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## Recommended Citation

Jennings DL, Kalus JS, Coleman CI, Manierski C, Yee J. Combination therapy with an ACE inhibitor and an angiotensin receptor blocker for diabetic nephropathy: A meta-analysis. Diabetic Medicine 2007; 24(5):486-493.

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DOI: 10.1111/j.1464-5491.2007.02097.x

# Combination therapy with an ACE inhibitor and an angiotensin receptor blocker for diabetic nephropathy: a meta-analysis

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*Accepted 24 October 2006*

## Abstract

**Aims** Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) prevent the progression of diabetic nephropathy (DN). Studies suggest that combination renin–angiotensin–aldosterone system (RAAS)-inhibiting therapy provides additive benefit in DN. However, these studies are small in size. We performed a meta-analysis of studies investigating combination therapy for DN.

**Methods** Studies were identified through a search of MEDLINE, EMBASE, CINAHL and the Cochrane Database. All trials involving combined ACEI and ARB for slowing progression of DN were included. The primary end point was 24-h urinary protein excretion. Blood pressure, serum potassium and glomerular filtration rate (GFR) were secondary end points.

**Results** In the 10 included trials, 156 patients received ACEI + ARB and 159 received ACEI only. Most studies were 8–12 weeks in duration. Proteinuria was reduced with ACEI + ARB ($P = 0.01$). This was associated with significant statistical heterogeneity ($P = 0.005$). ACEI + ARB was associated with a reduction in GFR [3.87 ml/min (7.32–0.42); $P = 0.03$] and a trend towards an increase in serum creatinine (6.86 μmol/l 95% CI –0.76–13.73; $P = 0.09$). Potassium was increased by 0.2 (0.08–0.32) mmol/l ($P < 0.01$) with ACEI + ARB. Systolic and diastolic blood pressure were reduced by 5.2 (2.1–8.4) mmHg ($P < 0.01$) and 5.3 (2.2–8.4) mmHg ($P < 0.01$), respectively.

**Conclusions** This meta-analysis suggests that ACEI + ARB reduces 24-h proteinuria to a greater extent than ACEI alone. This benefit is associated with small effects on GFR, serum creatinine, potassium and blood pressure. These results should be interpreted cautiously as most of the included studies were of short duration and the few long-term studies (12 months) have not demonstrated benefit.

Diabet. Med. 24, 486–493 (2007)

**Keywords** angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, combination therapy, diabetic nephropathy

**Abbreviations** ACEI, angiotensin-converting enzyme inhibitor; ARB, angtiotensin receptor blocker; DN, diabetic nephropathy; GFR, glomerular filtration rate; RAAS, rennin–angiotensin–aldosterone system

## Introduction

Diabetes mellitus currently affects 18.2 million Americans, roughly 6.3% of the total population [1]. Diabetic nephropathy (DN) affects 10–21% of people with diabetes mellitus, and is the leading cause of end-stage renal disease in the USA, accounting for approximately 43% of new cases of end-stage

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renal disease [2]. DN is characterized by the development of microalbuminuria, which, if left untreated, can lead to overt proteinuria, a progressive decline in renal function, and eventually renal failure [3].

Randomized trials have consistently demonstrated the benefit of ACE inhibitors (ACEIs) [4–8] and angiotensin receptor blockers (ARBs) [9–11] in slowing the progression of DN in patients with both Type 1 and Type 2 diabetes mellitus. The results of these trials are reflected in numerous guidelines. For instance, the American Diabetes Association position statement recommends an ACEI or an ARB for all patients with microalbuminuria or advanced stages of nephropathy [12]. The National Kidney Foundation guidelines on hypertension and anti-hypertensive agents in chronic kidney disease recommend that patients with diabetic kidney disease, with or without hypertension, should be treated with either an ACEI or an ARB [13].

Although this body of literature clearly supports the use of either an ACEI or an ARB, there is a growing interest in dual blockade of the renin–angiotensin–aldosterone system (RAAS) for the treatment of DN. The RESOLVD Pilot Study demonstrated that combining enalapril with candesartan provided superior suppression of left-ventricular remodelling and RAAS neurohormones than either therapy alone [14]. This trial demonstrates that single-drug therapy directed against the RAAS results in incomplete blockade of this system, a phenomenon commonly referred to as 'ACE escape'. While the notion of ACE escape provides a rationale for the combination of an ACEI and an ARB in treating diseases associated with the RAAS such as DN, the RESOLVD pilot study did not examine this end point.

