Journal of Nephrology & Therapeutics

Research Article **Open Access**

Effects of Dual Blockade of the Renin-Angiotensin System in Diabetic Kidney Disease: A Systematic Review and Meta-Analysis

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Abstract

Objective: There is substantial evidence for a renoprotective effect of inhibitors of the renin-angiotensin system (RAS) in diabetic kidney disease (DKD). However, it is unclear whether dual RAS blockade has additional benefits when compared to monotherapy in this population and whether any benefits outweigh the risks.

Data sources: A systematic review and meta-analysis of English language articles was performed using MEDLINE, EMBASE, CINAHL, and the Cochrane database of systematic reviews.

Study selection: All randomized, controlled trials comparing RAS blockade to monotherapy in patients with overt proteinuria were included.

Data extraction: Articles were reviewed independently by two of the authors using a standardized data collection form including study quality indicators.

Data synthesis: All pooled analyses were based on random-effects models. The primary efficacy outcome measure was the percent reduction in proteinuria with combination therapy versus monotherapy measured by difference in means. Secondary outcomes included changes in systolic blood pressure (SBP), glomerular filtration rate (GFR), and serum potassium, and incidence of hyperkalemia. The primary safety outcome was hyperkalemia.

Results: Compared to monotherapy, combination therapy with an angiotensin converting enzyme inhibitor (ACEI) plus angiotensin receptor blocker (ARB) reduced proteinuria by an additional 25% (mean difference -25, 95% CI -33,-17), whereas combination therapy with an aldosterone antagonist (ALDOA) plus ACEI or ARB reduced proteinuria by an additional 32% (mean difference -32, 95% CI -37,-27). SBP after treatment with combination therapy vs. monotherapy was significantly lower with both the ACEI/ARB and ALDOA combinations. Dual therapy was associated with an increase in serum potassium, in particular with the ALDOA combination.

Limitations: Most studies were small and of short duration, and none included major patient outcome data such as kidney failure or death.

Conclusion: Dual RAS blockade in patients with DKD reduces proteinuria and SBP but increases the risk of hyperkalemia.

Keywords: Dual blockade; Diabetes; Angiotensin converting enzyme inhibitor; Angiotensin receptor blocker; Diabetic nephropathy; Diabetic kidney disease; Proteinuria

Diabetic kidney disease (DKD) is the leading cause of end-stage kidney disease (ESKD) in the United States [1,2]. Inhibitors of the renin-angiotensin system (RAS), such as angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), can slow the progression of DKD. However, despite these medications, the proportion of individuals with overt DKD (albuminuria > 300 mg/day or 300 mg/g creatinine) who progress to ESKD remains high, with resultant high morbidity, mortality, and hospitalization rates [3]. Given the associated enormous human and financial costs of kidney failure, therapies to prevent the progression of kidney disease are vitally important.

Because of the beneficial effects of RAS inhibitors, there has been much interest in combination RAS inhibitor therapy in patients with DKD. However, this approach could increase risk, as individuals with DKD have an increased susceptibility to hyperkalemia [4]. A recent study in predominantly non-diabetic patients, ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial), has cast doubt on the efficacy and safety of combined therapy [5]. However, in that study, the subset of patients with overt DKD appeared to fare somewhat but not significantly better with combination therapy. The ongoing Veterans Affairs Cooperative Study

VA NEPHRON-D (Combination Angiotensin Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor for Treatment of Diabetic Nephropathy) [6] which is being carried out specifically in patients with overt DKD, will hopefully provide further risk/benefit information, though data from this study will not be available for several years.

The purpose of this meta-analysis was to determine the relative benefits [proteinuria and systolic blood pressure (SBP) reduction] and risks (hyperkalemia) as well as effects on glomerular filtration rate (GFR) of combined therapy vs. monotherapy in patients with overt DKD. Therefore, we restricted our analysis to randomized controlled trials of patients with overt proteinuria (studies of patients with microalbuminuria were not included). Since there are now

four different types of RAS blockers in clinical use [ACEIs, ARBs, aldosterone antagonists (ALDOAs), and direct renin inhibitors (DRIs)], studies using any dual combination therapy were included in this analysis providing there was a comparator monotherapy group. Both parallel-group and crossover trials were acceptable for inclusion.

Methods

Data sources and searches

We conducted searches of MEDLINE (Pubmed) (January 1966 to December 2011), EMBASE (January 1980 to December 2011) and CINAHL (January 1982 to December 2011) to identify all clinical trials published in English involving combination RAS blockers for treatment of DKD. Search terms used were "dual blockade OR combination therapy" AND "renin angiotensin system" AND "diabetes". In addition, we performed a manual search of the literature using the references of manuscripts and review articles. Finally, a search of the Cochrane database of systematic reviews was conducted. PRISMA guidelines were used for analysis and reporting in this manuscript [7].

