

Review Article

Clinical effect of mineralocorticoid receptor antagonist combined with angiotensin receptor blocker or angiotensin converting enzyme inhibitor in treating diabetic nephropathy: a systematic review and meta-analysis

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Abstract: Objective: To systematically assess the efficacy and safety of combined therapy with a mineralocorticoid receptor antagonist (MRA) and an angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACEI) for patients with diabetic nephropathy (DN). Methods: PubMed, MEDLINE, Cochrane Library, Embase and EBSCO were electronically searched to collect randomized controlled trials of the combined therapy of MRA and ARB/ACEI versus ARB/ACEI alone for DN patients. The following outcomes were assessed: systolic blood pressure (SBP), diastolic blood pressure (DBP), urinary albumin-to-creatinine ratio (UACR), 24-h urinary protein, serum creatinine, estimated glomerular filtration rate (eGFR), serum potassium, plasma renin activity, plasma aldosterone, hemoglobin A1c (HbA1c) and the incidence of hyperkalemia. Data were analyzed using RevMan 5.2. For continuous data, mean difference (MD) and 95% confidence interval (CI) were calculated. For dichotomous data, risk ratio (RR) and 95% CI were calculated. When heterogeneity was absent, meta-analysis was performed using a fixed-effects model. Otherwise, a random-effects model was used. Results: A total of 16 studies involving 905 patients were included. The meta-analysis showed that combined MRA with ARB/ACEI for DN patients reduce SBP [MD -1.21, 95% CI (-1.95, -0.47)], 24-h urinary protein [MD -0.33, 95% CI (-0.59, -0.08)], and UACR [MD -0.31, 95% CI (-0.56, -0.05)]. Compared with the control group, combination treatment demonstrated higher serum potassium level [MD 0.26, 95% CI (0.16, 0.35)], plasma renin activity [MD 0.52, 95% CI (0.21, 0.84)], plasma aldosterone [MD 0.59, 95% CI (0.39, 0.79)], HbA1c [MD 0.21, 95% CI (0.11, 0.32)] and the incidence of hyperkalemia [RR 3.89, 95% CI (2.20, 6.88)]. No statistical differences were observed for DBP, serum creatinine and eGFR. Conclusions: For patients with DN, combined therapy could further reduce albuminuria and blood pressure (BP), and inhibit plasma renin and aldosterone without decreasing renal function. A higher risk of hyperkalemia must be taken into consideration.

Keywords: Mineralocorticoid receptor antagonist, angiotensin-converting enzyme inhibitors, angiotensin receptor blocker, diabetic nephropathy, meta-analysis

Introduction

As a common complication of diabetes, the prevalence of diabetic nephropathy (DN) has reached nearly 9% in 2014 in the global adult population [1]. Previous studies of DN indicate that reduction in albuminuria not only slows the progression of end stage renal disease (ESRD), but also decreases the incidence and mortality of cardiovascular events [2, 3]. There-

fore, reducing albuminuria in DN patients is of great clinical significance [4].

Because the renin-angiotensin system (RAS) has been demonstrated to play an important role in the pathogenesis of chronic kidney disease (CKD) [5], angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) therapy is recommended to be an effective treatment for diabetes mellitus (DM),

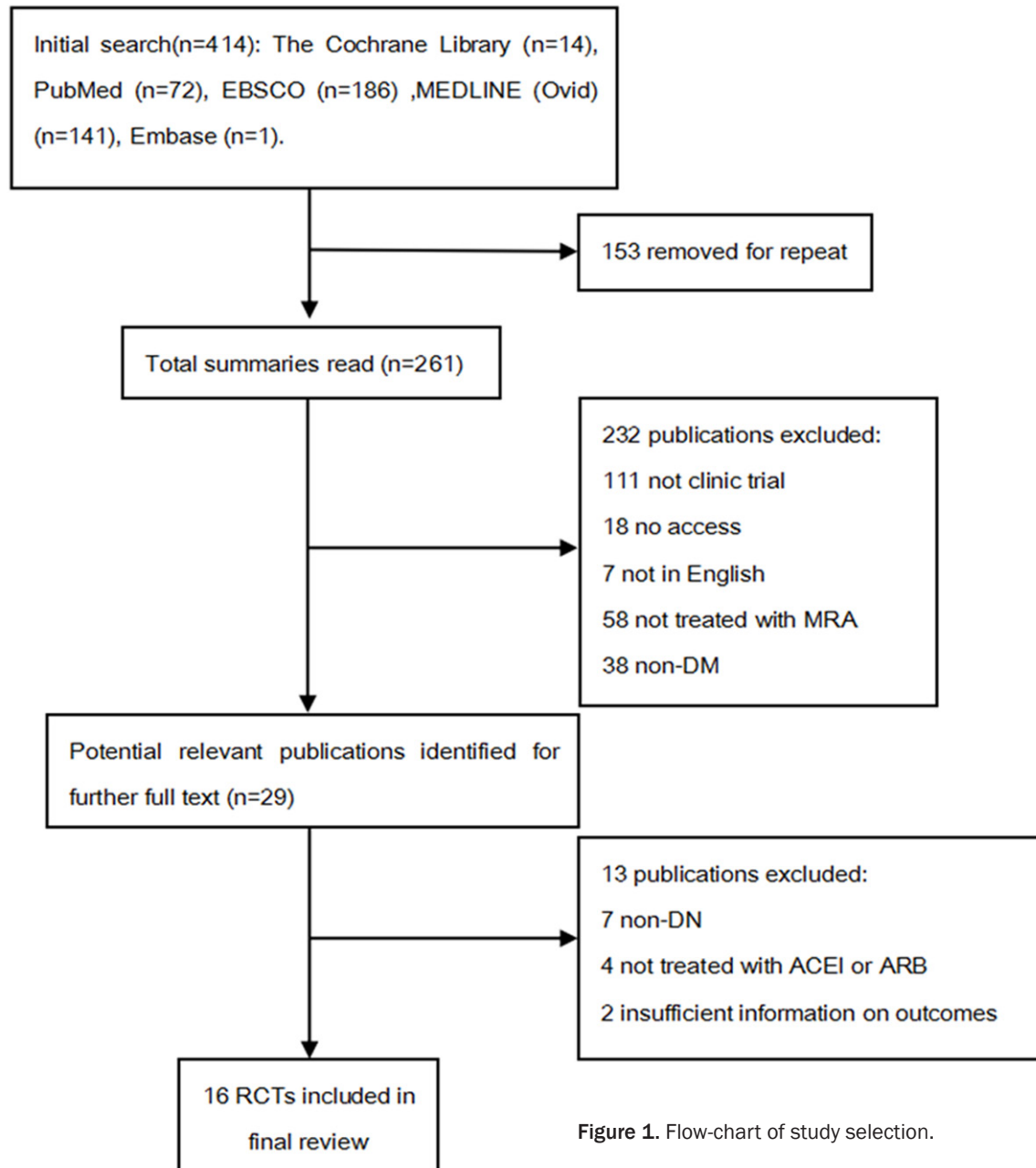


Figure 1. Flow-chart of study selection.

