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ORIGINAL ARTICLE

Effects of mineralocorticoid receptor antagonists on the progression of diabetic nephropathy

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Keywords
Diabetic nephropathy, Meta- analysis, Mineralocorticoid receptor antagonist

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ABSTRACT

Aims/Introduction: We aimed to evaluate the potential benefits and adverse effects of adding a mineralocorticoid receptor antagonist (MRA) to angiotensin-converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARB), as standard treatment in patients with diabetic nephropathy.

Materials and Methods: We scanned the Embase, PubMed and Cochrane Central Register of Controlled Trials databases for human clinical trials published in English until June 2016, evaluating renal outcomes in patients with diabetic nephropathy.

Results: A total of 18 randomized controlled trials involving 1,786 patients were included. Compared with ACEI/ARB alone, co-administration of MRA and ACEI/ARB significantly reduced urinary albumin excretion and the urinary albumin–creatinine ratio (mean difference −69.38, 95% confidence intervals −103.53 to −35.22, $P < 0.0001$; mean difference −215.74, 95% confidence intervals −409.22 to −22.26, $P = 0.03$, respectively). A decrease of blood pressure was also found in the co-administration of MRA and ACEI/ARB groups. However, we did not observe any improvement in the glomerular filtration rate. There was a significant increase in the risk of hyperkalemia on the addition of MRA to ACEI/ARB treatment (relative risk 3.74, 95% confidence intervals 2.30–6.09, $P < 0.00001$).

Conclusions: These findings suggest that co-administration of MRA and ACEI/ARB has beneficial effects on renal outcomes with increasing the incidence of hyperkalemia.

INTRODUCTION

Diabetic nephropathy (DN) is the leading cause of chronic kidney disease (CKD) in developed countries, and its prevalence has increased dramatically over the past decades. Although there has been a significant progress in slowing the progression of DN, renal dysfunction and the development of end-stage renal disease remain major concerns in diabetes[1,2]. However, a failure to achieve adequate anti-albuminuric renoprotective effects even after the administration of renin–angiotensin–aldosterone system inhibitors has been reported. An inadequate blockade of aldosterone could be one of the reasons why long-term administration of renin–angiotensin–aldosterone system inhibitors has not been effective in patients with DN. Mineralocorticoid receptor (MR) blockade is emerging as a new paradigm in diabetes[3]. In a number of animal models of type 1 and type 2 diabetes, studies have shown a beneficial effect of spironolactone, a MR antagonist (MRA), as well as that of the more selective MRA, eplerenone[4–7]. The effects of these agents in reducing albuminuria or urinary albumin excretion (UAE) and inhibiting the progression of DN have been evaluated in clinical trials, with small sample sizes. Finerenone is a novel non-steroidal MRA with a higher selectivity towards the MR compared with spironolactone, and a stronger MR-binding affinity compared with eplerenone. The addition of finerenone to angiotensin-converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARB) therapy resulted in an improvement of the urinary albumin–creatinine ratio (UACR) in patients with DN[8]. However, the risk of life-threatening hyperkalemia after MRA treatment in patients with DN could severely limit the clinical use of this drug.

Although a number of studies have examined the effects of spironolactone on DN, to date, no meta-analysis has been carried out to examine all MRAs, especially the novel MRAs, and their impact on DN progression. The objectives of the present study were to analyze the renal outcomes, the efficacy and the safety of adding an MRA to ACEI/ARB treatment of patients with DN, and to increase the understanding of dual blockade

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with co-administration of MRA and ACEI/ARB in this patient population.

MATERIALS AND METHODS

Search strategies

The Embase, PubMed and Cochrane Central Register of Controlled Trials databases (up to June 2016) were searched for clinical trials published in English, involving human subjects and evaluating the effect of MR blockade in patients with DN. The search terms used were 'spironolactone,' 'eplerenone,' 'finerenone,' 'mineralocorticoid receptor antagonist' 'aldactone,' 'mineralocorticoid receptor blockade,' 'aldosterone antagonist,' 'diabetic nephropathy,' 'albuminuria' 'glomerular filtration rate' and 'proteinuria.' The search was supplemented by reviewing lists of references, manual searching of relevant journals and by direct correspondence with authors. Case reports, commentaries, review articles, abstracts, case series and single-group cohort studies were excluded from this review. All subjects were patients with DN, and there were no restrictions on sample size or duration of follow up. The end-points identified in these studies included changes in UAE, UACR, glomerular filtration rate (GFR), systolic blood pressure (SBP) and diastolic blood pressure (DBP). Adverse effects, such as hyperkalemia, were also reviewed.

Data collection

Two reviewers (LJS and YNS) independently carried out data extraction. The search strategy was used to obtain titles and abstracts of studies relevant to the review. The reviewers independently assessed the retrieved abstracts and the full text, rejecting studies that did not meet the inclusion criteria. Disagreements between the reviewers were resolved by consensus or by a third investigator (GRJ).

Data on the first author, year and country of publication, study design, classification of MRA, treatment duration, sample size, and study end-point were collected. The indexes of renal outcome (UAE, UACR, GFR) and BP were extracted. Furthermore, data on safety and adverse events, including hyperkalemia, were also included.