Study selection

All randomized, controlled, parallel or crossover trials comparing combination RAS blockade to monotherapy for the treatment of DKD were considered for inclusion. Studies were subsequently included only if patients had overt albuminuria or proteinuria (> 300 mg/24h or > 300 mg/g creatinine on a random specimen). Studies of patients with microalbuminuria were not included. We also excluded studies in which both diabetic and non-diabetic patients were enrolled if data were not given to analyze diabetic patients separately from non-diabetic patients. Two of the authors (J.T.P. and D.J.L.) independently identified potential articles, reviewed each abstract, and determined suitability for inclusion. Disagreements were resolved by consensus without a third party. The full publications of selected titles were then obtained and reviewed independently.

Data extraction, quality assessment, and risk of bias

A standardized data collection form was used to extract data from each study for important design characteristics and for quality assessment. The quality of each included study was assessed using the Jadad approach to quality review [8]. The Jadad score is calculated on a scale of 0-5 by allotting one point for the following with five being the highest possible: randomization, valid method of randomization, double-blinded, matching placebos, and listing of drop-outs. In addition, risk of bias within studies was assessed by evaluating the methodological features of each study according to the Cochrane risk of bias assessment tool [9]. This tool takes into account random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. To assess publication bias, a funnel plot was performed [10].

Data synthesis and analysis

The primary outcome analyzed was the mean difference in percent reduction in proteinuria (either albuminuria or total proteinuria) between the combination therapy and monotherapy groups. In most studies, proteinuria outcome data were presented as the geometric mean and 95% confidence interval (CI). Consequently, when working with log-transformed data we used the methods of Higgins et al. [11] In studies which had two monotherapy comparator arms (ACEI or ARB), the average of the means and standard deviations of the two arms

was utilized. Secondary outcomes included change in SBP, change in GFR, change in serum potassium, and incidence of hyperkalemia. Statistical heterogeneity was assessed by the I^2 test, with results of low, moderate, and high heterogeneity represented to be 25%, 50%, and 75% respectively. Separate analyses were conducted in the following study subsets: combination ACEI/ARB studies, studies utilizing an ALDOA in combination with an ACEI or ARB, studies with the highest Jadad score of 5, and studies with low risk of bias based on the Cochrane tool. Forest plots were created with Review Manager software (version 5.0) using the random-effects model [10]. Although we analyzed the data using both a fixed-effects and random-effects assumption, results of the random-effects model (DerSimonian-Laird method) are reported because the analyses were similar.

Results

The result of the literature search is given in Figure 1. Sixteen articles were included in at least one analysis, with 12 articles suitable for primary outcome analysis. Summary results and selected characteristics of each clinical trial including study quality are given in Table 1. The risk of bias using the Cochrane assessment tool is shown in Table 2. Trial quality was variable, with Jadad scores varying from 1-5. Risk of bias was generally lower in studies with the highest Jadad scores. A funnel plot (Figure 2) suggests a low likelihood of publication bias.

Efficacy outcomes: proteinuria

Percent reduction in proteinuria: primary outcome: Twelve studies including 1067 patients were identified that met inclusion criteria and were analyzable for the primary outcome [12-23] (Table 1, studies included in the primary outcome analysis identified by an asterisk). Ten of the studies were crossover-design trials, and two were parallel-design trials. Renal function was variable but no study included patients with severe renal dysfunction (GFR < 20 mL/min). Four studies included only type 1 diabetic patients; the other studies were either in type 2 diabetic patients (6 studies) or either type 1 or type 2 (2 studies). In 7 studies, combination ACEI/ARB therapy was compared to monotherapy; in 4 studies, combination therapy with the ALDOA spironolactone plus either an ACEI or ARB was compared to monotherapy with ACEI or ARB, and in one study the DRI aliskiren plus ARB was compared to ARB alone.

Overall, there was an additional 27% (mean difference -27; 95% CI -32, -22) relative reduction of proteinuria with combination therapy versus monotherapy (Figure 3a). When only the highest quality studies (Jadad score of 5) were examined [15-21], dual therapy resulted in a 29% (mean difference -29; 95% CI -33, -25) additional reduction in proteinuria. When only studies with the lowest overall risk of bias were examined [12-21], nearly identical results were obtained (mean difference -30; 95% CI -33, -26) (Figures not shown). I^2 was 51%, indicating moderate heterogeneity among studies.