especially in DN patients [6]. However, despite RAS blockade by ARBs/ACEIs, a relatively high-level of albuminuria remains in DN patients receiving this treatment, and progression to ESRD can occur [7, 8]. This phenomenon is associated with aldosterone escape [9-11], which exists in nearly half of the patients receiving long-term treatment with RAS blockers [9, 12, 13]. To tackle this specific problem, several clinical studies have examined the combined use of mineralocorticoid receptor antagonist (MRA) with ACEIs/ARBs [14-16], and have dem-

onstrated effective renoprotection in DN patients [17-19].

Nevertheless, some disadvantages of the combined therapy have been reported. For instance, their renoprotection effects were accompanied with reduced estimated glomerular filtration rate (eGFR) [20-24]. Furthermore, it has been reported that combined use of ACEIs/ARBs with MRA may lead to hyperkalemia and gynecomastia [17, 18]. The clinical efficacy and safety of the combined therapy needs to be

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Table 1. Characteristics of 16 trials included in the meta-analysis

Reference, year	Country	Number M/C	Intervention		Design	Follow-up	Adverse events
			Combined therapy group	Control group			
Esteghamati A, 2013	USA	52/45	SPI 25 mg	ACEI	Parallel RCT	18 mo	Reported
Chrysostomou A, 2006	Australia	11/10	SPI 25 mg	Placebo	Parallel RCT	6 mo	Reported
van den Meiracker, 2006	Netherlands	24/29	SPI 50 mg	Placebo	Parallel RCT	12 mo	Reported
Ziaee A, 2013	Iran	29/31	SPI 25 mg	Placebo	Parallel RCT	12 mo	Reported
Schjoedt KJ, 2006	Denmark	20/20	SPI 25 mg	Placebo	Cross-over RCT	2 mo	Reported
Rachmani R, 2003	Israel	38/38	SPI 50 mg	Placebo	Cross-over RCT	6 mo	Reported
Mehdi UF, 2009	USA	17/21	SPI 25 mg	ARB	Parallel RCT	12 mo	Reported
Saklayen MG, 2008	USA	24/24	SPI 50 mg	Placebo	Cross-over RCT	3 mo	Reported
Nielsen SE, 2012	Denmark	21/21	SPI 25 mg	Placebo	Cross-over RCT	2 mo	Reported
Rossing K, 2005	Denmark	20/20	SPI 25 mg	Placebo	Cross-over RCT	2 mo	Reported
Schjoedt KJ, 2005	Denmark	20/20	SPI 25 mg	Placebo	Cross-over RCT	2 mo	Reported
Kato S, 2015	Japan	26/26	SPI 25 mg	Placebo	Parallel RCT	2 mo	Reported
Nielsen SE, 2013	Denmark	69/69	SPI 25 mg	Placebo	Cross-over RCT	2 mo	Unreported
Van Buren PN, 2014	USA	27/27	SPI 25 mg	Placebo	Parallel RCT	12 mo	Reported
Epstein M, 2002	USA	67/74	EPL 200 mg	Placebo	Parallel RCT	6 mo	Reported
Epstein M, 2006	USA	86/91	EPL 100 mg	Placebo	Parallel RCT	3 mo	Reported

Spironolactone (SPI); Eplerenone (EPL); Combined group (M); Control group (C); Month (mo).

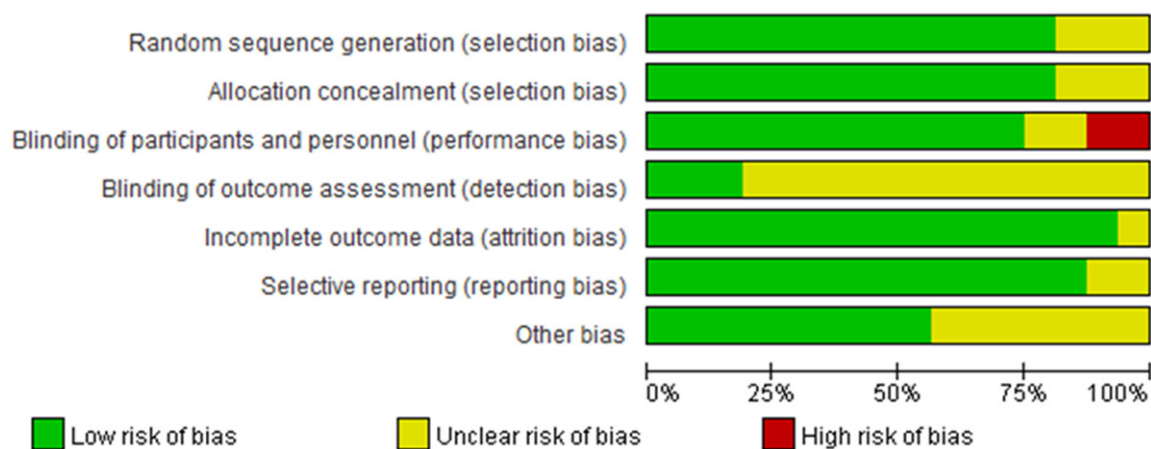


Figure 2. Risk of bias graph: Per the authors' judgement, each risk of bias item is described as percentages in all included studies.

further explored because of limited sample sizes used in existing studies. Thus, we performed this meta-analysis to provide more reliable evidence about efficacy and safety of the combined therapy.

