Systematic Review of Combined Angiotensin-Converting Enzyme Inhibition and Angiotensin Receptor Blockade in Hypertension

Timothy W.R. Doulton, Feng J. He, Graham A. MacGregor

Abstract—Some evidence suggests that long-term angiotensin-converting enzyme (ACE) inhibition may become less effective, thereby increasing angiotensin II levels, which could be inhibited by the addition of an angiotensin receptor blocker. We conducted a meta-analysis of randomized trials with searches of MEDLINE, EMBASE, and Cochrane databases. Overall, the combination of an ACE inhibitor and an angiotensin receptor blocker reduced ambulatory blood pressure by 4.7/3.0 mm Hg (95% confidence interval [CI], 2.9 to 6.5/1.6 to 4.3) compared with ACE inhibitor monotherapy and 3.8/2.9 mm Hg (2.4 to 5.3/0.4 to 5.4) compared with angiotensin receptor blocker monotherapy. Clinic blood pressure was reduced by 3.8/2.7 mm Hg (0.9 to 6.7/0.8 to 4.6) and 3.7/2.3 mm Hg (0.4 to 6.9/0.2 to 4.4) compared with ACE inhibitor and angiotensin receptor blocker, respectively. However, the majority of these studies used submaximal doses or once-daily dosing of shorter-acting ACE inhibitors and, when a larger dose of shorter-acting ACE inhibitor was given or a longer-acting ACE inhibitor was used, there was generally no additive effect of the angiotensin receptor blocker on blood pressure. Proteinuria was reduced by the combination compared with ACE inhibitor and angiotensin receptor blocker monotherapy, an effect that was independent of blood pressure in several studies, suggesting that the combination could have benefits in proteinuric nephropathies. None of the studies was of sufficient size and duration to determine whether there may be safety concerns. In conclusion, although there is a small additive effect on blood pressure with an ACE inhibitor–angiotensin receptor blocker combination, the routine use of this combination in uncomplicated hypertension is not recommended until more carefully controlled studies are performed. (Hypertension. 2005;45:880-886.)

Key Words: angiotensin-converting enzyme ■ hypertension ■ meta-analysis ■ proteinuria ■ receptors, angiotensin ■ renin-angiotensin system

The renin-angiotensin system (RAS) plays an important role in regulating blood pressure (BP).1,2 Both angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II type 1 receptor blockers (ARBs) inhibit the RAS and have been shown to be effective treatments for increased BP.3 At the same time, they have other beneficial effects that may be independent of their ability to lower BP, for example, reductions in the progression of nephropathy in diabetes mellitus (DM) and chronic renal failure (CRF).4–6 Administration of ACEI causes plasma levels of angiotensin II (Ang II) to become undetectable, whereas there is some evidence that chronic administration of ACEI results in partial escape, ie, there is incomplete suppression of Ang II levels at peak, which may reduce the effectiveness of ACEI as BP-lowering agents.7–9 Several studies have suggested that combining an ARB with an ACEI may provide a more complete blockade of the RAS in the treatment of diabetic and nondiabetic nephropathy and essential hypertension; in particular, it may lower BP and proteinuria further than monotherapy.10–13 However, the major-
inhibition with an ACEI and ARB compared with monotherapy with either class of drug from electronic databases: MEDLINE (1966 to July 2004) and EMBASE (1988 to July 2004). We also searched the Cochrane Library (The Cochrane Controlled Trials Register and the Cochrane Database of Systematic Reviews) with the terms “ACE inhibitor” and “angiotensin receptor” from 1995 to 2004. We reviewed the reference lists of original and review articles to search for further relevant trials. Searches were limited to English language.

Inclusion and Exclusion Criteria
For inclusion, trials needed to satisfy the following criteria: (1) participants were hypertensive (clinic sitting systolic BP [SBP] \( \geq 140 \) mm Hg and/or diastolic BP [DBP] \( \geq 90 \) mm Hg; mean ambulatory SBP \( \geq 130 \) mm Hg or ambulatory DBP \( \geq 85 \) mm Hg) or the use of antihypertensive drugs; (2) changes in BP were a primary or significant secondary outcome variable; and (3) allocations to trial interventions were randomized.

