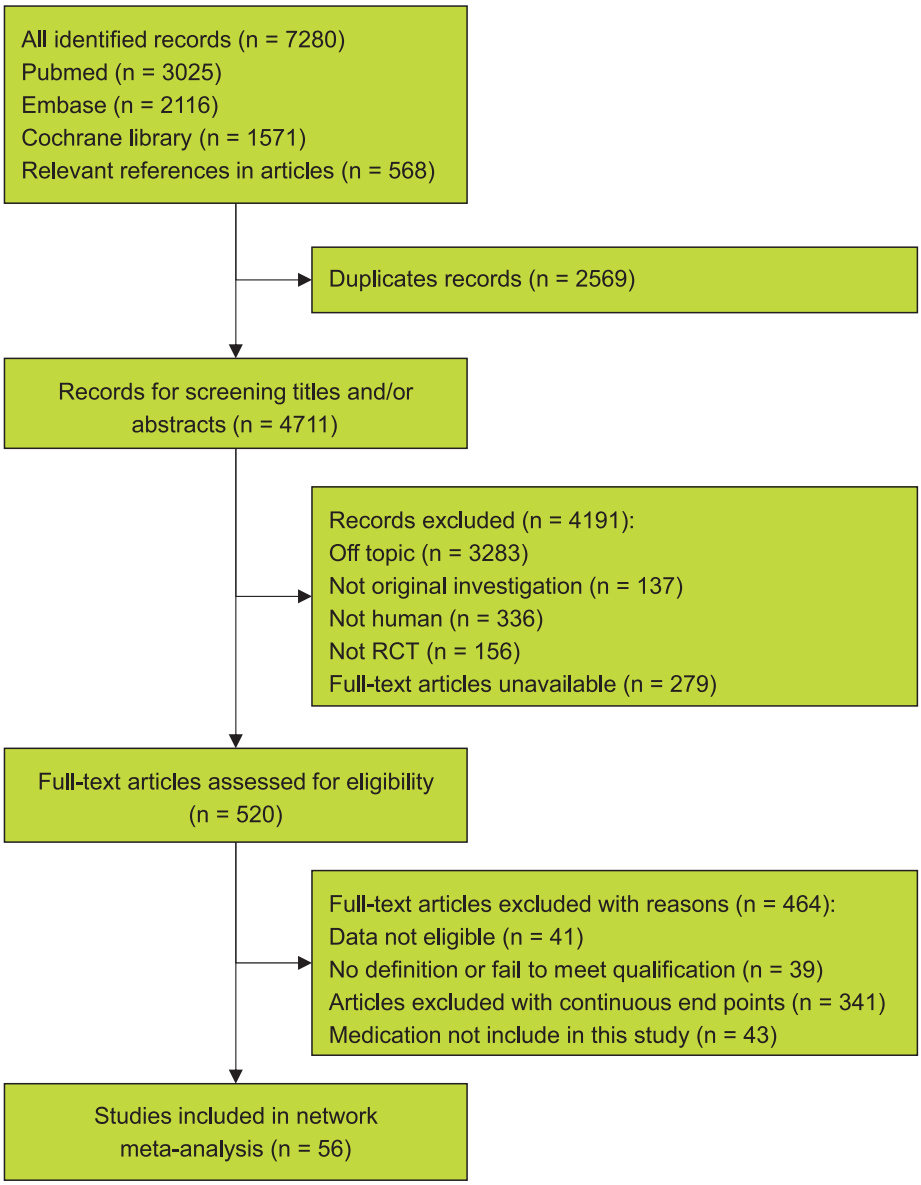

Figure 1. Flow diagram of the study selection process.

Risk of Bias and Network Plot of Direct Comparisons

The overall risk of bias of the included RCTs is showed in Figures 1A and 1B (Appendix). Figure 2 shows the results based on direct comparisons. The size of the nodes (green circles) corresponds to the sample size of interventions. Comparisons are linked with a line, of which the thickness corresponds to the number of trials that assessed the comparison. As shown in the network plot, the number of interventions varied in different subjects. There are 12 interventions for regression, 9 for ESRD and 11 for all-cause death. When consistent with Table 1 (Appendix), the largest sample size for the three end points all belonged to placebo, and ARB together with placebo was the most frequent comparison.