Analysis by drug types: Due to the heterogeneity observed in primary outcome when all studies were pooled, subsequent analyses were performed separately for each drug type combination. Combination therapy with an ACEI plus ARB reduced proteinuria by an additional 25% (mean difference -25, 95% CI -33,-17), whereas combination therapy with an ALDOA plus ACEI or ARB reduced proteinuria, by an additional 32% (mean difference -32, 95% CI -37,-27) (Figures 3b and 3c). There was only one study utilizing combination therapy with a DRI plus ARB, which resulted in a 20% reduction in

Author	DM Type	Proteinuria and/or GFR at baseline	Treatment/Design	Treatment Arms (daily dose in mg)	Control	N	Drop out/ Lost to follow-up	N analyzed	Study length	Jadad score (max 5)
Jacobsen 2002 (12)*	1	AER > 300 mg/24h GFR ≥ 20 mL/min	ACEI + ARB/RCCT	C100 or E/L20 + I 300 v. C100 or E/L20	Plac	21	2	19	8 wks	4
Jacobsen 2003 (13)*	1	AER > 300 mg/24h GFR ≥ 30 mL/min	ACEI + ARB/RCCT	B20 + V80 v. B20 or V80	Plac	20	2	18	8 wks	4
Jacobsen 2003 (14)*	1	AER > 300 mg/24h GFR ≥ 30 mL/min	ACEI + ARB/RCCT	E40 + I300 v. E40	Plac	24	0	24	8 wks	4
Mehdi 2009 (15)*	1/2	ACR ≥ 300 mg/g Cr ≤ 3.0 (females) 4.0 (males)	ACEI + ARB v. ACEI + ALDOA/RCT	L80 + Los100 or Sp25	Plac	80	21	59	48 wks	5
Parving 2008 (16)*	2	ACR > 300 mg/g (or 200 mg/g if pt taking RAS inhibitors) and <3500 mg/g eGFR ≥ 30 mL/min/1.73m2	DRI + ARB/RCT	A150-300 + Los100 v. Los100	Plac	599	75	524	6 mo	5
Rossing 2002 (17)*	2	AER > 300-1000 mg/24h GFR ≥ 25 mL/min	ACEI + ARB/RCCT	C100 or E/L20 + Cs8 v. C100 or E/L20	Plac	18	1	17	8 wks	5
Rossing 2003 (18)*	2	AER > 300-1000 mg/24h GFR ≥ 25 mL/min	ACEI + ARB/RCCT	C150 or E/L40 + Cs16 v. C150 or E/L40	Plac	20	0	20	8 wks	5
Rossing 2005 (19)*	2	AER > 300 mg/24h GFR ≥ 30 mL/min/1.73m2	ACEI or ARB + ALDOA/ RCCT	ACEI and/or ARB (various) + Sp25 v. ACEI or ARB	Plac	21	1	20	8 wks	5
Schjoedt 2005 (20)*	1	AER > 300 mg/24h GFR ≥ 30 mL/min/1.73m2	ACEI or ARB + ALDOA/ RCCT	ACEI and/or ARB (various) + Sp25 v. ACEI or ARB	Plac	22	2	20	2 mo	5
Schjoedt 2006 (21)*	1/2	AER > 2500 mg/24h GFR ≥ 30 mL/min/1.73m2	ACEI or ARB + ALDOA/ RCCT	ACEI and/or ARB various + Sp25 v. ACEI or ARB	Plac	20	0	20	2 mo	5
Song 2003 (22)*	2	PER > 1 g/24h CCr 25-90 mL/min	ACEI + ARB RCCT	R5-7.5 + Cs4-8 v. R5-7.5	Plac	20 (of 32 total)	2	18	16 wks	4
Tan 2010 (23)*	2	AER > 300 mg/24h	ACEI + ARB RCCT	E20 + Los 100 v. E10 + Los 50 v. E20 v. Los 100	No	36	2	34	8 wks	2
Cetinkaya 2004 (24)	?	PER > 300 mg/24h	ACEI + ARB RCCT	E10 + Los50 v. E20 or Los100	No	22	0	22	12 wks	1
Kim 2003 (25)	2	PER > 1 g/24h CCr 25-90 mL/min/1.73m2	ACEI + ARB RCCT	R5.7 (R5 or 7.5, 5.7 average dose) + Cs4 v. ACEI	Plac	24 (of 43 total)	2	22	12 wks	3
Matos 2005 (26)	2	PER 0.5-3 g/24h CCr ≥ 40 mL/min/1.73m2	ACEI + ARB RCCT	P8 + I300 v. P8 v. I300	No	20	5	15	16 wks	2
Song 2006 (27)	2	PER > 1 g/24h CCr 30-59 mL/min/1.73m2	ACEI + ARB RCCT	R5 + Cs8 v. R10 v. Cs16	No	25	4	21	16 wks	3

*Included in analysis for primary outcome; A, aliskiren; ACEI, angiotensin converting enzyme inhibitor; ACR, urinary albumin/creatinine ratio; AER, urinary albumin excretion rate; ALDOA, aldosterone antagonist; ARB, angiotensin receptor blocker; C, captopril; Cs, candesartan; CCr, creatinine clearance; DM, diabetes mellitus; DRI, direct renin inhibitor; E, enalapril; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; I, irbesartan; L, lisinopril; Los, losartan; P, perindopril; PER, protein excretion rate; Plac, placebo; R, ramipril; RCCT, randomized controlled crossover trial; RCT, randomized controlled (parallel group) trial; Sp, spironolactone; V, valsartan.