### TABLE 1. Overview of Study Entry Criteria, Study Design, Demographic Details of Participants, and Baseline BP

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Entry Criteria</th>
<th>Study Design</th>
<th>Duration of Intervention</th>
<th>n*</th>
<th>Age, y</th>
<th>Baseline BP</th>
<th>Study Intervention†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacobsen, 2002(^{10})</td>
<td>Type 1 DM BP &gt;(135/85) &gt;(1) g proteinuria</td>
<td>Crossover</td>
<td>8 wk</td>
<td>21</td>
<td>45</td>
<td>156/87$||§</td>
<td>ACEI + Irbesartan 300 od ACEI + placebo</td>
</tr>
<tr>
<td>Jacobsen, 2003(^{34})</td>
<td>Type 1 DM &gt;(300) mg proteinuria</td>
<td>Cross-over</td>
<td>8 wk</td>
<td>24</td>
<td>42</td>
<td>131/74$||§</td>
<td>Enalapril 40 od + Irbesartan 300 od Enalapril 40 od + placebo</td>
</tr>
<tr>
<td>Jacobsen, 2003(^{35})</td>
<td>Type 1 DM BP &gt;(135/85) &gt;(300) mg proteinuria</td>
<td>Cross-over</td>
<td>8 wk</td>
<td>20</td>
<td>43</td>
<td>141/81$||§</td>
<td>Benazepril 20 od + Valsartan 80 od Benazepril 20 od Valsartan 80 od Placebo</td>
</tr>
<tr>
<td>Mogensen, 2000(^{11})</td>
<td>Type 2 DM BP &lt;(300) mg proteinuria</td>
<td>Parallel group</td>
<td>12 wk</td>
<td>67</td>
<td>60</td>
<td>163/96$||§</td>
<td>Lisinopril 20 od + Candesartan 16 od Lisinopril 20 od + placebo Candesartan 16 od + placebo</td>
</tr>
<tr>
<td>Rossing, 2002(^{36})</td>
<td>Type 2 DM BP &gt;(135/85) &gt;(1) g proteinuria</td>
<td>Cross-over</td>
<td>8 wk</td>
<td>18</td>
<td>58</td>
<td>159/85$||§</td>
<td>ACEI + Candesartan 8 od ACEI + placebo</td>
</tr>
<tr>
<td>Rossing, 2003(^{29})</td>
<td>Type 2 DM BP &gt;(135/85) &gt;(300) mg proteinuria</td>
<td>Cross-over</td>
<td>8 wk</td>
<td>20</td>
<td>62</td>
<td>138/72$||§</td>
<td>ACEI + Candesartan 16 od ACEI + placebo</td>
</tr>
<tr>
<td>Agarwal, 2001(^{37})</td>
<td>CRF (DM/non-DM) MAP$||| &gt;(97) &gt;(1) g proteinuria</td>
<td>Crossover</td>
<td>4 wk</td>
<td>17</td>
<td>53</td>
<td>156/88$||§</td>
<td>Lisinopril 40 od + Losartan 50 od Lisinopril 40 od + placebo</td>
</tr>
<tr>
<td>Berger, 2002(^{17})</td>
<td>Non-DM CRF &gt;(1) g proteinuria</td>
<td>Cross-over</td>
<td>8 wk</td>
<td>12</td>
<td>52</td>
<td>128/79$||§</td>
<td>ACEI + candesartan 8 od ACEI + placebo</td>
</tr>
<tr>
<td>Ferrari, 2002(^{38})</td>
<td>Non-DM CRF &gt;(140/90) &gt;(1.5) g proteinuria</td>
<td>Cross-over</td>
<td>6 wk</td>
<td>10</td>
<td>48</td>
<td>144/91$||§</td>
<td>Fosinopril 20 od + Irbesartan 150 od Fosinopril 20 od (no placebo) Irbesartan 150 od (no placebo)</td>
</tr>
<tr>
<td>Nakao, 2003(^{12})</td>
<td>Non-DM CRF BP &gt;(135/85) &gt;(300) mg proteinuria</td>
<td>Parallel group</td>
<td>2.9 y</td>
<td>99</td>
<td>45</td>
<td>130/75$||§</td>
<td>Trandolapril 3 od + Losartan 100 daily Trandolapril 3 od + placebo Losartan 100 daily + placebo</td>
</tr>
<tr>
<td>Azizi, 2000(^{13})</td>
<td>Essential hypertension DBP &gt;(95/115)</td>
<td>Parallel group</td>
<td>6 wk</td>
<td>60</td>
<td>NS</td>
<td>161/105$||§</td>
<td>Enalapril 10 od + Losartan 50 od Enalapril 10 od (no placebo) Losartan 50 od (no placebo)</td>
</tr>
<tr>
<td>Stergiou, 2000(^{38})</td>
<td>Essential hypertension Ambulatory DBP &gt;(85)</td>
<td>Cross-over</td>
<td>5 wk</td>
<td>20</td>
<td>49</td>
<td>150/100$||§</td>
<td>Benazepril 20 od + Valsartan 80 od Benazepril 20 od (no placebo) Valsartan 80 od (no placebo)</td>
</tr>
<tr>
<td>Weir, 2001(^{39})</td>
<td>Essential hypertension DBP &gt;(95/115)</td>
<td>Parallel group</td>
<td>6 wk</td>
<td>23</td>
<td>48</td>
<td>146/97$||§</td>
<td>Benazepril 20 od + Valsartan 160 od Valsartan 320 od (no placebo)</td>
</tr>
<tr>
<td>Morgan, 2004(^{42})</td>
<td>Systolic hypertension ambulatory SBP &gt;(135) Older than 65 years</td>
<td>Cross-over</td>
<td>6 wk</td>
<td>23</td>
<td>76</td>
<td>160/88$||§</td>
<td>Candesartan 16 od + Lisinopril 20 od Lisinopril 20 od Candesartan 16 od + placebo</td>
</tr>
</tbody>
</table>