Material and methods

Search strategy

A literature search in PubMed, MEDLINE, Cochrane Library, Embase, EBSCO from inception to

March 2017 was conducted, for articles comparing combined therapy (MRA with ARB/ACEI) with a control group (ARB/ACEI alone) for patients with DN. The search terms included mineralocorticoid receptor antagonists, diabetic nephropathy, angiotensin II type 1 receptor blockers, angiotensin receptor blocker, angiotensin-converting enzyme inhibitors. The search terms used in PubMed were: ((Mineralocorticoid Receptor Antagonists) AND Diabetic Nephropathy) AND (((Angiotensin II Type 1 Recep-

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chrysostomou A,2006	+	+	+	?	+	+	?
Epstein M,2002	?	?	+	?	?	?	?
Epstein M,2006	?	?	+	?	+	?	?
Esteghamati A,2013	+	+	-	?	+	+	+
Kato S,2015	+	+	-	?	+	+	+
Mehdi UF,2009	+	+	+	?	+	+	+
Nielsen SE,2012	+	+	+	+	+	+	+
Nielsen SE,2013	+	+	+	?	+	+	?
Rachmani R,2003	?	+	?	+	+	+	+
Rossing K,2005	+	+	+	?	+	+	+
Saklayen MG,2008	+	+	+	+	+	+	?
Schjoedt KJ,2005	+	+	+	?	+	+	+
Schjoedt KJ,2006	+	+	+	?	+	+	+
Van Buren PN,2014	+	?	+	?	+	+	+
van den Meiracker,2006	+	+	+	?	+	+	?
Ziaee A,2013	+	+	?	?	+	+	?

Figure 3. Risk of bias summary: Per the authors' judgement, each risk of bias is described for each included study (green: low; yellow: unclear; red: high).

tor Blockers) OR Angiotensin Receptor Blocker) OR Angiotensin-Converting Enzyme Inhibitors).

Inclusion and exclusion criteria

Inclusion criteria were as follows: 1) published randomized controlled trials (RCTs) comparing combined therapy (MRA and ARB/ACEI) with the control group (ARB/ACEI alone) in the English language; 2) participants were patients with DN (defined as at least 30 mg albuminuria in a 24-h urine collection or an albumin-to-creatinine ratio of at least 30 mg/g of creatinine) [25]; 3) all patients were treated with the minimum recommended dose of ACEI or ARB at least 3 months; and 4) assessed outcomes included systolic blood pressure (SBP), diastolic blood pressure (DBP), serum creatinine, 24-h urinary protein, urinary albumin-to-creatinine ratio (UACR), eGFR, plasma potassium, plasma renin activity, plasma aldosterone, hemoglobin A1c (HbA1c) and hyperkalemia.

The exclusion criteria were as follows: 1) their quality was too low; 2) it was not possible to obtain complete data from original trials.

Study selection and data extraction

Two authors independently assessed all identified titles/abstracts using the eligibility criteria, and abstracted key

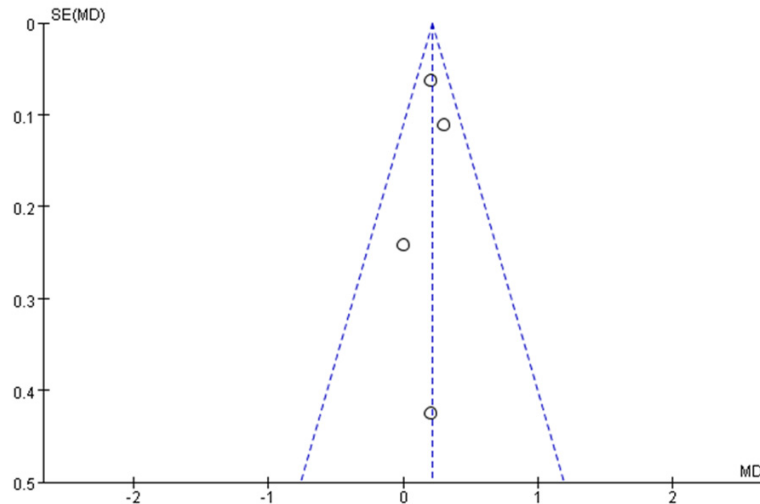


Figure 4. Funnel plots showing risk of bias in studies reporting hemoglobin A1c.

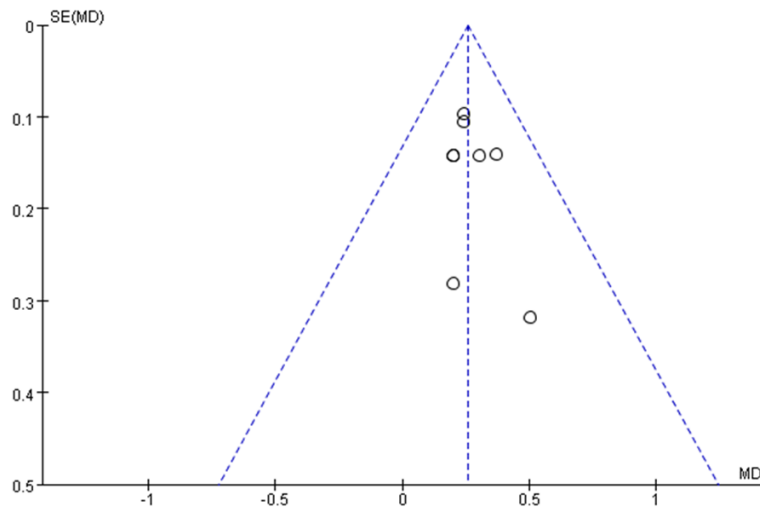


Figure 5. Funnel plots showing risk of bias in studies reporting serum potassium.

features of included RCTs. These included first author, year of publication, country, type of study, sample size, the intervention drugs, doses, follow-up time, main outcomes and treatment-related adverse events.

Assessment of data quality

Risk of bias in eligible studies was assessed using the Cochrane Collaboration's core risk of bias items [26]. The following items were considered: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants and personnel; 4) blinding of the out-

come assessments; 5) incomplete outcome data; 6) selective reporting; 7) other bias.

Statistical analysis

RevMan 5.2 (The Cochrane Collaboration, Oxford, UK) was used to perform statistical analysis. If different scales used in studies or the mean had a wide difference, standardized mean difference (SMD) were calculated. Otherwise, weighted mean difference (WMD) were calculated. Dichotomous variables were assessed using risk ratio (RR). Heterogeneity was assessed using the I^2 statistic with value of 25-50% considered as low heterogeneity, 50-75% considered as moderate heterogeneity, and > 75% considered as high heterogeneity [27]. When I^2 was $\leq 50\%$, fixed-effect analysis was used. Otherwise the random-effects model was applied. Funnel plots were used to detect publication bias.

Results

Literature search and study characteristics

Overall, a total of 414 records were identified in PubMed, MEDLINE, Cochrane Library, Embase, and EBSCO.

After screening the titles or abstracts, 29 records remained (**Figure 1**). After full-text assessment, 16 records published in English comprising 905 patients (551 in the combined therapy group and 548 in the control group) remained [17, 18, 20-24, 28-36]. The main characteristics of the included studies were shown in **Table 1**.