Assessment of risk of bias

The risk of bias in the included studies was assessed independently by two authors (LJS and YNS). Random sequence generation, allocation concealment, blinding of participants and

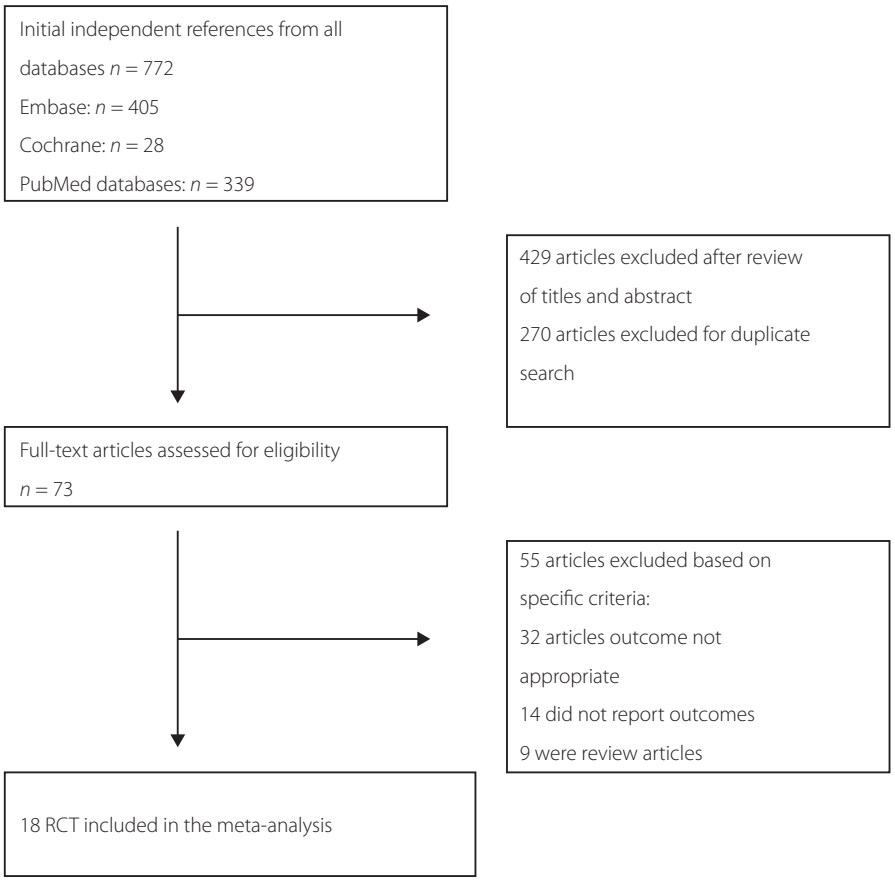

Figure 1 | Study flow chart for the process of selecting the final 18 randomized controlled trials (RCT).

Table 1 | Basic characteristics of diabetic nephropathy patients included studies

No	Author	Year	Country	Study design	Treatment number	Control number	Classification of MRA	Study duration	UAE	UACR	GFR	BP	Hyperkalemia
1	Mehdi *et al.*	2009	USA	Parallel RCT	27	26	Spironolactone	48 weeks	NR	R	R	N	R
2	Nielsen *et al.*	2012	Denmark	Cross-over RCT	21	21	Spironolactone	60 days	R	NR	R	R	R
3	Ogawa *et al.*	2006	Japan	Parallel RCT	20	10	Spironolactone	12 months	NR	R	NR	R	R
4	Rossing *et al.*	2005	Denmark	Cross-over RCT	21	21	Spironolactone	8 weeks	R	NR	R	R	R
5	Saklayen *et al.*	2008	USA	Cross-over RCT	24	24	Spironolactone	7 months	NR	R	R	R	R
6	Schjoedt *et al.*	2005	Denmark	Cross-over RCT	20	20	Spironolactone	2 months	R	NR	R	R	R
7	Schjoedt *et al.*	2006	Denmark	Cross-over RCT	20	20	Spironolactone	2 months	R	NR	R	R	R
8	Meiracker *et al.*	2006	Netherlands	Parallel RCT	24	29	Spironolactone	12 months	N	R	R	R	R
9	Hase *et al.*	2013	Japan	Parallel RCT	18	15	Spironolactone	24 weeks	NR	R	R	R	NR
10	Esteghamati *et al.*	2013	Iran	Parallel RCT	52	45	Spironolactone	18 months	R	NR	R	R	R
11	Momeni *et al.*	2015	Iran	Parallel RCT	20	20	Spironolactone	3 months	R	NR	R	R	R
12	Nielsen *et al.*	2013	Denmark	Cross-over RCT	69	69	Spironolactone	60 days	R	NR	R	R	NR
13	Ziaee *et al.*	2013	Iran	Parallel RCT	29	31	Spironolactone	12 weeks	NR	R	R	R	R
14	Buren *et al.*	2014	USA	Parallel RCT	27	27	Spironolactone	48 weeks	NR	NR	NR	NR	R
15	Kato *et al.*	2015	Japan	Parallel RCT	26	26	Spironolactone	8 weeks	N	R	N	R	R
16	Epstein *et al.*	2002	USA	Parallel RCT	67	74	Eplerenone	24 weeks	NR	N	NR	R	R
17	Epstein *et al.*	2006	USA	Parallel RCT	86	91	Eplerenone	12 weeks	NR	N	R	N	R
18	Bakris *et al.*	2015	23 countries	Parallel RCT	727	94	Finerenone	90 days	NR	R	R	N	R

BP, blood pressure; GFR, glomerular filtration rate; N, No numeric data; NR, not-reported; R, reported; RCT, randomized controlled trial, UACR: urinary albumin–creatinine ratio; UAE, urinary albumin excretion.

personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other potential sources of bias were assessed using the risk of bias assessment tool, and discrepancies were resolved by discussion with a third investigator (GRJ).