Several studies have examined the role of combined ACEI/ARB therapy for DN [15–27]. Although these studies support the benefit of combination therapy, all but one were small, involving only 24 patients or less. Therefore, less is known about the role of dual RAAS blockade in patients with DN. The purpose of this meta-analysis is to pool the results of these small studies in order to better understand the role of dual angiotensin II antagonism for the treatment of DN.

## Methods

### Identification and selection of studies

We conducted a search of MEDLINE (January 1966 to May 2006), EMBASE (1980 to May 2006) and CINAHL (1982 to May 2006) to identify all trials published in English involving the combination of an ACEI and an ARB for treatment of DN. We used the medical subject headings (including all subheadings) and text keywords 'ACE inhibitor and angiotensin receptor blocker and combination and diabetic nephropathy' as our search parameters. In addition, we performed a manual search of the literature using the references of original manuscripts and review articles. Finally, a search of the Cochrane database of systematic reviews was conducted. We included any randomized, controlled, parallel or crossover trial comparing an ACEI or an ARB to the combination of the two for the treatment of DN. Studies were also required to report 24-h urinary protein excretion for inclusion.

### Outcomes and statistical analysis

Summary results and selected characteristics of each clinical trial were tabulated. The primary outcome analysed was the comparative change in 24-h urinary protein excretion for an ACEI alone or in combination with an ARB. When reported, per cent reduction in protein excretion was also evaluated as a secondary analysis. In addition, systolic blood pressure, diastolic blood pressure, serum creatinine, serum potassium and glomerular filtration rate (GFR) were analysed in order to assess the safety of dual blockade of the RAAS.

Weighted mean differences were calculated using RevMan vs. 4.2.7 [28] utilizing a random effects model (DerSimonian and Laird methodology). Statistical heterogeneity was assessed with a $\chi^2$-test. Statistical heterogeneity is present when significant variability exists in the results of the studies included in the meta-analysis. A $P$-value of $< 0.1$ defined significant heterogeneity. To assess the potential for publication bias, a funnel plot analysis was also performed.

To establish the effect of clinical heterogeneity of the included studies on the results of the meta-analysis, subgroup analysis was performed. The effect of study medication dose, type of diabetes, change in systolic blood pressure and baseline level of proteinuria were examined. Sensitivity analyses were conducted to determine the robustness of our analysis. One of the analyses was conducted by excluding all non-randomized and unblinded studies. The other excluded two studies with designs that were dissimilar from the others in the analysis [23,25].

## Results

### Studies and patients

Ten studies were identified that met inclusion criteria (Table 1), nine of which were crossover trials. Three studies were excluded because 24-h urinary protein excretion was not reported [15,27,29]. Two other studies, one included and one excluded in this analysis, integrated both patients with diabetic and non-diabetic nephropathy [21,26]. The study that was included presented the results separately for the two different groups, allowing extraction of only the data referring to the patients with diabetes for our analysis [21]. The other study was excluded because the four patients without diabetes were not presented separately from those with diabetes [26]. A funnel plot suggested that publication bias cannot be ruled out (data not shown).

The baseline characteristics of the patients analysed are presented in Table 1. Of the 159 patients in the final analysis, 156 were exposed to combination therapy and 159 were exposed to the control (ACEI alone). Detailed exclusion criteria were provided for five of the 10 studies and included contraindications to either an ACEI or an ARB, a serum potassium greater than 4.6 mmol/l, a systolic blood pressure less than 100 mmHg, or a glomerular filtration rate less than 30 ml/min. Baseline