Assessment of data quality

All 16 included trials exhibited low bias risk according to the Cochrane Collaboration items. Details of bias risks are shown in **Figures 2** and

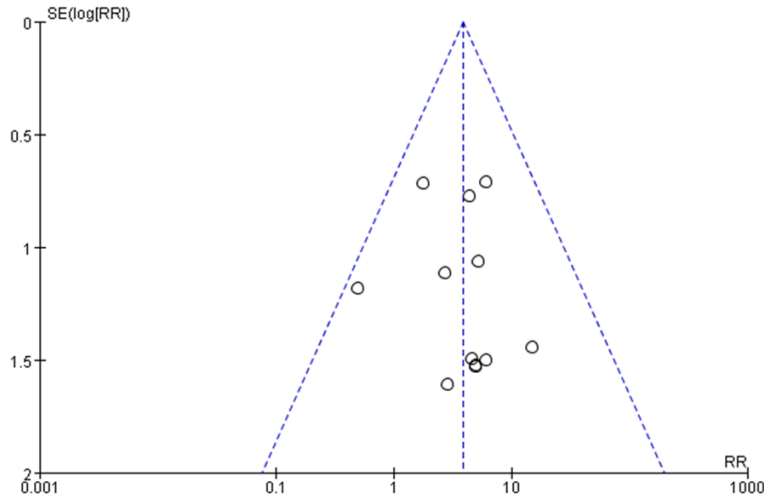


Figure 6. Funnel plots showing risk of bias in studies reporting hyperkalemia events.

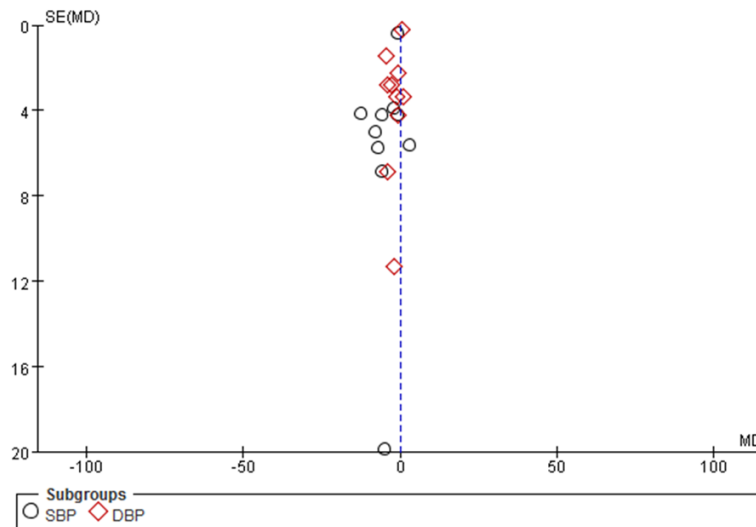


Figure 7. Funnel plots showing risk of bias in studies reporting blood pressure.

3. Selection bias was unclear in 18.75% studies, and low in 81.25%. Performance bias was low in 12 studies and detection bias was unclear in 3 studies. Attrition bias was low in 15 studies (93.75%) and unclear only in one study. There were 14 studies reporting bias. Nine studies were low in other bias. The funnel plot diagram of HbA1c, serum potassium and the incidence of hyperkalemia was symmetrical, indicating a low risk of publication bias. (Figures 4-6) However, as showed in Figures 7-10 (BP, renal function, albuminuria, plasma renin activity and plasma aldosterone), funnel plots of studies included in the meta-analysis ap-

peared to be asymmetric, indicating the presence of publication bias.

Outcome measures

Table 2 summarizes the effects of combined therapy on diabetic nephropathy patients.

Effects of combined therapy on blood pressure (BP) (Figure 11)

Ten studies reported data on BP without heterogeneity, and the fixed-effects model was used to merge WMD values for BP. Compared with control group, SBP was decreased in the combined therapy group (WMD -1.21, 95% CI: -1.95, -0.47; $P < 0.01$). There was no statistical difference regarding DBP between the two groups (WMD 0.34, 95% CI: -0.05, 0.73; $P = 0.09$).

Effects of combined therapy on renal function (Figure 12)

Nine studies reported serum creatinine without heterogeneity ($P = 0.84$, $I^2 = 0\%$). SMD was 0.05 (95% CI: -0.14, 0.23; $P = 0.64$), suggesting that there was no significant difference between the two groups. Nine studies reported eGFR without heterogeneity ($P = 0.87$, $I^2 = 0\%$). The fixed-effect

model was used to merge SMD values. The pooled data was -0.09 (95% CI: -0.26, 0.09; $P = 0.34$), demonstrating no significant difference between the two groups.

Effects of combined therapy on albuminuria (Figure 13)

In the combined therapy group, there was a significant reduction in 24-h urinary protein compared with the control group (SMD -0.33, 95% CI: -0.59, -0.08; $P = 0.01$). There was no significant heterogeneity among four studies ($P = 0.17$, $I^2 = 41\%$). Four studies reported UACR

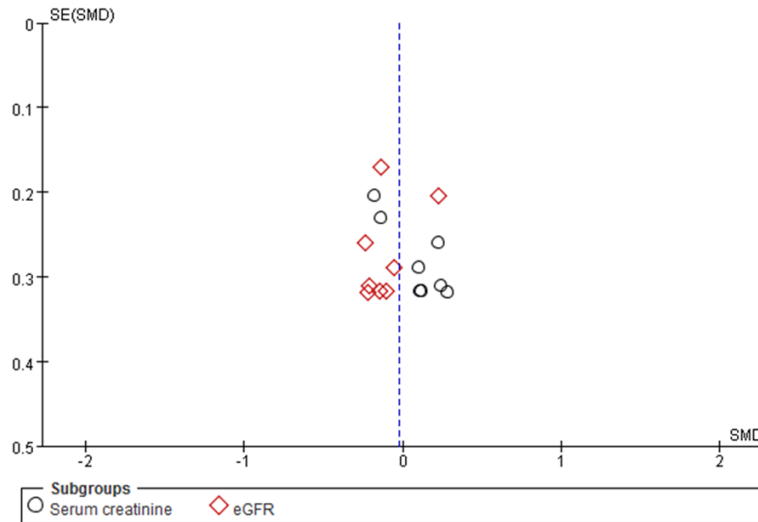


Figure 8. Funnel plots showing risk of bias in studies reporting renal function.