\(\|\|\|\) = mean; NS = not specified; MABP = mean arterial blood pressure; CRF = chronic renal failure; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; DBP = diastolic blood pressure; SBP = systolic blood pressure.
TABLE 1. Continued

*Number of participants receiving ACE–ARB combination; numbers in parentheses refer to total numbers of subjects in study in parallel group studies.†Numerical values refer to drug doses administered (in mg).
‡Clinic (office) sitting BP. §Baseline BP measured on antihypertensive medication. ¶Mean arterial blood pressure. |24-hour mean ambulatory BP.

**Morgan et al25 also compared combination with candesartan 32 od and lisinopril 40 od; for the purposes of the meta-analysis, we compared doses of monotherapy with the same doses administered in the combination.

ACEI indicates use of angiotensin-converting enzyme inhibitors (the dosages of which are given below); BP, blood pressure; CRF, chronic renal failure; daily, administration of given amount in divided dosages during the day; DBP, diastolic blood pressure; DM, diabetes mellitus; od refers to once-daily administration; od, administration of given amount as a single daily dose; SBP, systolic blood pressure.

Trials were excluded if: (1) participants were normotensive; (2) changes in BP were not the main or a significant secondary outcome variable, or were not reported; (3) allocation to trial interventions were not randomized; and (4) significant alterations in number and/or doses of concomitant antihypertensive medications were allowed during the course of the trial, unless these were clearly spread equally between study groups.

Data Extraction

Data were extracted independently by 2 of the authors (T.D., F.H.) using a standard form. Relevant data recorded were characteristics of the study, study design (parallel or crossover), type of the study (open, single-blind, or double-blind), study duration, pre-intervention and postintervention results for BP and proteinuria (when measured), and relevant safety data. For the purpose of pooled analyses, statistics that could be used to estimate the variances of the outcome measures were recorded.

Statistical Analysis

We calculated the treatment effect for SBP and DBP, which for crossover trials was the difference in BP between the end of the ACEI or ARB monotherapy (ie, control) period and the end of the ACE–ARB combination period, and for parallel trials was the difference between the 2 treatment groups in the change in BP from baseline to the end of the treatment period. Treatment effects were calculated for proteinuria in a similar manner. We also calculated the variance of the treatment effect for SBP, DBP, and proteinuria from standard deviations or standard errors of paired differences between baseline and the end of follow-up for each group in a parallel trial13 or between the 2 treatment periods in a crossover trial, or, if these statistics were not given, from confidence intervals, exact t or P values. If the exact variance of paired difference was not derivable, it was imputed either by inverting a boundary probability value (eg, P<0.05 became P = 0.05) or by assuming a correlation coefficient of 0.5 between the initial and final BP.16 Among the 14 trials included in our meta-analysis, only 1 had to have variance imputed. Mean effect sizes were calculated using random effects model on Cochrane Collaboration Review Manager 4.2.1 software.

Results

Searches by one of the authors (T.D.) of MEDLINE and EMBASE databases, using the search strategy outlined with secondary searches using the bibliographies of relevant articles, identified 1632 publications. A search of the Cochrane Library produced 986 further publications. In total, 2618 potentially relevant publications were identified and screened for retrieval. Of these, 2598 were excluded on the basis of title or abstract, because the publications were not randomized trials of an ACEI–ARB combination in hypertensive patients. Twenty potentially appropriate trials were retrieved for more detailed evaluation, resulting in 14 that were considered appropriate for inclusion in this meta-analysis.