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**Table 1** Comparison of trials with combination RAAS therapy for diabetic nephropathy

| Trial | Methods | Population | Demographics | Combination | Control | Albumin excretion | Included? |
|---|---|---|---|---|---|---|---|
| Jacobsen *et al*. [18] | R, DB, PC, CO, 8 weeks in each arm | Nineteen patients with Type 1 DM, HTN and proteinuria | Age: 45 ± 10 years<br>Male: 81%<br>DM: 29 ± 8 years<br>DN: 10 ± 5 years<br>CCB: 48% | Irbesartan 300 mg daily<br>+<br>lisinopril 20 mg, enalapril 20 mg or captopril 100 mg daily | Placebo<br>+<br>lisinopril 20 mg, enalapril 20 mg or captopril 100 mg daily | Baseline: 1866 ± 934<br>Control–Post: 1574 ± 1079<br>Combo–Post: 996 ± 801<br>$P < 0.001$ | Yes |
| Jacobsen *et al*. [16] | R, DB, PC, CO, 8 weeks in eacharm | Eighteen white patients with Type 1 DM and proteinuria | Age: 43 ± 7 years<br>Male: 72%<br>DM: 30 ± 7 years<br>DN: 10 ± 6 years<br>CCB: NR | Valsartan 80 mg daily<br>+<br>benazepril 20 mg daily | Placebo<br>or<br>valsartan 80 mg daily<br>or<br>benazepril 20 mg daily | Baseline: 701 ± 554<br>Control–Post: 239 ± 192<br>Combo–Post: 138 ± 127<br>$P < 0.01$ | Yes |
| Jacobsen *et al*. [17] | R, DB, PC, CO, 8 weeks in each arm | Twenty-four patients with Type 1 DM and proteinuria | Age: 42 ± 9 years<br>Male: 71%<br>DM: 31 ± 9 years<br>DN: 13 ± 5 years<br>CCB: 25% | Irbesartan 300 mg daily<br>+<br>enalapril 40 mg daily | Placebo<br>+<br>enalapril 40 mg daily | Baseline: NR<br>Control–Post: 519 ± 559<br>Combo–Post: 373 ± 497<br>$P < 0.001$ | Yes |
| Rossing *et al*. [20] | R, DB, PC, CO, 8 weeks in each arm | Seventeen patients with Type 2 DM, HTN and proteinuria | Age: 58 ± 8 years<br>Male: 76%<br>DM: 13 ± 6 years<br>DN: 8 ± 5 years<br>CCB: 65% | Candesartan 8 mg daily<br>+<br>lisinopril 20 mg, enalapril 20 mg or captopril 100 mg daily | Placebo<br>+<br>lisinopril 20 mg, enalapril 20 mg or captopril 100 mg daily | Baseline: 1764 ± 1383<br>Control–Post: 1764 ± 1383<br>Combo–Post: 1334 ± 1165<br>$P = 0.036$ | Yes |
| Rossing *et al*. [19] | R, DB, PC, CO, 8 weeks in each arm | Twenty white patients with Type 2 DM, HTN and proteinuria | Age: 62 ± 8 years<br>Male: 85%<br>DM: 15 ± 8 years<br>DN: NR<br>CCB: 65% | Candesartan 16 mg daily<br>+<br>lisinopril 40 mg, enalapril 40 mg or captopril 150 mg daily | Placebo<br>+<br>lisinopril 40 mg, enalapril 40 mg or captopril 150 mg daily | Baseline: NR<br>Control–Post: 706 ± 635<br>Combo–Post: 508 ± 617<br>$P < 0.001$ | Yes |
| Kim *et al*. [21] | R, DB, PC, CO, 12 weeks in each arm | Twenty-two patients with Type 2 DM and proteinuria | Age: 43 ± 19 years<br>Male: 59%<br>DM: NR<br>DN: NR<br>CCB: 88% | Candesartan 4 mg daily<br>+<br>rampril 5–7.5 mg daily | Placebo<br>+<br>rampril 5–7.5 mg daily | Baseline: 4000 ± 1400<br>Control–Post: 4100 ± 1407<br>Combo–Post: 3800 ± 938<br>$P$ = NS | Yes |
| Kuriyama *et al*. [22] | CO, 12 weeks in each arm | Nine patients with Type 2 DM, HTN, proteinuria and CKD | Age: 50 ± 10 years<br>Male: 44%<br>DM: NR<br>DN: NR<br>CCB: NR | Candesartan 4 mg daily<br>+<br>temocapril 2 mg daily | Temocapril 2 mg daily | Baseline: 4300 ± 1800<br>Control–Post: 3500 ± 1700<br>Combo–Post: 2600 ± 1300<br>$P < 0.01$ | Yes |