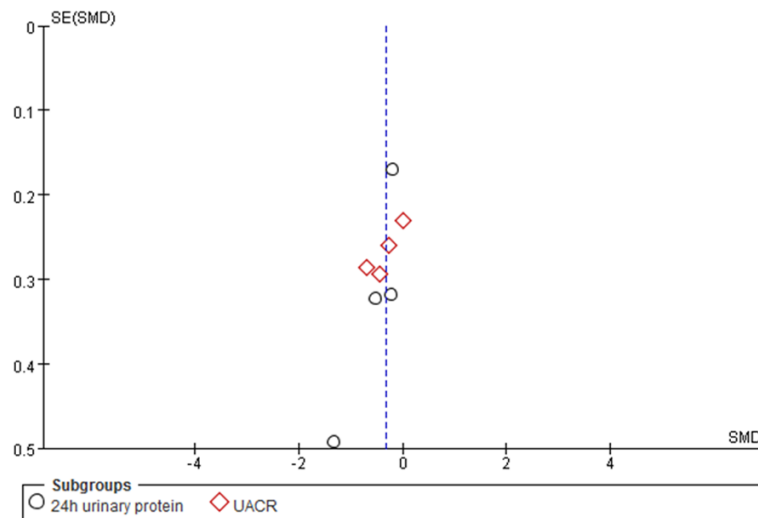


Figure 9. Funnel plots showing risk of bias in studies reporting albuminuria.

without heterogeneity ($P = 0.26$, $I^2 = 26\%$), and the fixed-effect model was used. SMD was -0.31 (95% CI: -0.56 , -0.05 ; $P = 0.02$), suggesting that UACR in the combined therapy group was decreased.

Effects of combined therapy on Renin-angiotensin-aldosterone System (RAAS) (Figure 14)

There was an increase in plasma renin activity in the combined therapy group compared with control (SMD 0.52 , 95% CI: 0.21 , 0.84 ; $P < 0.01$). There was no between-study heteroge-

neity ($P = 0.33$, $I^2 = 13\%$) among four studies. Plasma aldosterone was increased in the combined therapy group compared with controls (SMD 0.59 , 95% CI: 0.39 , 0.79 ; $P < 0.01$). There was no between-study heterogeneity ($P = 0.39$, $I^2 = 5\%$) among seven studies.

Effects of combined therapy on hemoglobin A1c (HbA1c) (Figure 15)

Of the sixteen studies, four reported HbA1c without between-study heterogeneity ($P = 0.70$, $I^2 = 0\%$). The fixed-effect model was used to merge WMD values. WMD was 0.21 (95% CI: 0.11 , 0.32 ; $P < 0.01$), demonstrating a statistical difference in HbA1c between the two groups, with a higher level in the combined therapy group.

Safety of combined therapy

Of the sixteen studies, eight compared serum potassium without significant heterogeneity ($P = 0.97$, $I^2 = 0\%$). WMD was 0.26 (95% CI: 0.16 , 0.35 ; $P < 0.01$, **Figure 16**), which revealed that there was an increase in serum potassium in the combined therapy group, compared with control

group. There were thirteen studies reporting the incidence of hyperkalemia without between-study heterogeneity ($P = 0.88$, $I^2 = 0\%$). Compared with the control group, the meta-analysis indicated an increase of hyperkalemia in the combined therapy group (RR = 3.89 , 95% CI: 2.20 , 6.88 ; $P < 0.01$, **Figure 17**).

Discussion

In this meta-analysis, we systematically evaluated the efficacy and safety of combined therapy of MRA and ARB/ACEI for DN patients. The included studies reveal that additional

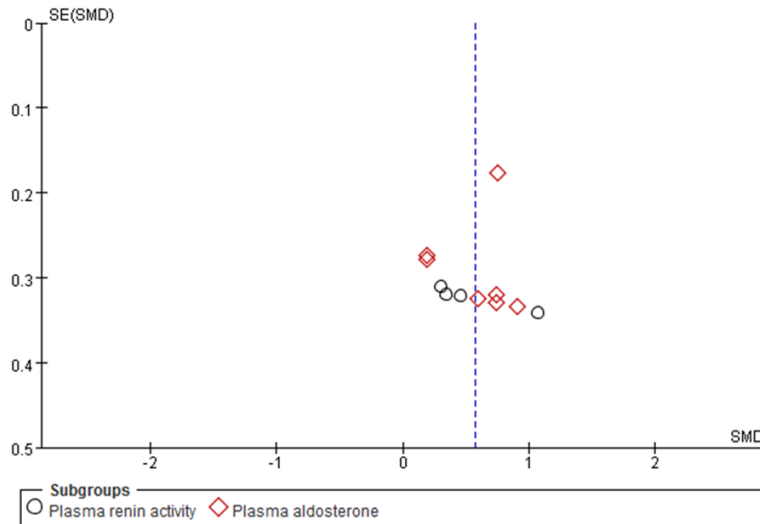


Figure 10. Funnel plots showing risk of bias in studies reporting on the renin-angiotensin-aldosterone system.

MRA could significantly decrease albuminuria and BP, and inhibit plasma renin and aldosterone without decreasing in renal function in DN patients. However, the findings indicated higher risk of hyperkalemia in those treated with combined therapy.

In DN patients, albuminuria reduction has been shown to be a crucial contributor in the delaying of CKD progression as well as in reducing risk of cardiovascular events [4, 37, 38]. Previous publications have explored the effects of MRA on albuminuria reduction. Alireza et al [17] reported that combining spironolactone with ARB/ACEI could gradually reduce urinary albumin excretion (UAE) over a period of 3-18 months. Similarly, eplerenone has been demonstrated to have the antialbuminuric effects when administered together with an ARB [24]. Of note, in our meta-analysis, the 8 studies [20, 21, 23, 28, 29, 31, 32, 36] further confirmed that adding MRA to ARB/ACEI for DN could further diminish albuminuria, regardless of whether the UACR was assessed by 24-h urine collection or a urine spot collection.

More than half of selected studies have reported combined therapy to be more effective than continuous ARB/ACEI treatment in downregulating both SBP and DBP. In this meta-analysis, compared with the control group, SBP demonstrated a much more remarkable reduction in the combined therapy group.

Several studies have shown that plasma aldosterone levels are correlated with gluconeogenesis and insulin resistance [39-41]. Aldosterone could stimulate the expression of gluconeogenesis-related enzymes and inhibit the expression of insulin receptors [42-45]. Conversely, a hyperglycemia state could enhance the effects of aldosterone. This vicious cycle of aldosterone and hyperglycemia can lead to hypertension and the development of nephropathy [46]. As aldosterone levels increase with combined therapy, HbA1c levels increase, as verified in our meta-analysis. In light of this,

we suggest that for DN patients receiving combined therapy, regular blood glucose detection should be performed, and a glucocorticoid receptor antagonist or antioxidant N-acetylcysteine added if necessary.