Four studies were undertaken in patients with uncomplicated essential or isolated systolic hypertension, 4 in patients with CRF, and 3 each in patients with type 1 and type 2 DM. Ten studies were crossover designs and 4 were parallel group studies. Allocation to trial medication was open in 2 studies, single-blinded in 1 other, and the remaining 11 studies were double-blinded. In total, 434 subjects received combination ACEI–ARB therapy. The mean age of participants was 52 years (range, 42 to 76) and 71% were male. In 10 studies in which patients had an ACEI and/or ARB added to existing antihypertensive medication, the mean baseline BP or on placebo (the latter in the case of studies in which no baseline BP was provided) was 148/88 mm Hg (range, 131 to 159/74 to 100 mm Hg) for clinic BP (n = 7) and 132/75 mm Hg (range, 128 to 138/72 to 79 mm Hg) for 24-hour ambulatory BP (n = 3). In 4 studies in which antihypertensive medication had been withdrawn, clinic BP at randomization was 157/95 mm Hg (range, 144 to 162/88 to 105). An ACEI–ARB combination was compared with ACEI monotherapy in 13 studies, and with ARB monotherapy in 7 studies. Study characteristics are summarized in Table 1.

Effects on BP

The combination of an ACEI and ARB reduced 24-hour ambulatory BP by 4.7/3.0 mm Hg (95% confidence interval [CI] 2.9 to 6.5/1.6 to 4.3) when compared with ACEI monotherapy, and by 3.8/2.9 mm Hg (95% CI, 2.4 to 5.3/0.4 to 5.4) when compared with ARB monotherapy (Figures 1 and 2, respectively). Clinic BP (sitting or supine) was reduced by 3.8/2.7 mm Hg (95% CI, 0.9 to 6.7/0.8 to 4.6) and 3.7/2.3 mm Hg (95% CI, 0.4 to 6.9/0.2 to 4.4) versus ACEI and ARB monotherapy, respectively (Figures 1 and 2). However, the majority of studies used submaximal doses or once-daily dosing of shorter-acting ACEI, and in the 1 study in which a longer-acting ACEI (trandolapril) was used, there was no additive effect on BP when an ARB was added.12

Further analysis according to whether the participants had essential hypertension, DM, or CRF was undertaken. Because the results of the overall analysis showed that reductions in ambulatory and clinic BP were similar, we combined ambu-
latory and clinic measurements for this analysis by using ambulatory BP results; if these were unavailable, clinic BP results (but not both) were used. Because of the small numbers of studies in which combination therapy was compared with ARB monotherapy (n=7; hypertension 3, diabetes 3; CRF 1), we only looked at the combination compared with ACEI monotherapy. In participants with essential or isolated systolic hypertension, BP was reduced by 4.0/2.3 mm Hg (95% CI, 1.9 to 6.0/0.2 to 4.4) and in those with DM the reduction was 6.8/4.7 mm Hg (95% CI, 4.4 to 9.2/3.3 to 6.0). There was no reduction in BP in participants with CRF (0.7/0.4 mm Hg; 95% CI, −0.6 to 1.3/−1.2 to 2.7).

Effects on Proteinuria

Eight trials reported data on proteinuria, albuminuria, or urinary albumin creatinine ratio (UACR) that was suitable for analysis. For simplicity, when we refer to “proteinuria” hereafter, we are referring to albuminuria, proteinuria, or UACR. Because the treatment effect was expressed in terms of percentage changes in “proteinuria” in all of the trials included, we have combined these different methods of expressing urinary protein excretion for the purposes of the meta-analysis. Two trials reported effects on proteinuria but could not be included in the analysis because of insufficient provision of data, with attempts to contact the
TABLE 2. Safety Data