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**Table 1** *Continued*

| Trial | Methods | Population | Demographics | Combination | Control | Albumin excretion | Included? |
|---|---|---|---|---|---|---|---|
| Hebert *et al*. [23] | CO, 1 week in each arm | Seven patients with Type 1 and Type 2 DM and proteinuria | Age: 59 ± 16 years<br>Male: 57%<br>DM: NR<br>DN: NR<br>CCB: 57% | Losartan 50–100 mg daily<br>+<br>captopril 100–150 mg, enalapril 10–20 mg, lisinopril 10 mg or fosinopril 20 mg daily | Captopril 100–150 mg, enalapril 10–20 mg, lisinopril 10 mg or fosinopril 20 mg daily | Baseline: 5970 ± 5580<br>Control–Post: 5300 ± 2100<br>Combo–Post: 5300 ± 2100<br>*P* = NR | Yes |
| Tutuncu *et al*. [25] | R, P, 12 months | Twenty-two patients with Type 2 DM and proteinuria | Age: 54 ± 7 years<br>DM: 8 ± 6 years<br>DN: NR<br>CCB: NR | Losartan 50 mg daily<br>+<br>enalapril 5 mg daily | Losartan 50 mg daily<br>or<br>enalapril 5 mg daily | Control–Pre: 85.0 ± 31.3<br>Control–Post: 35.4 ± 19.6<br>*P* = 0.0001<br>Combo–Pre: 102.0 ± 32.8<br>Combo–Post: 40.7 ± 29.5<br>*P* = 0.0003 | Yes |
| Cetinkaya *et al*. [24] | R, CO, 12 weeks in each arm | Eleven patients with HTN, Type 2 DM and proteinuria | Age: 54 ± 8 years<br>Male: 55%<br>DM: NR<br>DN: NR<br>CCB: NR | Losartan 50 mg daily<br>+<br>enalapril 10 mg daily | Enalapril 10 mg daily | Baseline: 4820 ± 1110<br>Control–Post: 3170 ± 690<br>Combo–Post: 2360 ± 400<br>*P* < 0.05 | Yes |
| Morgensen *et al*. [15] | R, DB, P, 12 weeks | One hundred and ninety-nine patients with HTN, Type 2 DM, and micro-proteinuria | Age: 59.8 ± 9.2 years<br>Male: 65%<br>DM: 9.1 ± 7.5 years<br>DN: NR<br>CCB: NR | Candesartan 16 mg daily<br>+<br>lisinopril 20 mg daily (67 patients) | Candesartan 16 mg daily (66 patients)<br>or<br>lisinopril 20 mg daily (64 patients) | 18% (–20% to +44%) increase in urine albumin -to-creatnine ratio<br>*P* > 0.2 | No |
| Agarwal *et al*. [26] | R, PC, CO, 4 weeks in each arm | Sixteen patients with HTN, proteinuria > 1 g/day (12 had DM) | Age: 53 ± 9 years<br>Male: 88%<br>DM: NR<br>DN: NR<br>CCB: NR | Losartan 50 mg daily<br>+<br>lisinopril 40 mg daily | Placebo<br>+<br>lisinopril 40 mg daily | +1% (–20% to +28%) increase in urine protein excretion<br>*P* = 0.89 | |
| Fujisawa *et al*. [27] | Observational, 12 weeks | Twenty-seven patients with Type 2 DM | Age: 62.4 ± 8.5 years<br>Male: 55%<br>DM: 14 ± 6.9 years<br>DN: NR<br>CCB: NR | Candesartan 4 mg daily<br>+<br>imidapril 5 mg daily | Candesartan 8 mg daily<br>or<br>imidapril 10 mg daily | 34% (14% to 49%) reduction in urinary albumin index<br>*P* = 0.003 | No |
| Andersen *et al*. [29] | R, DB, P, 12 months | Seventy-five patients with Type 1 or Type 2 DM and HTN | Age: 54–56 ± 9 years<br>Male: 75%<br>DM: 11 years<br>DN: NR<br>CCB: 23% | Lisinopril 20 mg daily<br>+<br>candesartan 16 mg daily | Lisinopril 40 mg daily | | |

BP, blood pressure; CCB, calcium channel blocker; CO, crossover; DB, double-blind; DM, diabetes mellitus; DN, diabetic nephropathy; HTN, hypertension; NR, not reported; P, parallel; PC, placebo controlled; R, randomized.