Results of Bayesian Network Meta-Analysis on End Points

First, 50 000 times of iterations was increased to get satisfactory convergence as showed in diagnostic and trace plots (Appendix S2). We compared the comparative effects of all interventions against placebo with OR and 95% CI. Data for direct comparisons and network estimates for regression,

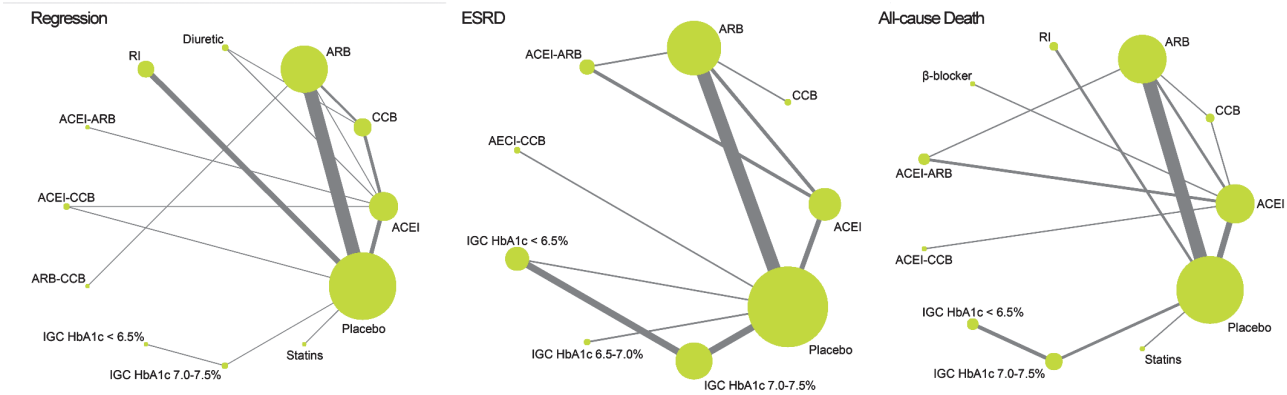

Figure 2. Network plot of treatment comparisons for Bayesian network meta-analysis. The size of the nodes (green circles) corresponds to the sample size of interventions. Comparisons are linked with a line, of which the thickness corresponds to the number of trials that assessed the comparison.

ESRD and all-cause death are summarized in the Appendix S3.

The primary end point. For regression, in pairwise meta-analysis, only ACEI and ARB showed statistical significance compared with placebo, indicating more regression of DKD (OR, 0.15; 95% CI, 0.038 to 0.52; OR, 0.19; 95% CI, 0.10 to 0.34; respectively). Figure 3 showed ACEI-ARB ranked first (OR, 6.2; 95% CI, 5.2 to > 999), followed by ARB-CCB (OR, 16.0; 95% CI, 1.4 to > 999), ARB (OR,