Statistical analysis

Analyses were carried out using Revman 5.3 (The Cochrane Collaboration, London, UK). For dichotomous outcomes (hyperkalemia), results were expressed as relative risks (RR) with 95% confidence intervals (CI). Continuous variables (UAE, UACR, BP and GFR) were analyzed using the mean difference (MD) and 95% CI. Statistical heterogeneity was measured using the I^2-statistic and the χ^2-test. Heterogeneity was not considered to be significant when I^2 was <50%, whereas $I^2 > 50\%$ was considered an indication of statistically significant heterogeneity among the included studies. Data were pooled using a fixed-effects model when I^2 was <50%. We chose the random-effects model to analyze data when I^2 was >50%. A *P*-value <0.05 for any test or model was considered statistically significant.

Sensitivity analyses (excluding 1 study at a time) were carried out to assess the contribution of the individual trials to the pooled effect estimates by sequentially omitting each trial. Forest plots were used for graphic representation of the data.

RESULTS

Search results

The combined search of the Embase, PubMed and Cochrane Central Register of Controlled Trials databases identified 772

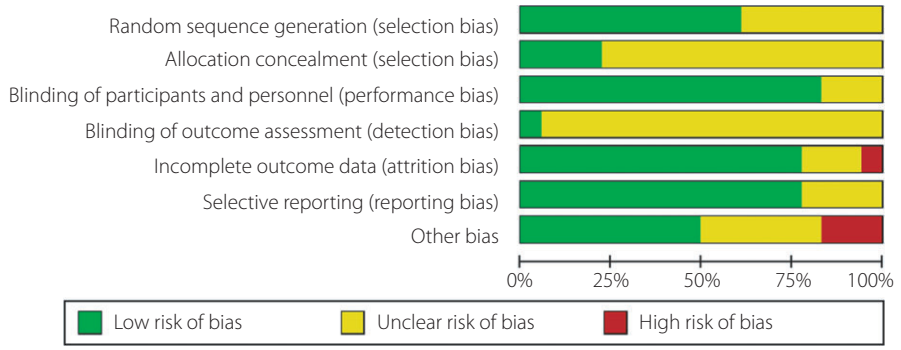

Figure 2 | Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

citations. We excluded 429 articles after a review of the title and abstract, and 270 articles because of a duplication of studies; 73 articles were retrieved for a detailed evaluation, and 18 randomized controlled trials (RCTs) involving 1,786 patients satisfying the inclusion criteria were finally analyzed in a meta-analysis published between 2002 and 2015. The process used to select studies for the meta-analysis is shown in Figure 1. Table 1 shows the baseline characteristics of patients with DN in each trial included in the present study.

Risk of bias

The risks of bias in the included studies are shown in Figures 2 and 3. Random sequence generation was unclear in seven studies, and allocation concealment was adequate in four out of 18 trials (22.2%) and unclear in the remaining 14 studies (77.8%). Blinding of participants was unclear in three studies, and outcome assessors blinding was clear in only one study. Incomplete outcome was clear in 14 studies (77.8%) and unclear in three studies. There was selective reporting in 14 studies. Seven studies were unclear in other biases. Publication bias was not evident in the present study.

Study outcomes

Effects of MRA on Proteinuria in Patients with DN

There was a significant reduction in UAE after MRA plus ACEI/ARB therapy (7 studies, 287 patients; MD −69.38, 95% CI: −103.53 to −35.22, $P < 0.0001$) compared with ACEI/ARB monotherapy[9–15]. No significant heterogeneity was observed between the trials included in this analysis ($\chi^2 = 7.84$, $P = 0.25$, $I^2 = 23\%$). Forest plots showing the effect of MRA plus ACEI/ARB on UAE changes are shown in Figure 4a.

Of the 18 trials, just four recorded UACR from baseline to the end of the study[16–19]. The results showed that MRA plus ACEI/ARB therapy, compared with ACEI/ARB monotherapy, significantly improved UACR in patients with DN (MD −215.74, 95% CI: −409.22 to −22.26, $P = 0.03$; Figure 4b). We chose a random model, because obvious heterogeneity was found in this analysis ($\chi^2 = 61.09$, $P < 0.00001$, $I^2 = 95\%$). Three studies reported UACR percentage change from the baseline, and the differences between the groups were significant (MD −14.71, 95% CI: −29.03 to −0.39, $P = 0.04$)[20–22]. We found no heterogeneity in this analysis ($\chi^2 = 1.47$, $P = 0.48$, $I^2 = 0\%$; Figure 4c).

Effects of MRA on GFR in patients with DN

Compared with ACEI/ARB monotherapy, MRA plus ACEI/ARB therapy did not improve GFR in 11 RCTs (MD −2.48, 95% CI: −4.96 to 0.00, $P = 0.05$)[9–15,17–20], and no heterogeneity was found in this analysis ($\chi^2 = 3.73$, $P = 0.96$, $I^2 = 0\%$; Figure 5a). No significant improvement in GFR change from the baseline to the end of the study was observed after MRA plus ACEI/ARB therapy, compared with ACEI/ARB monotherapy (MD 4.32, 95% CI: −3.58 to 12.23, $P = 0.28$)[21,22], and heterogeneity was found in this analysis (Figure 5b).