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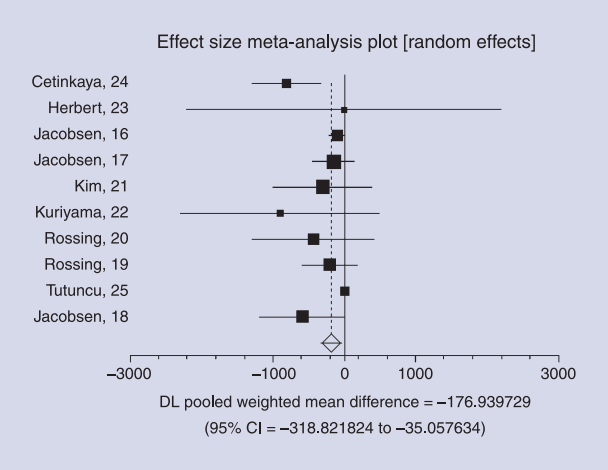


**FIGURE 1** This figure presents the overall results of the meta-analysis. The black diamond represents the weighted mean difference and 95% confidence interval. WMD, weighted mean difference. *Statistical heterogeneity is demonstrated by $P = 0.005$. **Overall significance is demonstrated by $P = 0.01$.

blood pressure was reported for eight of 10 studies, and of these trials, populations in six of the eight were considered hypertensive. Most studies were 8–12 weeks in duration.

### Quantitative data analysis

#### *Efficacy end point*

The meta-analysis of 10 trials demonstrated a reduction in 24-h proteinuria ($P = 0.01$, Fig. 1); this reduction was associated with significant statistical heterogeneity between trials ($P < 0.005$).

In the subgroup analysis of the effect of dose of medication used in the various studies, we divided the studies into two groups, those in which an ARB was added to maximal doses of ACEI [17,19], and those in which an ARB was added to submaximal doses of an ACEI (Fig. 2a) [16,18,20–25]. There was only a trend toward benefit in the maximal dose subgroup ($P = 0.17$), while analysis of the eight studies using submaximal doses did demonstrate benefit ($P = 0.03$). Subgroup analysis in which patients with Type 1 [16–18] and Type 2 [19–25] diabetes were analysed separately demonstrated a trend favouring combination therapy for both Type 1 and Type 2 diabetes mellitus ($P = 0.06$ for both subgroups, Fig. 2b).

In order to explore the influence of baseline level of proteinuria, per cent reduction in protein excretion was analysed (available for five of the included studies) [16–20]. In this analysis, there was an additional 39.4% (95% CI = 9.3–69.5%, $P = 0.010$) reduction in protein excretion with combination therapy. A subgroup analysis was also completed in an effort to address this issue. In this analysis, baseline level of proteinuria was used to divide the studies into tertiles. The beneficial effects of combination therapy appeared to decline as baseline level of proteinuria declined (Fig. 2c).

A final subgroup analysis evaluated the impact of blood pressure reduction on proteinuria. In this analysis, mean change in systolic blood pressure was used to divide the studies into tertile subgroups. Change in proteinuria tended to be most pronounced when larger reductions in blood pressure were present and least pronounced when there was little or no reduction in blood pressure (Fig. 2d).

#### *Sensitivity analysis*

Removal of non-randomized, unblinded studies from our analysis did not alter the results for the primary end point significantly ($P = 0.007$); however, the heterogeneity was greatly reduced ($P = 0.67$). Removal of the only study that did not employ a crossover design [25] and the study that was only 1 week in duration [23] had little impact on the results ($P = 0.004$). These results are presented in more detail in Fig. 2.