Table 1: Summary results and selected characteristics of each clinical trial.

Author (ref)	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting
Jacobsen 2002 (12)*	Low[1]	Low[1]	Unclear[3]	Low[6]	Low[7]	Unclear[9]
Jacobsen 2003 (13)*	Low	Low	Unclear	Low	Low	Unclear
Jacobsen 2003 (14)*	Low	Low	Unclear	Low	Low	Unclear
Mehdi 2009 (15)*	Unclear[2]	Low	Low[4]	Low	Low	Unclear
Parving 2008 (16)*	Low	Low	Low	Low	Low	Unclear
Rossing 2002 (17)*	Low	Low	Low	Low	Low	Unclear
Rossing 2003 (18)*	Low	Low	Low	Low	Low	Unlcear
Rossing 2005 (19)*	Low	Low	Low	Low	Low	Unclear
Schjoedt 2005 (20)*	Low	Low	Low	Low	Low	Unclear
Schjoedt 2006 (21)*	Low	Low	Low	Low	Low	Unclear
Song 2003 (22)*	Unclear	Unclear[2]	Unclear	Low	Low	Unclear
Tan 2010 (23)*	Unclear	Unclear	High[5]	Low	Low	Unclear
Cetinkaya 2004 (24)	Unclear	Unclear	High	Low	Unclear[8]	High[10]
Kim 2003 (25)	Unclear	Unclear	Unclear	Low	Low	High
Matos 2005 (26)	Low	Unclear	High	Low	Low	High
Song 2006 (27)	Low	Unclear	High	Low	Low	High

*Included in analysis for primary outcome; [1]Method stated and appropriate; [2]Method not stated; [3]Characteristic of placebo not stated; [4]Matching placebo; [5]No placebo control; [6]Not likely to be influenced by lack of blinding, even if present; [7]Dropouts accounted for appropriately; [8]Unclear if dropouts occurred; [9]Insufficient information to judge; [10]Primary outcome unable to be included in meta-analysis

Table 2: Risk of Bias in Included Studies Based on Cochrane Assessment Tool.

proteinuria (mean difference -20, 95% CI -30, -10) compared to ARB monotherapy [16].

We found no effect of baseline proteinuria on the primary outcome with either drug combination. There was a significant antiproteinuric effect of dual blockade with ACEI plus ARB in patients with < 1 g daily proteinuria at baseline (mean difference -29; 95% CI -35, -23) as well as in patients with ≥ 1 g daily proteinuria at baseline (mean difference -24, 95% CI -42, -6). Similarly, there was a significantly greater antiproteinuric effect of dual blockade with an ALDOA plus ACEI or ARB both in patients with less proteinuria at baseline (< 1 g/24h or < 1 g/g creatinine) (mean difference -30, 95% CI -42, -18) and in patients with greater degrees of baseline proteinuria (≥ 1 g/24h or ≥ 1 g/g creatinine) (mean difference -33, 95% CI -39, -26) (Figure not shown). In the one study using a DRI plus ARB, baseline albuminuria was < 1 g/g [16].

Effect of combination therapy on SBP: There was a 3.5 mmHg decrease (mean difference -3.5, 95% CI -6.5, -0.6) in SBP with ACEI plus ARB vs. monotherapy (Figure 4a), and 6.2 mmHg decrease (mean difference -6.2, 95% CI -11.6, -0.7) with ALDOA in combination with an ACEI or ARB vs. monotherapy (Figure 4b). There was a 2 mmHg decrease in SBP with DRI plus ARB vs. ARB alone, which was not significant [16].

Effect of combination therapy on GFR: There was a slight but insignificantly greater decline in GFR with dual blockade relative to monotherapy with both the ACEI/ARB combination (-0.6 mL/min; 95% CI -7.6, 6.4), and with dual blockade containing an ALDOA (-1.0 mL/min; 95% CI -6.1, 4.1) (Figure not shown). There was a slightly but not significant decrease in GFR (-1.4 mL/min) with a DRI plus ARB vs. ARB alone [16].