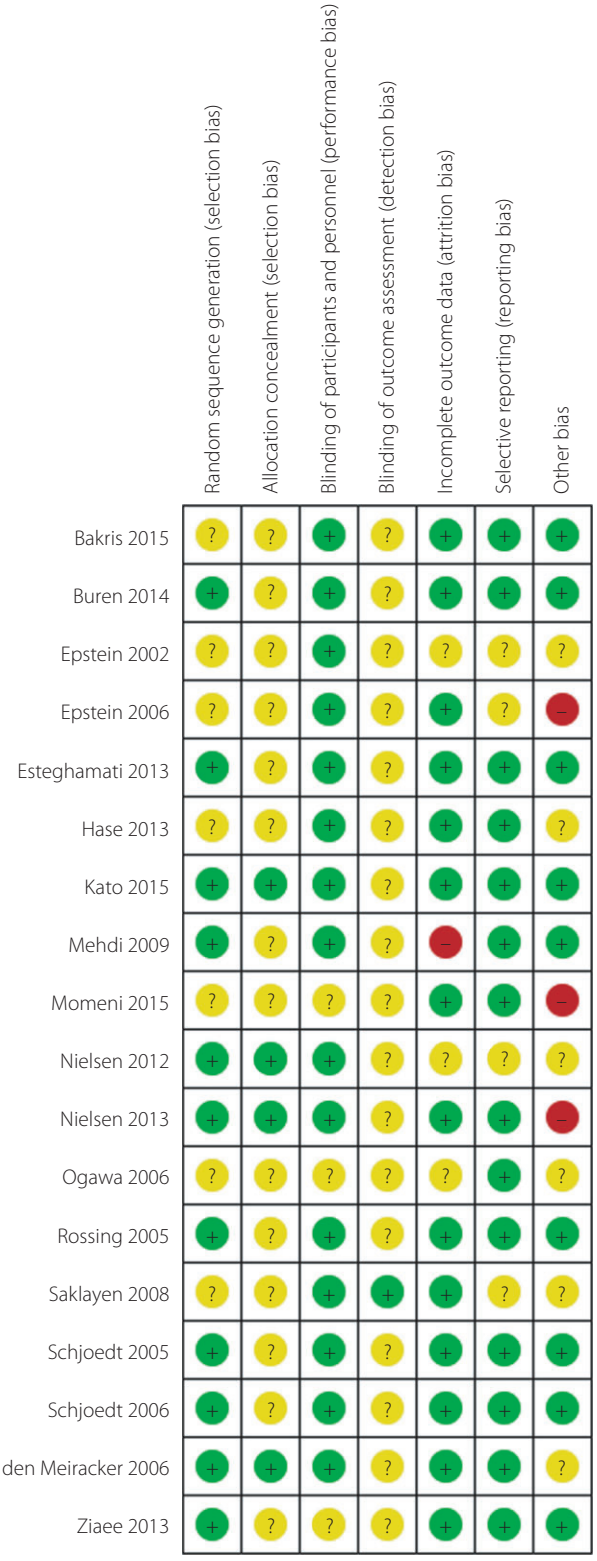

Figure 3 | Risk of bias summary: review authors' judgements about each risk of bias item for each included study. Green refers to a low risk of bias, yellow refers to an unclear risk of bias, and red refers to a high risk of bias.