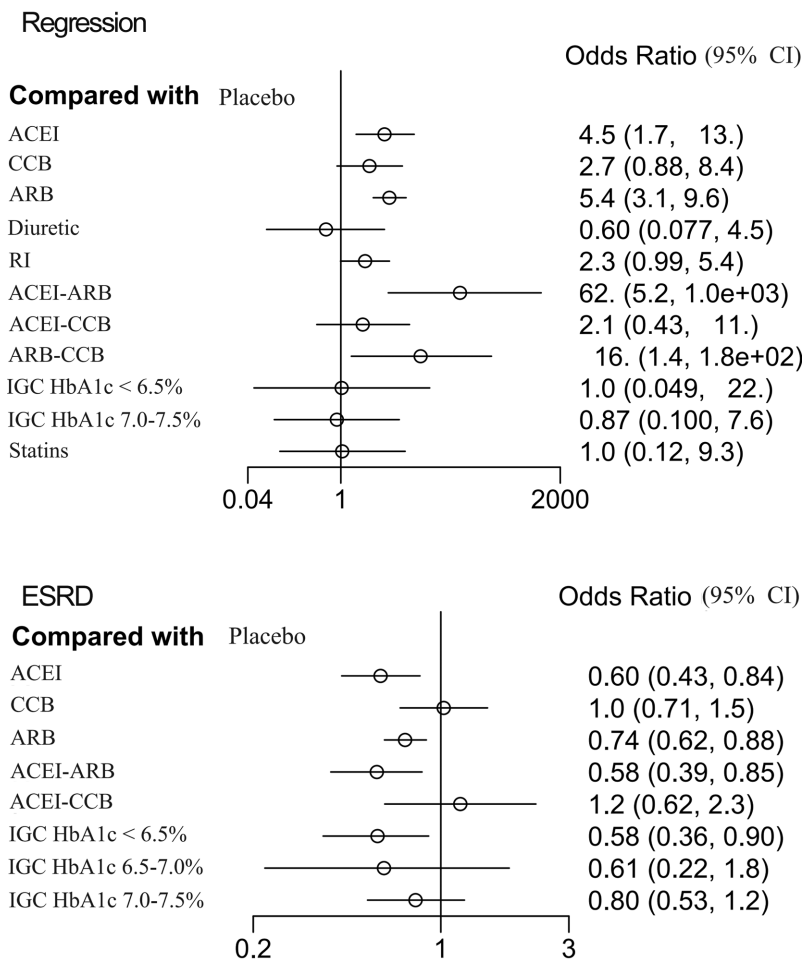

Figure 3. Relative forest plots for efficacy of 11 treatments compared to placebo on regression (the upper) and 8 treatments compared to placebo on the reduction of ESRD (the lower).

5.4; 95% CI, 3.1 to 9.6), and ACEI (OR, 4.5; 95% CI, 1.7 to 13), others (including IGC and statins) showed no statistical significance.

The secondary end points. For ESRD, ACEI and ARB in pair-wise meta-analysis exerted a trend of prevention of ESRD (OR, 1.9; 95% CI, 1.2 to 2.9; OR, 1.3; 95% CI, 1.1 to 1.6; respectively). The IGC HbA1C less than 6.5% showed significant superiority over IGC HbA1C of 7.0% to 7.5% (OR, 1.4; 95% CI, 1.1 to 1.9). Figure 3 also shows ACEI-ARB was the best intervention in the reduction of ESRD (OR, 0.58; 95% CI, 0.39 to 0.85), followed by IGC HbA1C less than 6.5% (OR, 0.58; 95% CI, 0.36 to 0.90), ACEI (OR, 0.60; 95% CI, 0.43 to 0.84), and ARB (OR, 0.74; 95% CI, 0.62 to 0.88). Whereas the effects of other interventions were not significant, such as IGC HbA1C of 6.5% to 7.0% (OR, 0.61; 95% CI, 0.22 to 1.8) and IGC HbA1C of 7.0% to 7.5% (OR, 0.80; 95% CI, 0.53 to 1.2).

For all-cause death, all interventions available were not significant in pair-wise meta-analysis. As depicted in Figure 4A, only ACEI-CCB showed a trend of reduction of all-cause death (OR, < 0.001; 95% CI, < 0.001 to 0.30). There were no statistical differences among other interventions (including IGC and statins) in the occurrence of all-cause death.

Surface Under Cumulative Ranking Area Probabilities of Meaningful Interventions on End Points

The ranking probabilities for all the interventions are presented in Appendix S4. The graphical and value results (Figure 5; Appendix S4A) of estimated SUCRA and MR indicated that ACEI-ARB (SUCRA = 83.7%, MR = 2.08) was the best treatment for regression of DKD, followed by ARB-CCB (SUCRA = 77.7%, MR = 3.5), ARB and ACEI monotherapy (SUCRA = 74.8%, MR = 3.8;