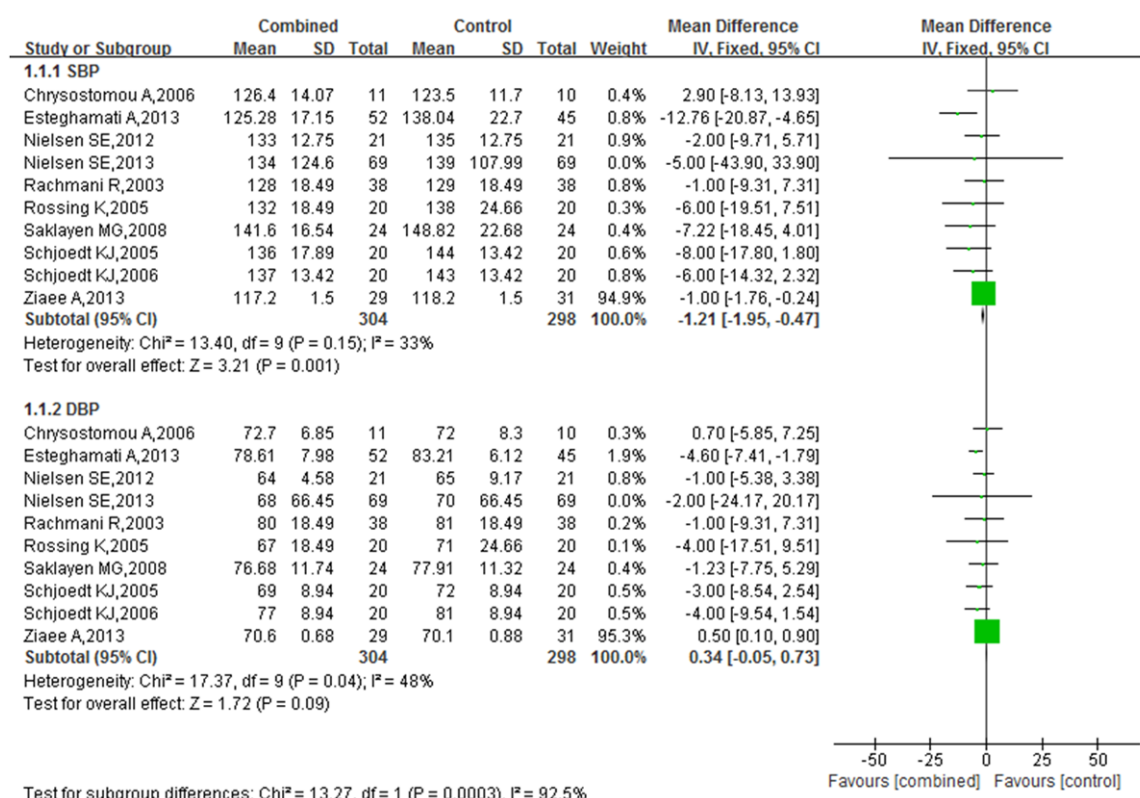
Studies by Saklayen et al [29] and Nielsen et al [30] have reported that GFR declines and serum creatinine increases with combined therapy. However, no significant differences in eGFR and serum creatinine were observed between the two groups in our study, and we cannot draw the conclusion that combining an MRA with RAS inhibitors has a harmful effect in DN based on our findings.

When adding an MRA to ARB/ACEI treatment in DN patients, a leading concern is the patient's serum potassium levels. All clinical studies included in the meta-analysis reported that the combined therapy is more likely lead to raised serum potassium, and potentially hyperkalemia. Apart from patients with severe hyperkalemia who were withdrawn from studies, the majority of subjects had been effectively controlled by dietary intervention and/or temporary diuretics administration, such as in Nielsen et al [30]. It has been suggested that patients with higher baseline serum potassium, severe renal function impairment and the elderly are more likely to develop hyperkalemia [21]. Therefore it seems reasonable to suggest that MRA treatment should start with low doses with regular assessment of potassium levels, particu-

Table 2. Summary of the effects of combined therapy on diabetic nephropathy patients

Outcome	No. studies	No. patients	Heterogeneity		Effect model	Std.mean net change (95% CI)	P value
			I^2 index (%)	Q-stastic P-value			
SBP	10	602	33	0.15	Fixed	-1.21 (-1.95, -0.47)	< 0.01
DBP	10	602	48	0.04	Fixed	0.34 (-0.05, 0.73)	0.09
Serum creatinine	9	443	0	0.84	Fixed	0.05 (-0.14, 0.23)	0.64
eGFR	9	505	0	0.87	Fixed	-0.09 (-0.26, 0.09)	0.34
24 h urinary protein	4	239	41	0.17	Fixed	-0.33 (-0.59, -0.08)	0.01
UACR	4	237	26	0.26	Fixed	-0.31 (-0.56, -0.05)	0.02
Plasma renin activity	4	162	13	0.33	Fixed	0.52 (0.21, 0.84)	< 0.01
Plasma aldosterone	7	406	5	0.39	Fixed	0.59 (0.39, 0.79)	< 0.01
HbA1c	4	196	0	0.70	Fixed	0.21 (0.11, 0.32)	< 0.01
Serum potassium	8	343	0	0.97	Fixed	0.26 (0.16, 0.35)	< 0.01
Hyperkalemia	13	892	0	0.88	Fixed	3.89 (2.20, 6.88) ^a	< 0.01

^aFor dichotomous data, the risk ratio (RR) was calculated.

**Figure 11.** Effects on blood pressure for the combined mineralocorticoid receptor antagonist group versus control group.

larly in patients with impaired renal function. It has been reported that finerenone at doses of 2.5 to 10 mg/day reduced albuminuria from baseline in patients with CKD and heart failure, with a lower incidence of hyperkalemia than spironolactone [47], indicating that finerenone may be preferable over spironolactone. Besi-

des, two studies [17, 18] reported gynecomastia in the combined therapy group, and only two cases happened.