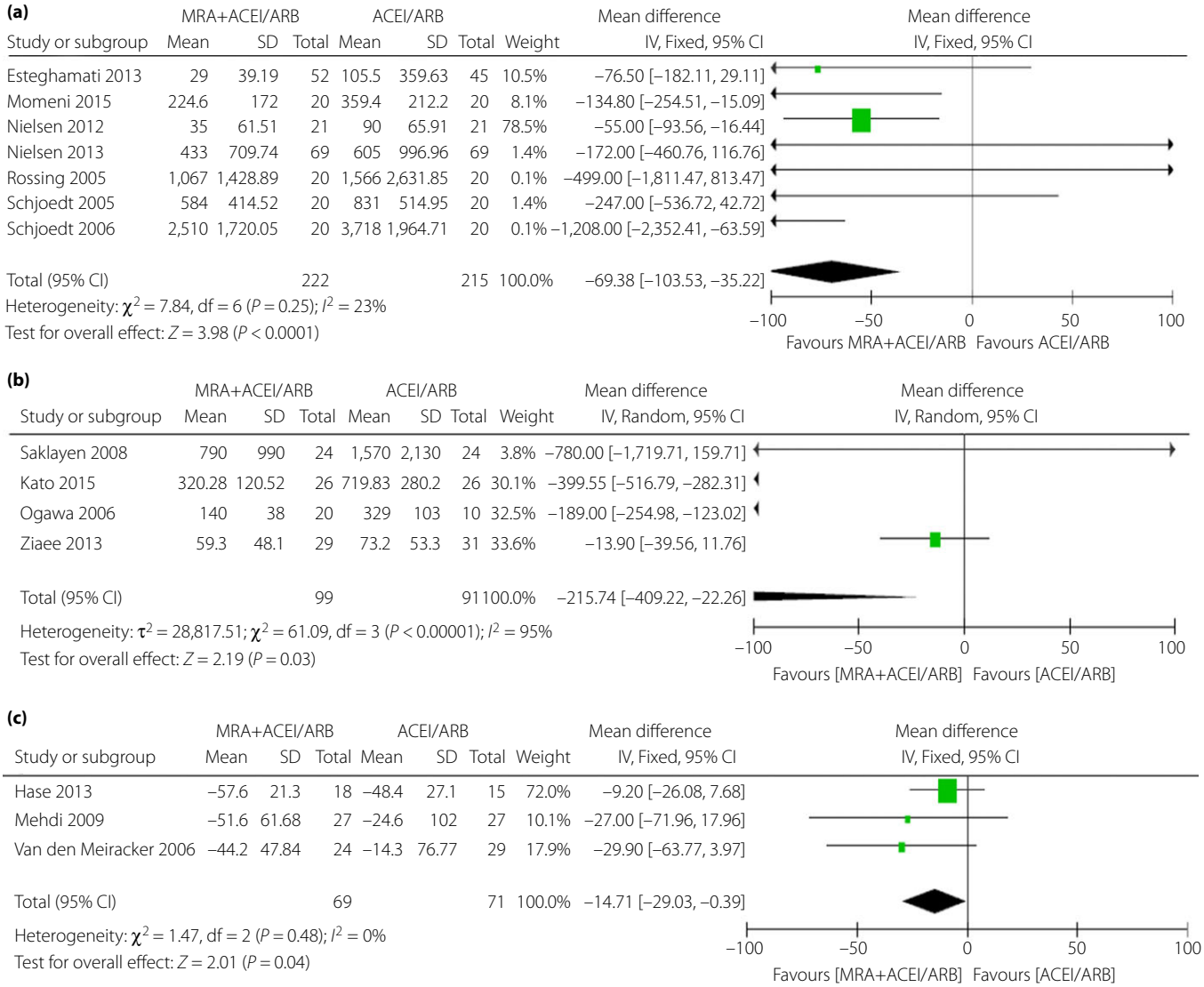

Figure 4 | Forest plot of therapeutic effect on proteinuria in patients with diabetic nephropathy, pooled mean difference and 95% confidence interval (CI) for mineralocorticoid receptor antagonist (MRA) plus angiotensin-converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARB) therapy vs ACEI/ARB monotherapy. (a) Urinary albumin excretion (UAE) value at the end of the study. (b) Urinary albumin–creatinine ratio (UACR) value at the end of the study. (c) UACR percentage change from the baseline.

Effects of MRA on BP in patients with DN

SBP and DBP were recorded in 296 patients receiving MRA plus ACEI/ARB therapy, and in 281 patients receiving ACEI/ARB monotherapy[9–13,15–18,20]. It is important to note that SBP and DBP were significantly decreased in MRA plus ACEI/ARB therapy, compared with ACEI/ARB monotherapy in patients with DN (MD −5.61, 95% CI: −9.38 to −1.84, $P = 0.004$; MD −2.17, 95% CI: −4.23 to −0.11, $P = 0.04$, respectively). We found obvious heterogeneity in this analysis ($\chi^2 = 29.05$, $P = 0.006$, $I^2 = 69\%$; $\chi^2 = 31.31$, $P = 0.0003$, $I^2 = 71\%$, respectively; Figure 6a,b). Just three RCTs recorded BP changes from the baseline to the end of the study[13,21,22]. We also found that MRA plus ACEI/ARB therapy significantly improved the SBP change and the DBP change from the baseline to the end of the study (MD −4.83, 95% CI: −9.50 to −0.16, $P = 0.04$; MD −3.27, 95% CI: −5.99 to −0.56, $P = 0.02$, respectively), and no heterogeneity was found in this analysis ($\chi^2 = 1.10$, $P = 0.58$, $I^2 = 0\%$; $\chi^2 = 0.71$, $P = 0.70$, $I^2 = 0\%$, respectively; Figure 6c,d).

Effects of MRA on hyperkalemia in patients with DN

As shown in Figure 7, the incidence of hyperkalemia after the MRA plus ACEI/ARB therapy was significantly higher than that after ACEI/ARB monotherapy (16 studies, 1,684 patients; RR 3.74; 95% CI: 2.30 to 6.09; $P < 0.00001$)[9–14,16–21,23–26]. No significant heterogeneity was observed among the trials included in this analysis ($\chi^2 = 8.98$, $P = 0.62$, $I^2 = 0\%$).