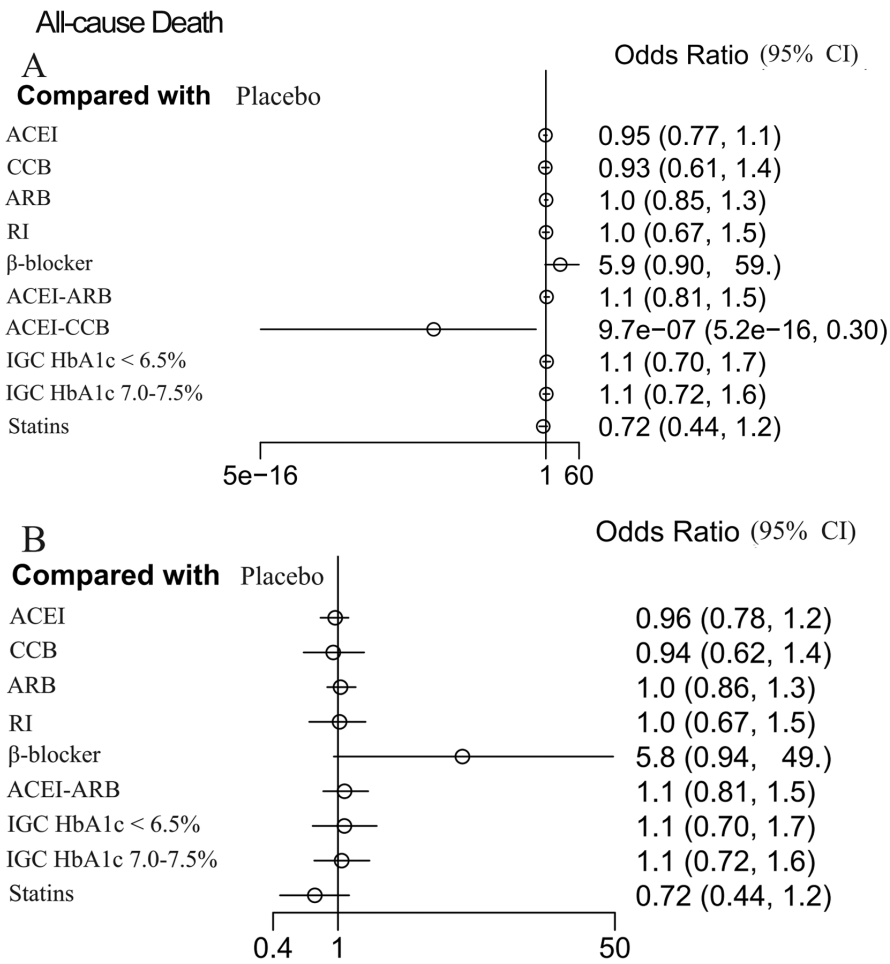

Figure 4. Relative forest plots for efficacy of 10 treatments compared to placebo on all-cause death. A, ACEI-CCB included; B, ACEI-CCB excluded.