#### *Safety end points*

Analysis of the systolic and diastolic blood pressure for these studies demonstrated a reduction in both parameters. The mean change in systolic and diastolic blood pressure was −5.2 mmHg (95% CI −8.4 to −2.1; $P < 0.01$) and −5.3 mmHg (95% CI −8.4 to −2.2; $P < 0.01$), respectively. Three studies were not included in this analysis; two because the blood pressure was only reported as mean arterial pressure, and another because blood pressure data was not available for all patients [21,23,24].

Dual blockade of the RAAS was associated with a mean decrease in GFR of 3.87 ml/min (95% CI 7.32–0.42; $P = 0.03$) [16–22] with a trend towards an increase in serum creatinine (6.86 μmol/l 95% CI −0.76–13.73; $P = 0.09$) [16–20,22–24]. Serum potassium was increased by a mean of 0.2 mmol/l (95% CI 0.08–0.32; $P < 0.01$) with combination therapy [16–23].

## Discussion

The pathophysiologic basis for dual blockade of the RAAS is rooted in the multiple pathways in which angiotensin II and aldosterone are generated. In addition to ACE, other enzymes such as chymase can produce angiotensin II, suggesting incomplete blockade of the RAAS with ACEI or ARBs alone [14,30]. The ability of these two therapeutic agents to synergistically antagonize the RAAS can also be explained by their complimentary mechanisms of action. For example, ACE inhibition leads to a prolonged half-life of bradykinin, a potent vasodilator believed to be renoprotective [31]. ARBs do not increase the half-life of bradykinin. They can further ablate the damaging effects resulting from the production of angiotensin II by non-ACE pathways, which is not completely blocked by an ACEI. Thus, it seems plausible that combining these two agents could more effectively oppose the RAAS than either agent alone.

The results of this meta-analysis suggest that short-term (i.e. most studies were 8–12 weeks in duration) combination therapy with an ACEI and an ARB is superior to ACE inhibition alone in reducing 24-h urinary protein excretion in patients with DN. Given the paucity of studies longer than 12 weeks in


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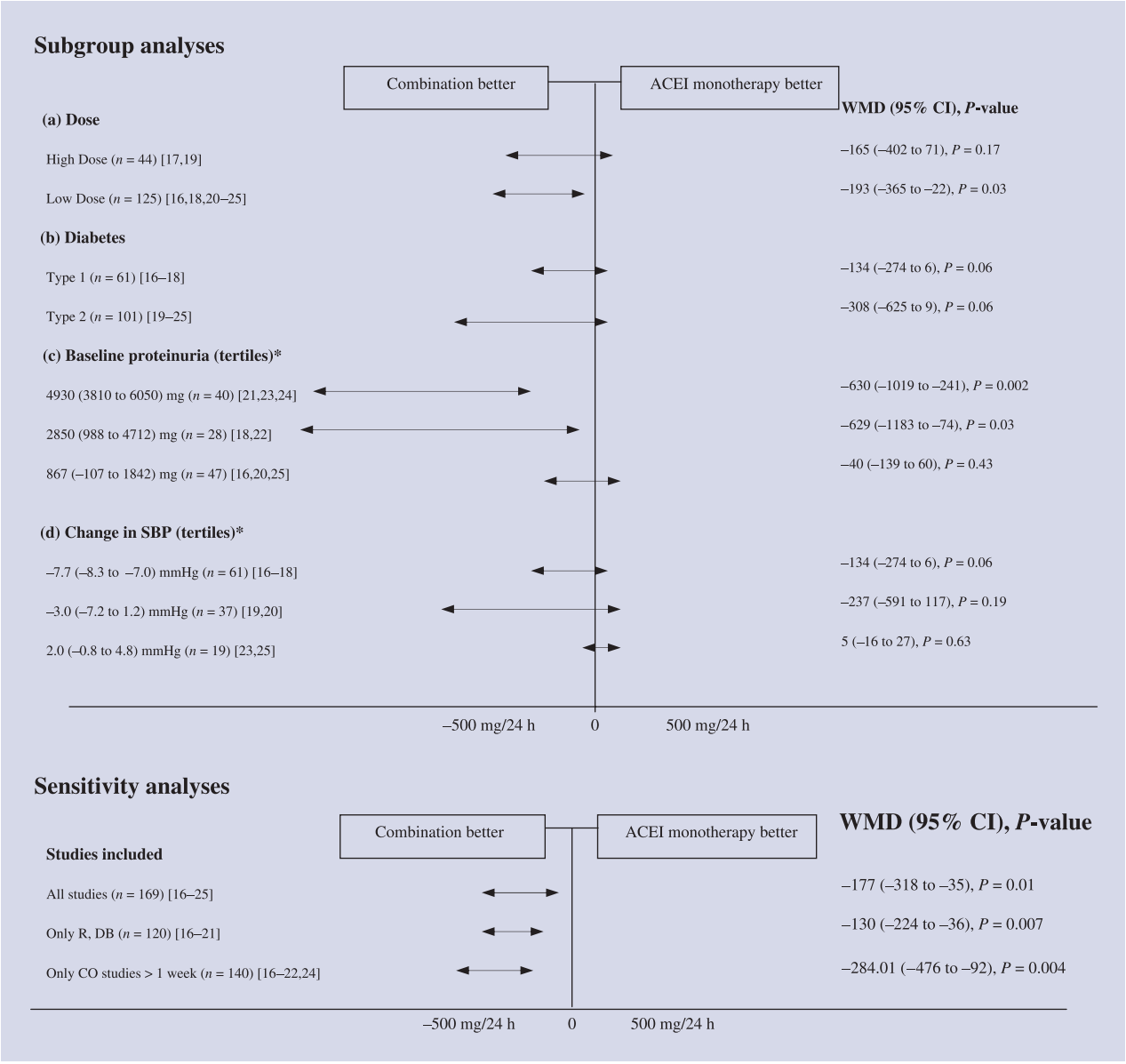