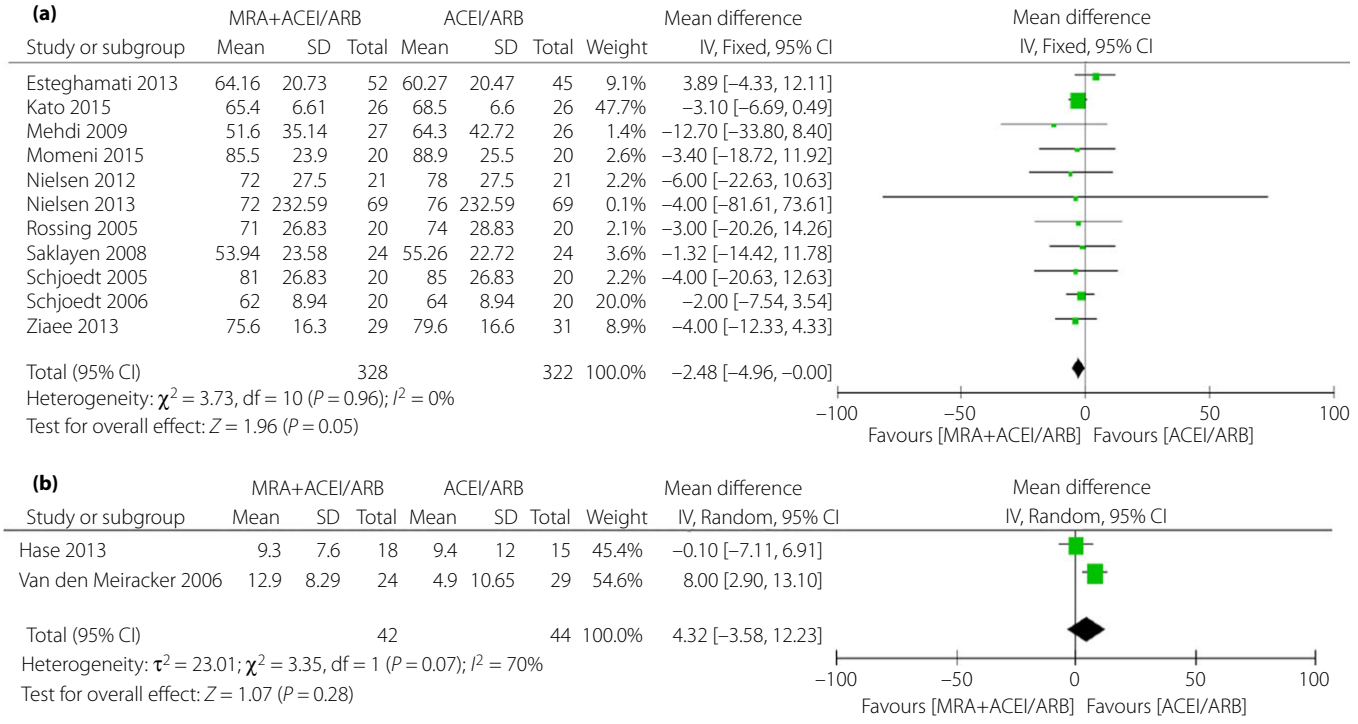

Figure 5 | Forest plot of therapeutic effect on glomerular filtration rate (GFR) in patients with diabetic nephropathy, pooled mean difference and 95% confidence interval (CI) for mineralocorticoid receptor antagonist (MRA) plus angiotensin-converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARB) monotherapy. (a) GFR value at the end of the study. (b) GFR change from the baseline to the end of the study.

DISCUSSION

The present findings show that MRA plus ACEI/ARB therapy, compared with ACEI/ARB monotherapy, significantly improved the UAE and UACR in patients with DN. We also observed a significant reduction in the SBP and DBP in the present study population. However, MRA plus ACEI/ARB therapy does not seem to improve the GFR, which is an important index of renal function. There was a significant difference in the incidence of hyperkalemia between the MRA plus ACEI/ARB therapy patients and the ACEI/ARB monotherapy patients.

DN is a leading cause of chronic kidney disease worldwide. Although efforts have been made to develop novel therapeutic approaches, DN remains a severe disease condition with high rates of morbidity and mortality. An inadequate blockade of aldosterone might fail to achieve adequate anti-albuminuric effects in patients with DN. Studies show that renin–angiotensin–aldosterone system blockade with ACEI/ARB alone sometimes does not achieve adequate renoprotective effects and does not reduce the progression of kidney disease, despite therapy[27]. There is increasing evidence suggesting that the use of MRA in combination with ACEI/ARB has a protective effect on CKD patients; however, this combination treatment still requires further investigation[28,29]. Several studies have reported the effects of spironolactone therapy on renal outcomes in patients with CKD[30–32]. The available data confirmed the protective effects of MRA plus ACEI/ARB treatment on major renal events in CKD patients; however, these studies were not limited to DN patients and did not include a novel MRA, such as finerenone. The present study focused on a 'DN' population, and specifically analyzed three MRAs including finerenone. The current data about finerenone on DN are very limited, only one study was involved in our analysis, so our pool results were consistent with previous studies.

UAE and UACR are considered important markers for proteinuria. Increased UAE or UACR can accelerate the progression of DN, and a reduction in UAE or UACR has been associated with a favorable effect on renal outcome. Our pooled analysis of these studies showed a significant improvement in the UAE and UACR after MRA plus ACEI/ARB therapy compared with their values after ACEI/ARB monotherapy. The overall findings are consistent, to a certain extent, with previous studies. In 2006, Epstein *et al.*[25] reported that compared with ACEI monotherapy, co-administration of eplerenone with an ACEI significantly reduced the UACR in patients with DN; however, we did not include this RCT in our UACR analysis, because we were unable to obtain detailed data from the authors. Some studies showed beneficial effects of MRAs on