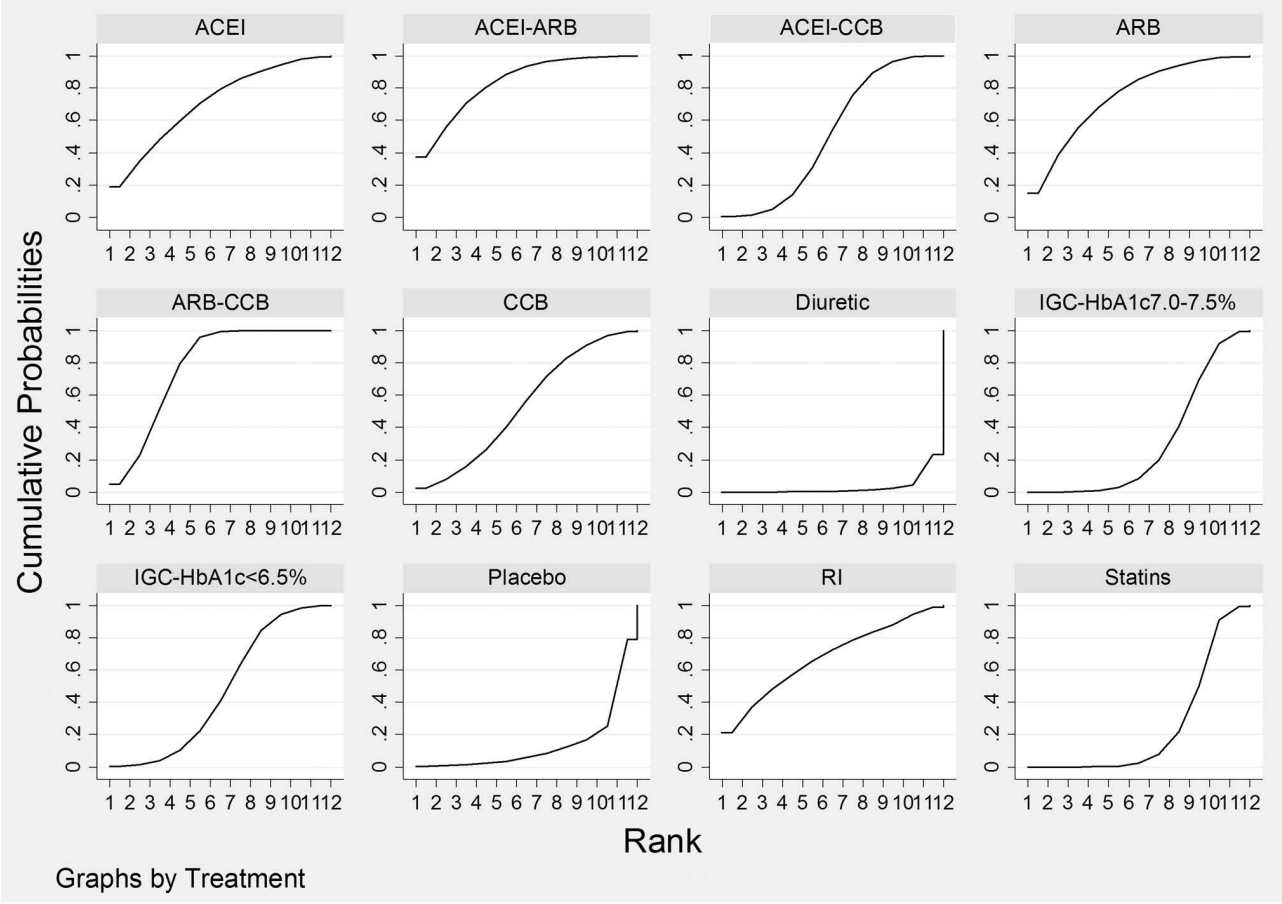

Figure 5. Graphical results of estimated cumulative ranking area and median rank on regression.

SUCRA = 71.0%, MR = 4.2; respectively). Diuretics ranked last (SUCRA = 2.9%, MR = 11.7).

As seen in Appendix S4B on prevention of ESRD, ACEI-AEB (SUCRA = 79.5%, MR = 2.6) was the best treatment, followed by IGC HbA_{1C} < 6.5% (SUCRA = 77.2%, MR = 2.8), ACEI and ARB monotherapy (SUCRA = 77.7%, MR = 2.8; SUCRA = 53.0%, MR = 4.8).

For the reduction of all-cause death (Appendix S4C), all interventions apart from ACEI-CCB (SUCRA = 100%, MR = 1.0) were not significant, we could draw that there was no obvious difference among the current interventions for the prevention against all-cause death.

Heterogeneity Analysis on End Points

It was undeniable that there was an apparent heterogeneity in the comparision between ARB and placebo for regression of DN (pair-wise I^2 = 90.7%, network I^2 = 90.2%; Appendix S5A). We found that most trials with ARB and placebo were spilt from big RCTs with 3 arms where different doses of homologues were compared with placebo. This might explain the source of the big heterogeneity, but data were scant for some treatments, making it difficult to prove. There was little heterogeneity in the results of ESRD and all-cause death (Appendixes S5B and S5C).

Inconsistency Between the Direct and Indirect Evidence

Using the loop-specific approach, inconsistency factor (IF) closer to "0" was more likely to show that there was no inconsistency,[78] except for only one loop on regression (ACEI – ACEI-CCB – Placebo; IF = 1.07, 95% CI, 0.35 to 1.79; Appendix S6A). Using the node-splitting approach, we found no statistically significant value (Appendix S6), indicating that the direct and indirect evidence were consistent.

Publication Bias and Sensitivity Analysis

The results of the comparison-adjusted funnel

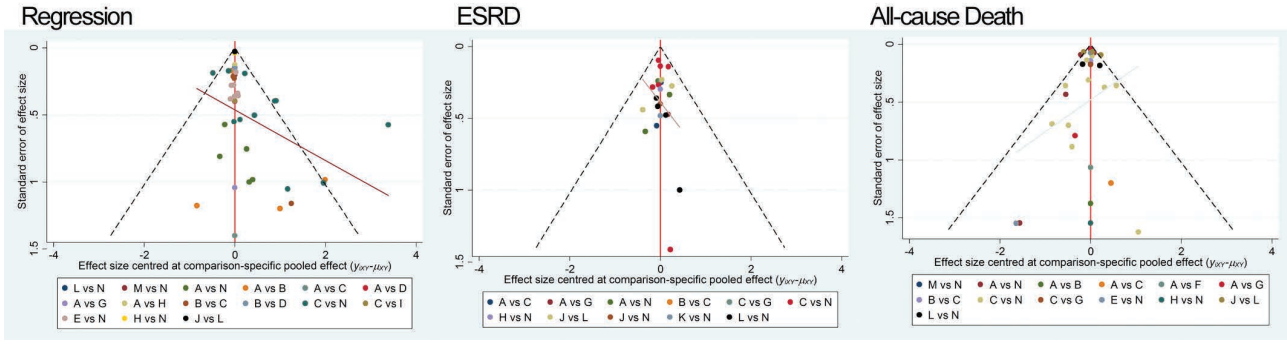

Figure 6. Publication bias of funnel plot of included trials (A: ACEI, B: CCB, C: ARB, D: Diuretic, E: RI, F: β-blocker, G: ACEI-ARB, H: ACEI-CCB, I: ARB-CCB, J: HbA1c < 6.5%, K: IGC HbA1c 6.5 - 7.0%, L: IGC HbA1c 7.0 - 7.5%, M: Statins, N: Placebo).

plots didn't reveal evidence of apparent asymmetry (Figure 6), but egger's test showed there were some publication bias (Appendix S7A) for regression. A sensitivity analysis was conducted to examine the impact of studies according to the treatment effects on all-cause death. Allowing for there was only one trial with ACEI-CCB whose sample size was just only 138, we got rid of this trial to get the new results (Figure 4B) with no significant differences among the various interventions like before, indicating the result for all-cause death was broadly robust.