**FIGURE 2** Visual representation of subgroup and sensitivity analyses. Each line represents the weighted mean difference and 95% confidence interval for the analysis. Lines crossing zero represent analyses in which there was no significant difference between combination therapy and ACE inhibitor monotherapy. Lines falling completely to the left of zero represent analyses where combination therapy was superior. ACEI, Ace inhibitor; CO, crossover; DB, double blind; R, randomized; SBP, systolic blood pressure; WMD, weighted mean difference (mg/24 h). *Mean (95% confidence interval) reported for each tertile.

duration, this meta-analysis is not able to provide insight into the effect of longer durations of dual RAAS blockade. Combination therapy resulted in a statistically and clinically significant decrease in GFR. This decrease may have been because of the observed reductions in both systolic and diastolic blood pressure, which could have resulted in diminished renal perfusion. The duration of the included studies was relatively short; therefore, this decrease in GFR could also have been a transient reduction. However, a decrease of nearly 4 ml/min in GFR after only 2–3 months of dual therapy is somewhat concerning and should be considered in assessing the risk/benefit of this treatment strategy. There was also a statistically significant increase in serum potassium with dual blockade of the RAAS in our analysis. Although this increase was small and is probably not clinically significant, it is still a potential disadvantage to this strategy, especially when one considers the short duration of most of the included studies. It should be noted that hyperkalaemia ($K^+ > 5.0$ mmol/l) was only reported in seven of the included patients [16–19,21].

The COOPERATE study determined the role of dual RAAS blockade in slowing the progression of nephropathy in patients without diabetes [32]. In this study, combination therapy with

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losartan and trandolapril resulted in an approximate 50% reduction in the rate of doubling of serum creatinine or development of end-stage renal disease over a 3-year period, when compared with either agent alone. The patient population ($n = 263$) in this study was larger and the duration of treatment (3 years) was longer than any of the DN studies included in this meta-analysis. Additionally, this study demonstrated improvement in an accepted clinical end point, doubling of serum creatinine or progression to end-stage renal disease, instead of proteinuria. While COOPERATE provides strong evidence for dual RAAS blockade in non-diabetic nephropathy, our meta-analysis highlights the need for more study of this strategy in DN.