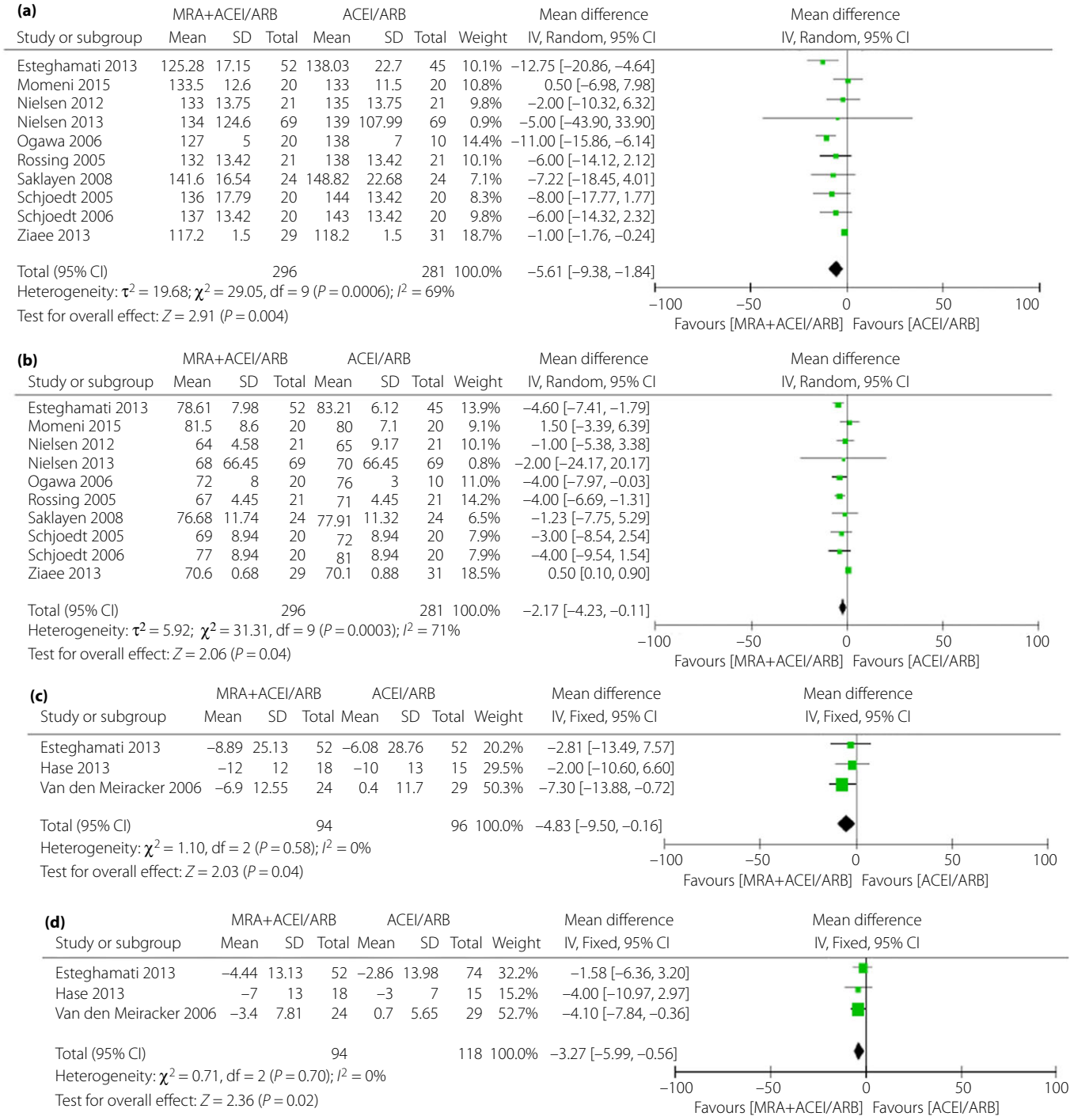

Figure 6 | Forest plot of therapeutic effect on blood pressure in patients with diabetic nephropathy, pooled mean difference and 95% confidence interval (CI) for mineralocorticoid receptor antagonist (MRA) plus angiotensin-converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARB) monotherapy. (a) Systolic blood pressure value at the end of the study. (b) Diastolic blood pressure value at the end of the study. (c) Systolic blood pressure change from baseline to the end of the study. (d) Diastolic blood pressure change from baseline to the end of the study.

proteinuria; however, these studies did not include data for a combined MRA plus ACEI/ARB treatment. Therefore, we did not include these studies in our analysis[33,34]. Thus, the present analysis was limited owing to insufficient data on proteinuria parameters in the trials included in this study. Additionally, the number of the trials included in this study was too small.