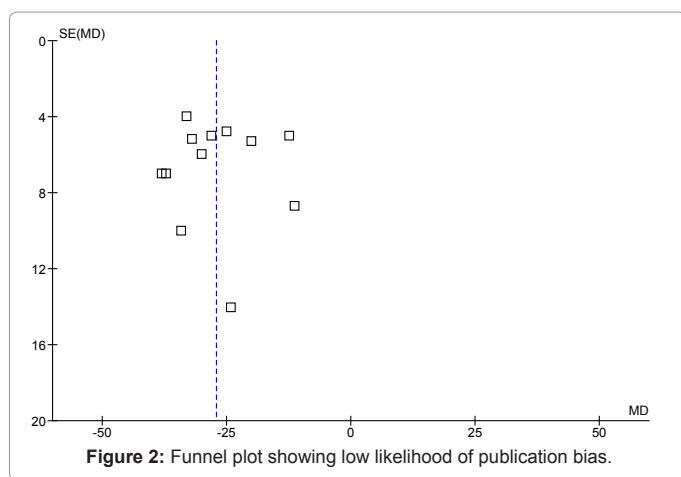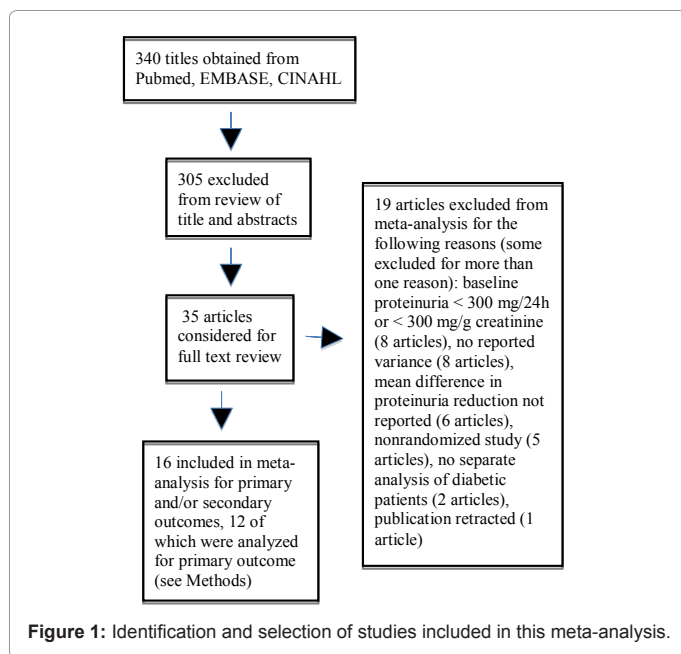## Safety outcomes: change in serum potassium and incidence of hyperkalemia

Serum potassium was slightly but not significantly higher with the ACEI/ARB combination (mean difference 0.09 meq/L; 95% CI -0.01, 0.20). On the other hand, it was significantly higher with the ALDOA combination (mean difference 0.23 meq/L; 95% CI 0.07, 0.39) (Figures 5a and 5b).

In some studies, the number of hyperkalemic episodes was reported. ACEI/ARB combination therapy was associated with a 2.16-fold (0.70-6.67) increase in risk (Figure 5c) vs. a 2.99-fold (0.86-10.38) increase in studies using an ALDOA combination (Figure 5d). In the one study using DRI plus ARB, there was a 2.77-fold (1.01-7.60) increase in risk. In all but 5 instances, hyperkalemia was clinically significant (i.e. serum potassium was > 6.0 meq/L, the patient required treatment for hyperkalemia, and/or the patient was dropped from the study due to hyperkalemia).

Discussion

Dual blockade of the RAS has been proposed to further improve clinical outcomes in patients with DKD. Higher levels of proteinuria are associated with a faster rate of decline in renal function in DKD [28,29] and reduction in proteinuria and BP by ACEIs or ARBs is associated with decreased risk of progression [30,31,32] Thus it is reasonable to predict that a further reduction in proteinuria and BP by dual RAS blockade might further decrease progression. In this meta-analysis, we found that combination RAS inhibitor therapy was indeed more effective than monotherapy in reducing proteinuria in DKD, and this occurred both when baseline proteinuria was < 1 gram/day as well as when it was ≥ 1 gram/day at baseline. Dual RAS blockade was also associated with a greater decline in SBP. On the other hand, inhibition of the RAS in patients with DKD predisposes to hyperkalemia [33]. Combination RAS inhibition would be expected to further increase this risk, especially in patients with impaired GFR. In our meta-analysis, although the overall increment in serum potassium was relatively low (~0.1 – 0.2 meq/L), a substantial number of patients (~5% in ACEI/ARB and ~23% in ALDOA groups) developed clinically significant hyperkalemia. In addition to the well-known adverse and potentially fatal cardiac risk of severe hyperkalemia, even modest degrees of hyperkalemia appear to offset the renoprotective effects of RAS blockade [34].