DISCUSSION

According to the data from the International Diabetes Federation, there were about 382 million people with diabetes in 2013), and this number may rise to 592 million by 2035.[79] The current main therapy for DKD including anti-hypertension, IGC and lipid-lowering which improve the renal outcomes.[5-7] However, the comparative efficacy of the three main therapeutic strategies on renoprotection remains unavailable. To address the issue, we firstly summarized renal indicators to get a total "regression." For the first time, we conducted this study to assess the comparative effects of antihypertension, IGC, and lipid-lowering on renoprotection based on regression, ESRD and all-cause death.

The results from Bayesian NMA indicated that ACEI-ARB ranked first in regression, followed by ARB-CCB which was consistent with the previous study,[80] ARB and ACEI. However, IGC and lipid-lowering therapy showed insignificance and this was different from the previous study,[81] in which Coca and coworkers reported that IGC reduced the risk of microalbuminuria and macroalbuminuria.

As for the reduction of ESRD, although both the ORs of ACEI-ARB and IGC HbA_{1C} < 6.5% were 0.58, ACEI-ARB ranked first (SUCRA = 79.5%, MR = 2.6), superior to IGC HbA1C less than 6.5% (SUCRA = 77.2%, MR = 2.8). The possible explanation was that the smaller 95% CI for the former (0.39 to 0.85) versus the latter (0.36 to 0.90), and more reliable the evidence would be found in literature.[82] Figure 3 showed IGC HbA1C less than 6.5% (OR, 0.58; 95% CI, 0.36 to 0.90) had priority over IGC HbA1C of 6.5% to 7.0% (OR, 0.61; 95% CI, 0.22 to 1.8), and IGC HbA1C of 7.0% to 7.5% (OR, 0.80; 95% CI, 0.53 to 1.2) in the reduction of ESRD, this result indicated that lower HbA1C might enable better therapeutic effect, which even exceed monotherapy of ACEI (OR, 0.60; 95% CI, 0.43 to 0.84) or ARB (OR, 0.74; 95% CI, 0.62 to 0.88). It is similar to the results in pair-wise meta-analysis that IGC HbA1C less than 6.5% had significant superiority over IGC HbA1C of 7.0% to 7.5% (Appendix S3B). However, what should not be ignored was that IGC conversely increased the risk of hypoglycemia (< 2.8 mmol/L) which was an important cause of death or disability in diabetic patients.[70]

As for all-cause death, only ACEI-CCB reduced all-cause death compared with placebo. There was only one trial with ACEI-CCB, and the sample size was only 138, so a sensitivity analysis was conducted to examine the credibility of the results, revealing that there was no obvious difference between other interventions on all-cause death decline.

Why ACEI-ARB showed good therapeutic effects on regression and the reduction of ESRD, yet poor performance in the prevention of all-cause death? This might be due to the increased prevalence of acute kidney injury and hyperkalemia when ACEI

and ARB were combined.[83] Another issue worth noting was that the anti-hypertensive target of ACEI-ARB in most trials was under (130 - 140)/80 mmHg, which was less intensive than that of ACEI-CCB (under 120/80 mmHg). Interestingly, ACEI-ARB was superior to ACEI-CCB in regression and ESRD decline, which showed that the better therapeutic effect was due to the application of anti-hypertension agents rather than the target blood pressure control.

Our study has some potential limitations. Firstly, we cannot classify the baseline of renal function into different stages at the beginning of the NMA. Secondly, the exploration of the source of bias and heterogeneity on account of scant evidence relating to endpoints should be further discussed. Thirdly, we should compare more end points to conduct a more practical and comprehensive analysis. The last but not least was that due to insufficient data available, it is necessary to perform larger size, multi-centered RCTs to acquire more robust results.

CONCLUSIONS

Compared with antihypertension interventions, IGC including IGC HbA1c less than 6.5% and lipid-lowering, ACEI-ARB showed the best renoprotective effects in patients with DM.

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CONFLICT OF INTEREST

None declared.

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