This meta-analysis had several limitations that warrant discussion. First, only including studies published in English may lead to language

A meta-analysis of MRA with ARB/ACEI in DN

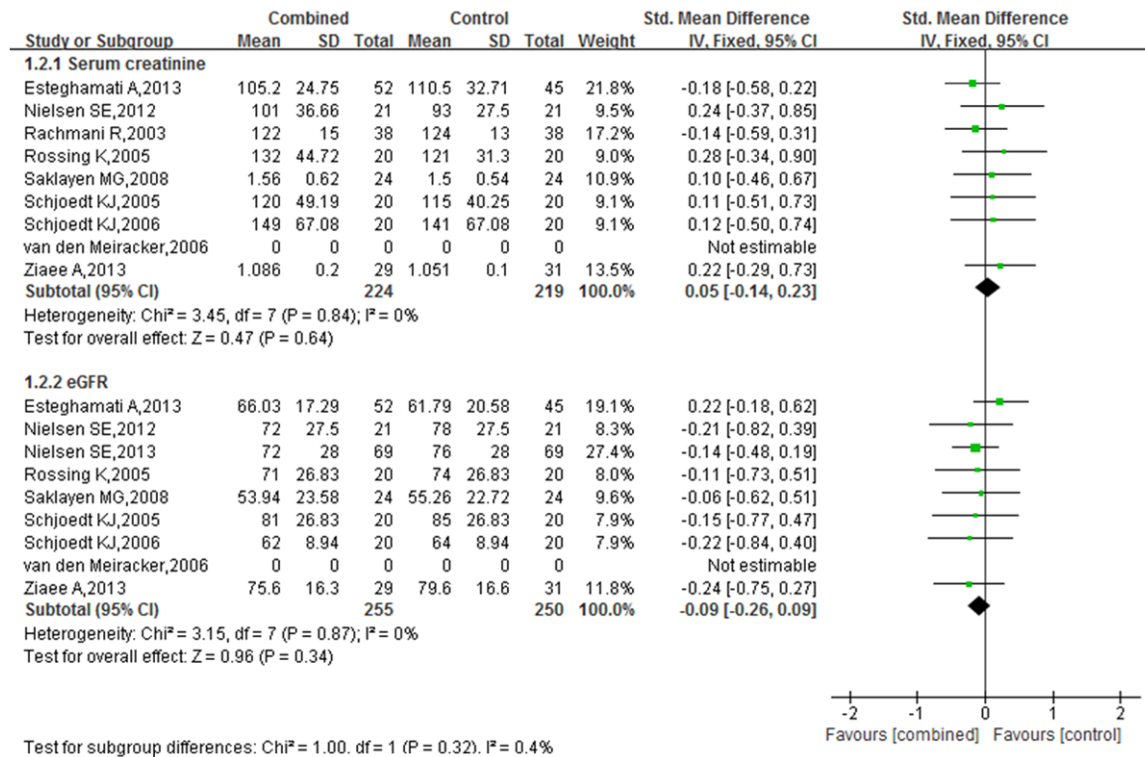


Figure 12. Effects on renal function for the combined mineralocorticoid receptor antagonist group versus control group.

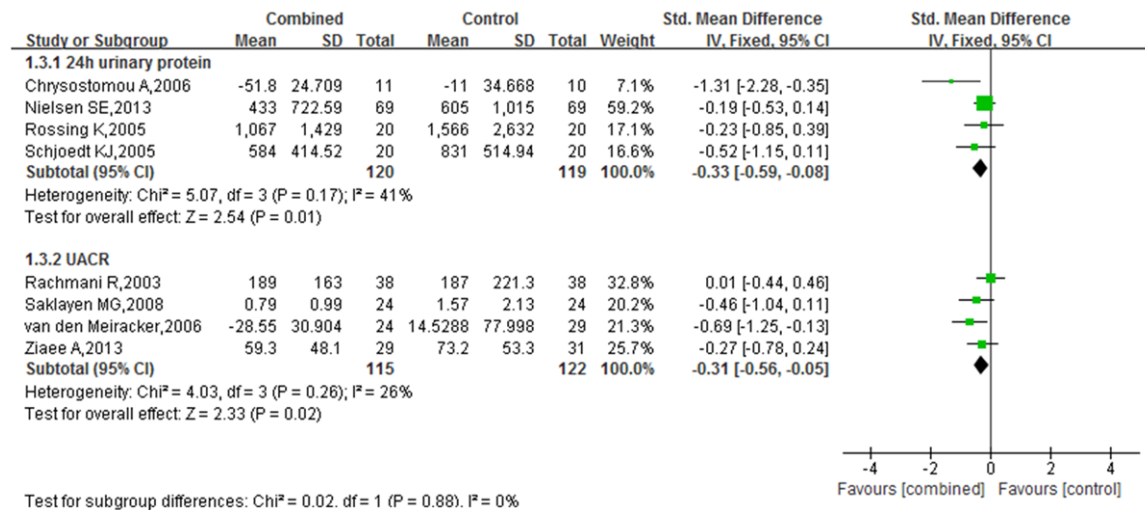


Figure 13. Effects on albuminuria for the combined mineralocorticoid receptor antagonist group versus control group.

bias. Second, only one article [33] published in the last three years was included in this study. Third, units of measurement and the way data were described varied among the 16 studies, including 24-h urinary protein, UACR, serum creatinine, plasma aldosterone and plasma renin activity. Fourth, limited washout periods

may have influenced efficacy in the cross-over RCTs included [22, 23, 28-31, 36]. Finally, most studies only depicted short-term (< 6 months) observations, except for five studies that had follow-up for > 12 months. This indicates that the long-term effects of MRA therapy need to be investigated further.