Most studies investigating dual RAS blockade in various renal diseases have focused on combination ACEI/ARB therapy [12-14,17,18,22-27]. Both ACEIs and ARBs suppress aldosterone secretion; however, with prolonged treatment, aldosterone levels increase, a phenomenon termed "aldosterone escape" [35]. Moreover, there is a secondary increase in renin with either ACEI or ARB therapy. It has

Figure 1: Identification and selection of studies included in this meta-analysis.

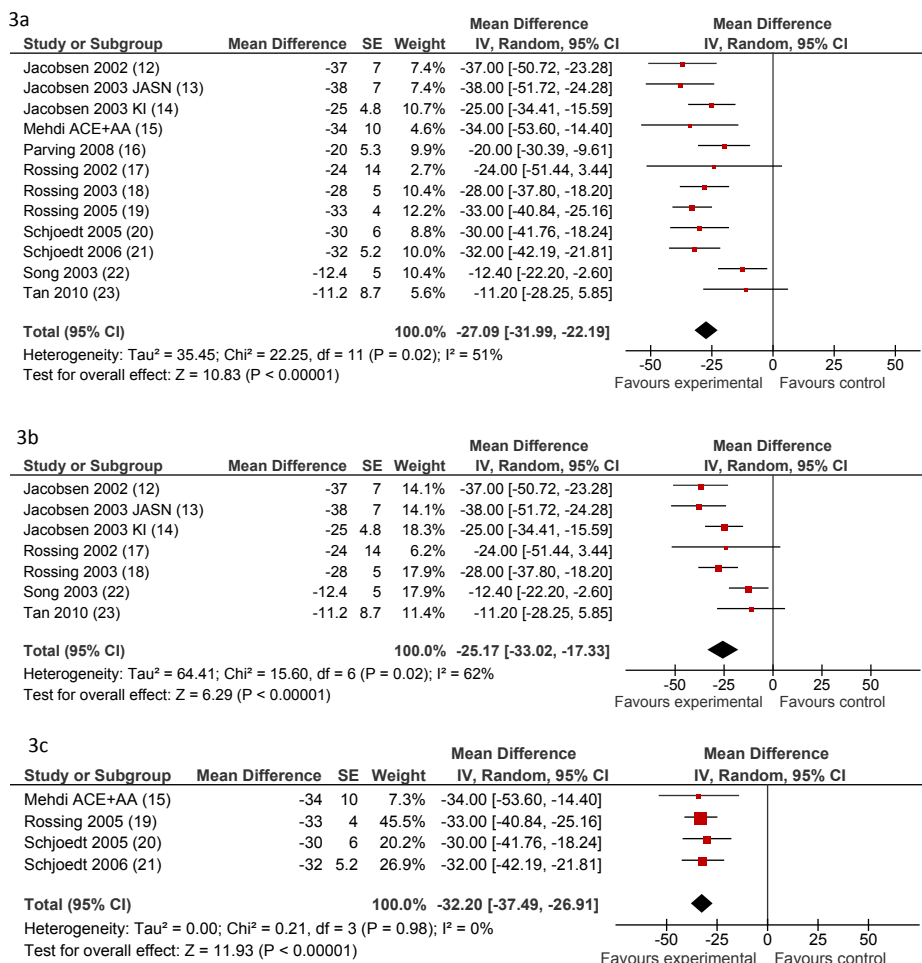**Figure 2:** Funnel plot showing low likelihood of publication bias.

Figure 3: A) Percent reduction in proteinuria. Combination therapy resulted in an additional 27% relative reduction in proteinuria compared to monotherapy. **B)** Combination therapy with an ACEI and ARB vs. monotherapy led to further 25% reduction in proteinuria. **C)** Combination therapy with an ALDOA plus an ACEI or ARB vs. ACEI or ARB alone led to 32% further reduction in proteinuria.
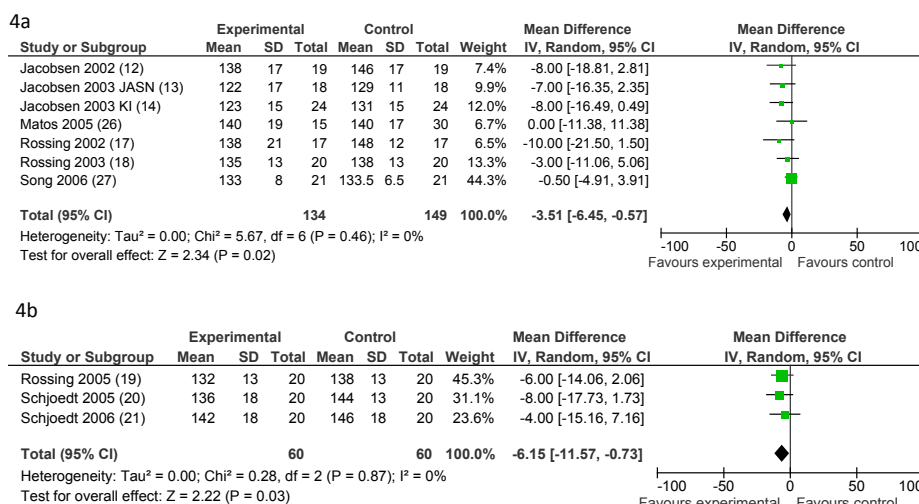