This analysis is limited by the quality of the studies available for inclusion. Studies included in this analysis were relatively small, heterogeneous in design, patient population and intervention, short in duration and only evaluated albumin/protein excretion, instead of more definitive clinical end points (doubling of serum creatinine, rate of end-stage renal disease or mortality). In order to deal with some of these limitations, subgroup analysis was performed to address clinical heterogeneity and the effect of combination therapy on GFR was assessed to provide more information than simply effect on albumin/protein excretion. Although these measures are not ideal for eliminating the influence of the primary studies' limitations, they do help to clarify the issue and enable hypotheses to be generated.

Only one of the studies included in this analysis was greater than 12 weeks [25]. This study was 12 months in duration and demonstrated no difference between combination therapy and ACEI alone ($P = 0.798$). The CALM II study was also 12 months in duration and demonstrated no difference in urinary albumin-to-creatinine ratio (Table 1) [29]. CALM II was not included in this meta-analysis because urinary albumin excretion was not reported; however, these two studies together seem to suggest that the early beneficial effect of combination therapy on protein excretion may not translate into long-term benefit.

It should also be noted that our meta-analysis demonstrated a reduction in blood pressure with combination therapy. The majority of the studies included in this analysis not only showed an improvement in both proteinuria and blood pressure, but they also demonstrated statistically significant correlations between these two parameters. Numerous studies examining monotherapy with an ACEI or an ARB have shown significant renoprotective effects of these medications independent of changes in blood pressure [4–7,9–11]. However, a recent meta-analysis of these studies reported a strong relationship between blood pressure reduction and reduction in proteinuria [33]. The subgroup analysis of blood pressure tertiles in this paper was an attempt to address the issue of whether blood pressure reduction may be the major factor in slowing the progression of renal dysfunction with combination therapy. Although a meta-analysis is not the optimal method for clarifying this issue, this subgroup analysis suggests that additive blood pressure reduction cannot be discounted as playing a role in reducing albumin/protein excretion with combination therapy. Future studies comparing dual blockade to an ACEI combined with other anti-hypertensive agents targeting similar blood pressure levels will have to be conducted in order to fully address this issue.

Another important issue relates to the variability of the baseline level of protein excretion in the studies included in the analysis. In the overall analysis, data from studies enrolling patients with microalbuminuria were combined with studies including patients with macroalbuminuria or nephrotic range proteinuria. This introduction of clinical heterogeneity was addressed by determining per cent reduction in protein excretion and by analysing subgroups divided by tertiles of baseline level of proteinuria. It appeared that those with the greatest degree of proteinuria derive the greatest benefit from combination therapy. When baseline level of proteinuria was smaller, there was no benefit with combination therapy. This is consistent with the CALM study, as no benefit was observed with combination therapy in a microalbuminuric patient population [15].

A final issue stems from the variety of medications and doses employed in the studies included in our analysis (Table 1). The majority of the studies included in this meta-analysis involved the addition of an ARB to submaximal doses of an ACEI. Further, the optimal anti-proteinuric dose for ACE inhibitors and the ARBs has never been established. However, recent studies have demonstrated that higher doses of ACEI or ARB are superior to lower doses for reducing proteinuria [11,34]. Therefore, it is unclear from this analysis whether combination therapy would be beneficial if an ARB was added to a maximal dose of an ACEI. Future trials will first need to clarify the optimal anti-proteinuric doses for both ACE inhibitors and ARBs, and then study these optimal doses in mono- vs. combination therapy for DN.

In conclusion, our meta-analysis suggests that patients with diabetic nephropathy derive short-term benefit from combination ACEI/ARB therapy. Given the limitations of the current body of literature in this area, it is unclear whether short-term beneficial effects on protein excretion persist with long-term therapy or will translate to significant improvements in other important end points. Future studies, evaluating accepted clinical end points (doubling of serum creatinine, onset of end-stage renal disease) are needed to establish the long-term benefit of this treatment, as well as to define the optimal dose of each agent and test the optimal doses of monotherapy against dual RAAS blockade.

## Competing interests

None to declare.

### Acknowledgements

We would like to thank Dr Kasper Rossing for providing data needed for this analysis that were not included in his original publication.


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