A meta-analysis of MRA with ARB/ACEI in DN

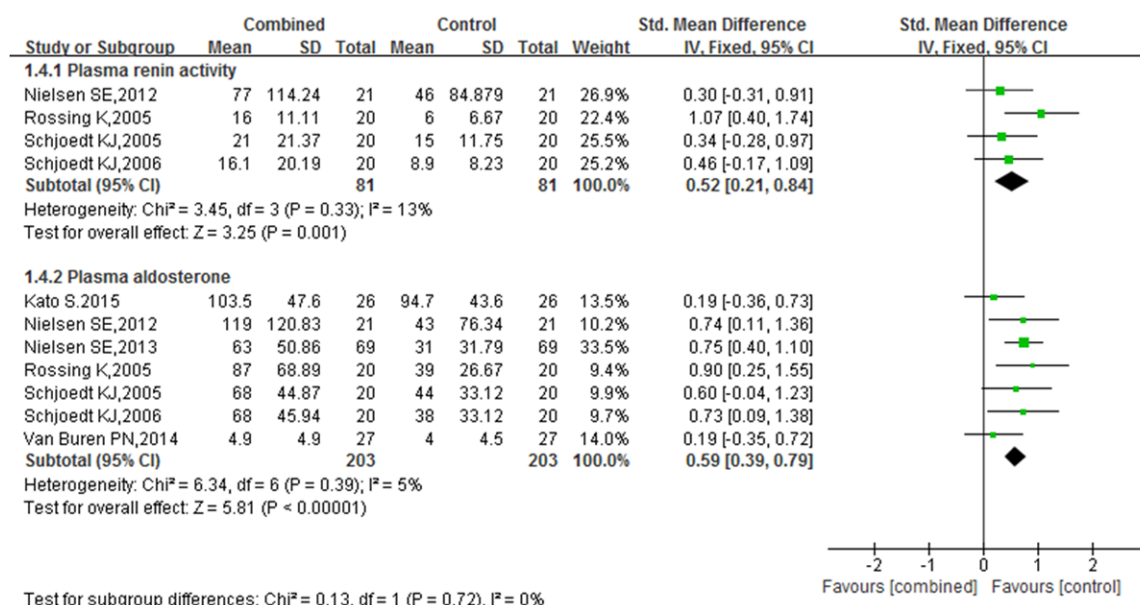


Figure 14. Effects on the renin-angiotensin-aldosterone system for the combined mineralocorticoid receptor antagonist group versus control group.

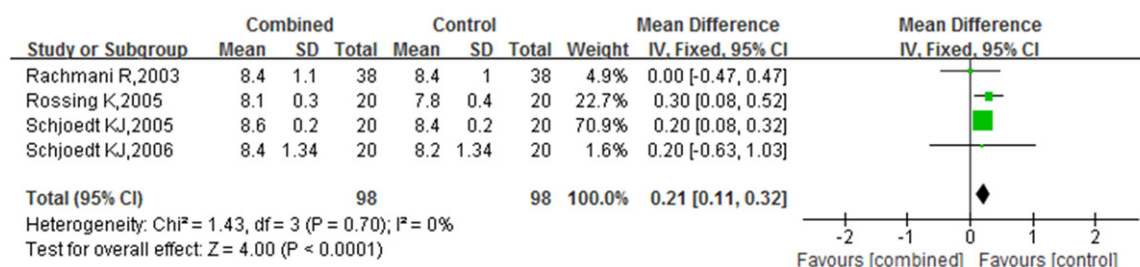


Figure 15. Effects on hemoglobin A1c for the combined mineralocorticoid receptor antagonist group versus control group.

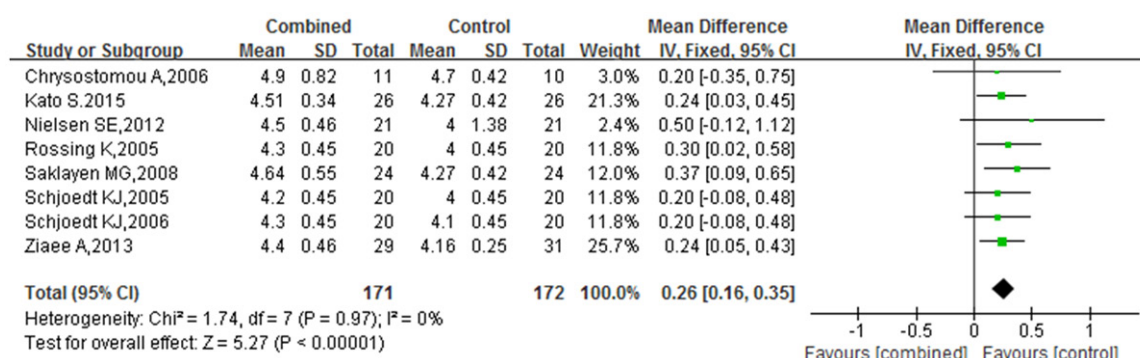


Figure 16. Effects group on serum potassium for the combined mineralocorticoid receptor antagonist group versus control group.

In summary, compared with the control group, our meta-analysis revealed that combined therapy demonstrates antihypertensive and anti-proteinuric effects, and can inhibit the effect

of renin and aldosterone in patients with DN. Combined treatment may be beneficial for DN, and may be a promising therapeutic option. It is important to note that our meta-analysis indi-

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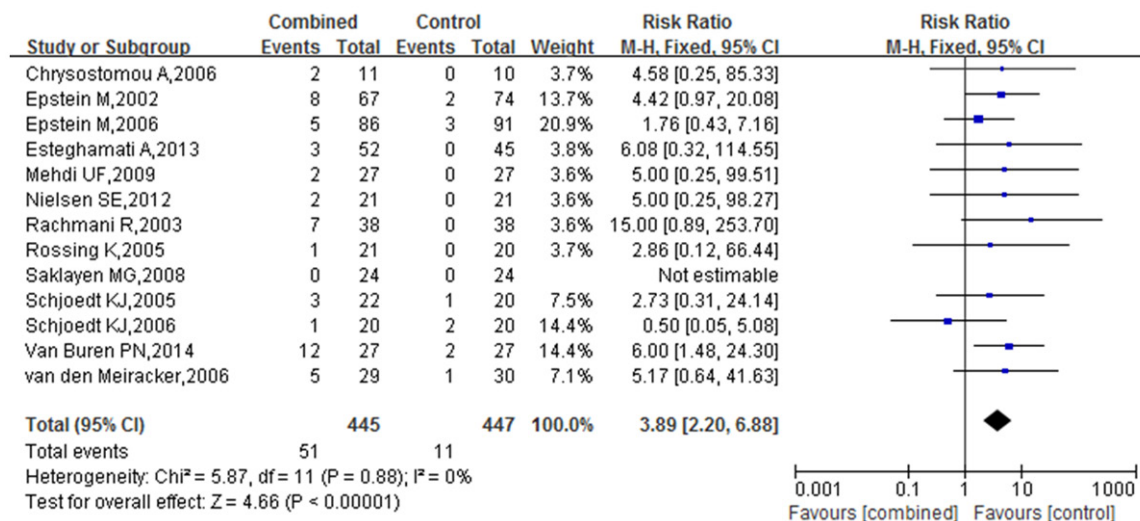


Figure 17. Effects on hyperkalemia events for the combined mineralocorticoid receptor antagonist group versus control group.

cated that combining MRA with ARB/ACEI may increase HbA1c levels and serum potassium, which warrants careful attention. Because of limitations in sample size and the length of follow-up, further high quality studies with larger sample sizes and longer duration are needed to confirm our findings.

Disclosure of conflict of interest

None.

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