Figure 4: A) Difference in SBP after treatment with ACEI/ARB combination therapy vs. monotherapy. SBP was slightly (-3.5 mmHg) but significantly lower after combination therapy. **B)** Difference in SBP after treatment with ALDOA combination therapy vs. monotherapy. SBP was slightly (-6.2 mmHg) but significantly lower after combination therapy.

thus been proposed that the addition of an ALDOA or DRI to ACEI or ARB will have additional renoprotective benefits in DKD [16]. However, although ALDOAs can reduce proteinuria, combination therapy including an ALDOA results in a substantial risk of hyperkalemia, especially in patients with more severe chronic kidney disease [15,36]. In the recent study of Mehdi et al. [15], in which some subjects had substantial renal dysfunction, serum potassium > 6 meq/L was noted in 52% of patients treated with combined high-dose ACEI plus low-dose (25 mg) spironolactone. In a large study of microalbuminuric patients with generally preserved renal function (thus not included in this analysis), the ALDOA eplerenone when added to the ACEI lisinopril decreased albuminuria by about 40% but 8% of patients treated with the higher dose of eplerenone had to be withdrawn from the study due

to hyperkalemia [36]. Thus the relative benefit vs. risk of dual therapy including an ALDOA needs to be considered even in patients with less severe kidney disease. Moreover, the mechanism of proteinuria reduction with ALDOAs may not be due to aldosterone blockade, as addition of furosemide to either ACEI or ARB also decreases proteinuria [37]. The combination of the DRI aliskiren and an ARB decreased proteinuria more than ARB alone with a relatively low rate of hyperkalemia in one study [16]. However, a larger study comparing the combination of aliskiren and either an ACEI or ARB to an ACEI or ARB alone was terminated after 18-24 months in December 2011 due to an increased risk for non-fatal stroke, renal complications, hyperkalemia, and hypotension in patients taking aliskiren [38].
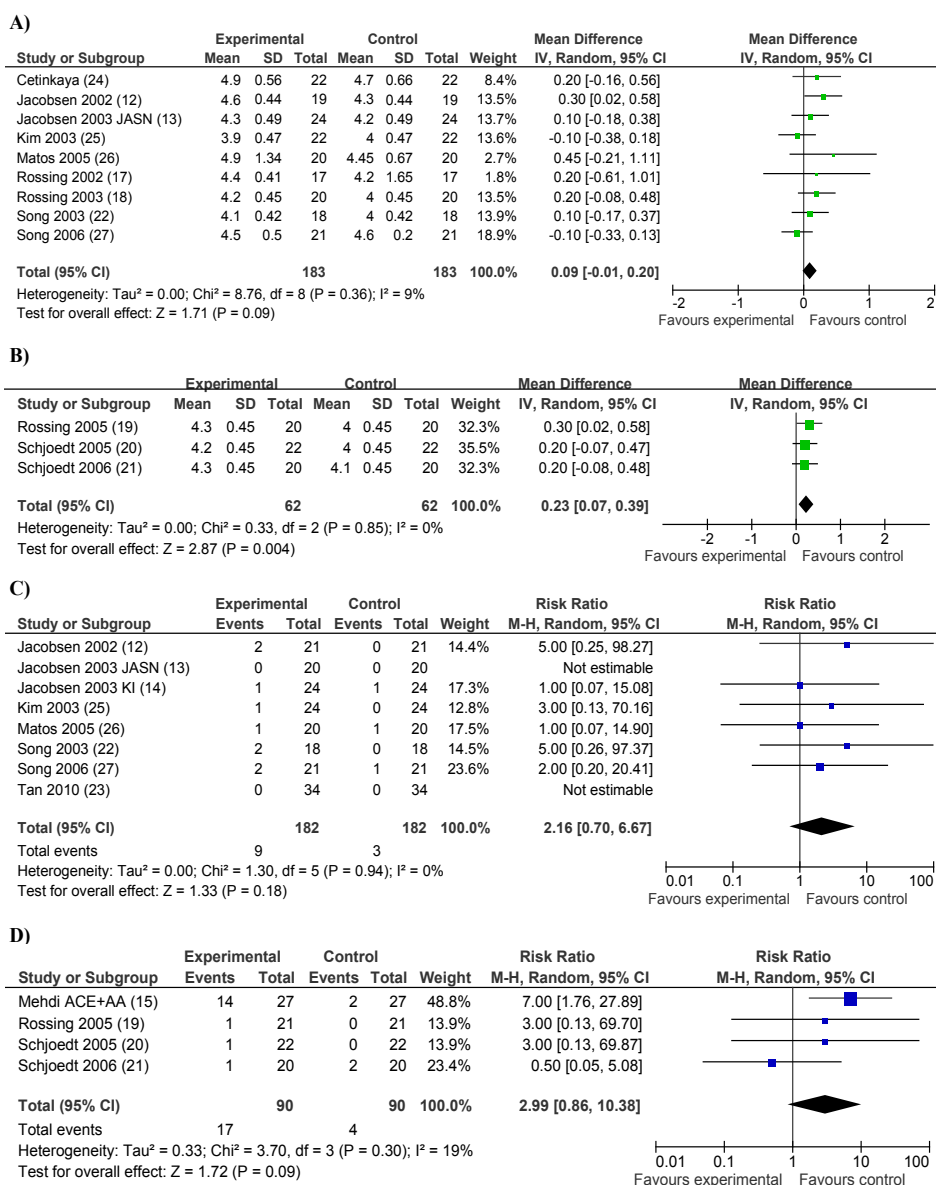