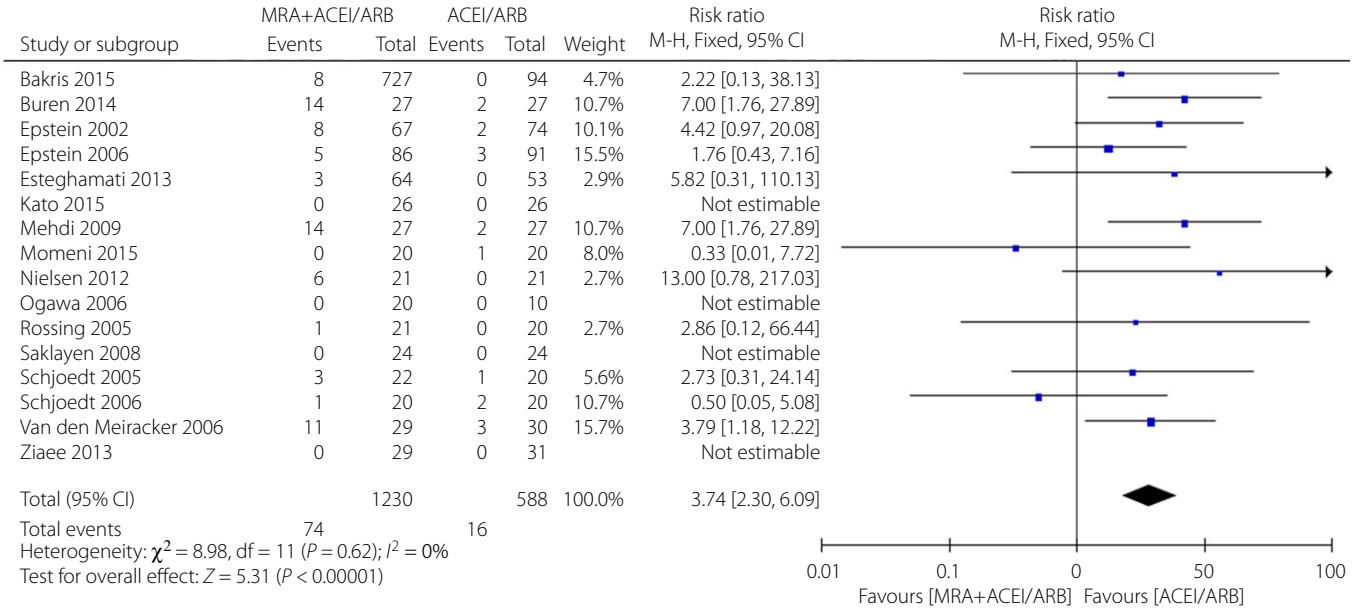

Figure 7 | Forest plot of therapeutic effect on adverse events of hyperkalemia in patients with diabetic nephropathy, pooled relative risk and 95% confidence interval (CI) for mineralocorticoid receptor antagonist (MRA) plus angiotensin-converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARB) monotherapy.

Further RCTs are necessary to investigate the validity of our conclusions.

The GFR is an important index for the evaluation of renal function. We observed that co-administration of MRA and ACEI/ARB had no impact on GFR compared with ACEI/ARB monotherapy in patients with DN. However, the present results might have been affected by the fact that just 11 RCTs in our analysis reported the GFR, whereas GFR data were not reported in a number of the reviewed trials, and others reported GFR data but did not provide complete information. While discussing the GFR findings, it is important to note that the GFR was only examined in the context of a study population with DN, and this has not been extensively studied in other populations. It seems plausible that co-administration of MRA and ACEI/ARB maintain a relatively stable GFR in patients with DN.

Control of BP is another crucial factor in the treatment of DN, and is associated with survival and renal prognosis. Our pooled analysis of 10 RCTs showed a significant reduction in SBP and DBP after MRA and ACEI/ARB therapy, compared with ACEI/ARB monotherapy. In three RCTs, we observed a reduction in SBP and DBP compared with the baseline BP. Improved BP control after a combination therapy significantly reduces the elevated systemic blood pressure to the glomeruli, which can lead to beneficial effects on renal outcome, specifically, proteinuria, and GFR[35,36].

As the evidence supporting the use of MRA in the treatment of DN accumulates, the question of safety arises, particularly given the pre-existing risk of hyperkalemia. In a recent narrative review, Mavrakanas[3] analyzed the effects of MRA combined with ACEI/ARB in patients with DN. That review included just nine trials, and confirmed that combined treatment increased the risk of hyperkalemia. We carried out an analysis of the development of hyperkalemia, even though each trial included in our analysis defined hyperkalemia differently. We confirmed that the risk of hyperkalemia was significantly higher after MRA and ACEI/ARB therapy compared with that after ACEI/ARB monotherapy in patients with DN. This finding is consistent with previous studies. Some studies have reported on the safety of including MRA in the treatment of DN or end-stage renal disease population treated with ACEI/ARB[25,37]. For example, Epstein *et al.*[25] found that eplerenone plus ACEI had no significant effect on serum potassium levels compared with ACEI monotherapy in patients with DN. The most likely explanation is the careful selection of patients, with the exclusion of patients with a previous event of hyperkalemia. There are reports that finerenone with ACEI did not change potassium levels in patients with DN[25]. Furthermore, co-administration of MRA and ACEI/ARB in patients with DN should be carried out under appropriate laboratory surveillance.

The present study had several limitations. First, the short study duration designed to assess surrogate end-points might affect the results. Further limitations include the relatively small sample size, and the limited or absent long-term follow-up data on the cumulative effects of MRA and ACEI/ARB therapy on study end-points. In addition, some relevant data were not available or complete. More detailed information is required to clarify the effect of MRA on renal outcome. Second, although

our statistical analyses suggested a low probability of publication bias, which remains a concern. Selection bias cannot be completely ruled out, as we only retrieved articles from English-language journals and published trials. Third, although most studies were RCTs, there were cross-over design studies, and some trials did not report their study methods in enough detail to determine the methods used and the trial quality. Finally, heterogeneity was found in some of our analyses, and a single, heavily weighted study could confuse the outcomes of the present meta-analysis.

In conclusion, the co-administration of MRA and ACEI/ARB in patients with DN confers greater renoprotection compared with ACEI/ARB alone. However, the inclusion of MRA to the ACEI/ARB therapy results in a higher incidence of hyperkalemia, suggesting that co-administration of MRA and ACEI/ARB, under appropriate laboratory surveillance, might be a reasonable treatment option in these patients.

The potential effects of MRA remain unclear and require further clarification. The majority of studies focused on spironolactone, whereas studies on DN involving new MRAs, such as finerenone, are currently limited. Large-scale, multicenter, randomized, double-blind, placebo-controlled trials are required to provide new insights into the effects of MRA, as a therapeutic agent, on the renal outcomes in patients with DN.

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DISCLOSURE

The authors declare no conflict of interest.

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