Figure 5: A) Difference in serum potassium after treatment with ACEI/ARB combination therapy vs. monotherapy. Serum potassium was slightly (0.09 mEq/L) but not significantly higher after combination therapy. **B)** Difference in serum potassium after treatment with ALDOA combination therapy vs. monotherapy. Serum potassium was slightly (0.23 mEq/L) but significantly higher after combination therapy. **C)** Risk of hyperkalemia after treatment with ACEI/ARB combination therapy vs. monotherapy. There was a 2.16-fold increased risk of hyperkalemia with combination therapy. **D)** Risk of hyperkalemia after treatment with ALDOA combination therapy vs. monotherapy. There was a 2.99-fold increase risk of hyperkalemia with combination therapy.

The recent ONTARGET study has cast doubt on the efficacy and in particular safety of dual RAS blockade with ACEIs and ARBs [5]. However, it is difficult to apply the results of this study to patients with DKD, as this study was in primarily non-diabetic patients, and only 4% of the diabetic patients in this trial had overt proteinuria. One of the major concerns of the ONTARGET trial was the increased need for acute dialysis in the combination treatment arm due to rapid worsening of renal function in some patients. It is well known that BP reduction, especially with RAS inhibitors, can lead to a decline in GFR during the first several months of therapy [39,40]. Assessing changes in GFR in short-term studies using RAS inhibitors is thus problematic. Interestingly, despite the fact that many studies were of short duration, we did not find differences in change in GFR between the control and intervention groups in this meta-analysis.

In a previous meta-analysis of combination RAS blockade for DKD, only ACEI plus ARB therapy was examined, the authors included nonrandomized studies and studies of microalbuminuric patients (e.g., without overt proteinuria), and only one study was longer than 12 weeks in duration [41]. Other meta-analyses examining combination therapy have combined together various etiologies of renal disease, thus including patients with and without DKD [42]. In contrast, we focused our study on patients with DKD and overt proteinuria and included only randomized studies. Another strength of our meta-analysis is the inclusion of studies involving various types of RAS blocker combinations, including some recent larger-scale studies which employed ALDOAs and DRIs which are now used in clinical practice.

However, our study does have limitations. Not all studies included were of high quality or free of bias, and the majority of the studies were small in sample size and of limited duration. However, restriction of the analysis to only higher quality studies or studies with low risk of bias did not appreciably change the findings. Another confounding factor could be differences in degree of renal impairment among studies. The absence of patient outcome data necessitated use of a surrogate marker (proteinuria) for the primary outcome. Furthermore, there was likely an underrepresentation of African and/or African-American patients.

Summary and Conclusion

In conclusion, dual RAS inhibition is an option to decrease proteinuria and control BP in patients with DKD but is associated with an increased risk of hyperkalemia. Reduction in proteinuria and BP are clearly surrogate outcomes, and no large scale randomized clinical trials assessing the effects of dual RAS blockade on clinical outcomes such as progression to ESKD, cardiovascular morbidity and mortality, and death have been completed. Two such trials, both using combination ACEI plus ARB therapy compared to monotherapy, the aforementioned NEPHRON-D [6] and the VALID trial (Preventing ESRD in Overt Nephropathy in Type 2 Diabetes) [43], are currently in progress. In our meta analysis, the increase in serum potassium was somewhat less with combined ACEI/ARB than with other combinations. We believe that, at this time, dual therapy should probably only be attempted with the ACEI/ARB combination and only in selected patients (e.g., those with macroalbuminuria and normal serum potassium levels on RAS blockade monotherapy).

Acknowledgements

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