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Mean Change in Serum/Plasma Potassium, mmol/L</th>
<th>Significant Hyperkalemia, n*</th>
<th>Change in Renal Function [Parameter Measured]‡</th>
<th>Change in Hb, mmol/L</th>
<th>Withdrawal From Study Because of AE (n) [Event]‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacobsen, 2002</td>
<td>+0.3</td>
<td>4</td>
<td>NS§ [EDTA-GFR]</td>
<td>NS</td>
<td>1 [hyperkalemia]</td>
</tr>
<tr>
<td>Jacobsen, 2003</td>
<td>NS</td>
<td>1</td>
<td>NS [EDTA-GFR]</td>
<td>−0.4</td>
<td>None</td>
</tr>
<tr>
<td>Jacobsen, 2003</td>
<td>+0.3</td>
<td>1</td>
<td>—</td>
<td>−0.4 (P&lt;0.05 vs ACEI only)</td>
<td>None</td>
</tr>
<tr>
<td>Mogensen, 2000†</td>
<td>+0.3 (?P&lt;0.05)</td>
<td>—</td>
<td>−4.4 mL/min [CrCl]</td>
<td>—</td>
<td>17 [dizziness]</td>
</tr>
<tr>
<td>Rossing, 2002¶</td>
<td>NS</td>
<td>None</td>
<td>−5 mL/min [EDTA-GFR]</td>
<td>—</td>
<td>1 [nausea]</td>
</tr>
<tr>
<td>Rossing, 2003¶</td>
<td>NS</td>
<td>None</td>
<td>NS [EDTA-GFR]</td>
<td>—</td>
<td>None</td>
</tr>
<tr>
<td>Aganwal, 2001†</td>
<td>NS</td>
<td>—</td>
<td>NS [Scr]</td>
<td>NS</td>
<td>None</td>
</tr>
<tr>
<td>Berger, 2002†</td>
<td>NS</td>
<td>—</td>
<td>NS [Scr]</td>
<td>—</td>
<td>None</td>
</tr>
<tr>
<td>Ferrari, 2002‡</td>
<td>NS</td>
<td>2</td>
<td>NS [CrCl]</td>
<td>—</td>
<td>None</td>
</tr>
<tr>
<td>Nakao, 2003‡</td>
<td>—</td>
<td>7/88 vs 8/86 in ACE group vs 4/89 in ARB group</td>
<td>“No significant acute deterioration in renal function”</td>
<td>—</td>
<td>18 [various reasons] vs 19 in ACEI group, vs 11 in ARB group</td>
</tr>
<tr>
<td>Azizi, 2000†</td>
<td>“No change”</td>
<td>—</td>
<td>“No change”</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Stergiou, 2003‡</td>
<td>NS</td>
<td>None</td>
<td>NS [Scr]</td>
<td>—</td>
<td>None</td>
</tr>
<tr>
<td>Weir, 2001†</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Morgan, 2004‡</td>
<td>NS</td>
<td>4 vs 1 and 2 on monotherapy</td>
<td>NS [Scr]</td>
<td>—</td>
<td>None</td>
</tr>
</tbody>
</table>

*Significant hyperkalemia is defined in all studies as serum potassium >5.0 to >5.2 mmol/L in subjects receiving combination ACE–ARB, when stated, except for Nakao et al.,12 who do not define “significant hyperkalemia.”
†EDTA-GFR: glomerular filtration rate determined by standard 125I-EDTA isotope techniques; CrCl, creatinine clearance; Scr, serum creatinine concentration.
‡Attributable to a participant receiving combination ACEI-ARB; reporting of side effects such as cough varied widely between different studies and so these data could not be analyzed in a meaningful manner.
§NS indicates no significant difference between study groups (P>0.05, where given).

The combination of an ACEI and ARB reduced proteinuria by 30% (95% CI, 23% to 37%) compared with monotherapy with an ACE inhibitor, and by 39% (95% CI, 31% to 48%) compared with ARB monotherapy.

Safety Data
In the majority of the studies reviewed, there were no significant changes in serum potassium or hemoglobin. A large acute deterioration in renal function was reported in just 1 patient in the 14 studies reviewed, and this did not necessitate renal replacement therapy or result in significant morbidity for that individual. In 3 studies, a small increase of serum potassium (0.3 mmol/L) was reported, and significant hyperkalemia was reported in 19 individuals receiving both an ACEI and an ARB, out of a total of 434 participants. Six episodes of hyperkalemia occurred in diabetic participants (3.5%) and 9 episodes occurred in participants with nondiabetic CRF (6.5%). Further details of safety data can be found in Table 2.

Compliance and Publication Bias
Compliance with study medications was determined by tablet count in 7 studies and was generally reported to be >90% with no differences between treatment groups in individual studies. In 2 further studies compliance was assessed, although how this was achieved was not stated, and in 5 remaining studies no information about compliance was provided.

Funnel plots were drawn to determine publication bias by plotting the net change in systolic BP against the reciprocal of the standard error of change in systolic BP.18 The graphical plots for comparisons with both ACEI and ARB were asymmetrical, suggesting under-reporting of trials showing no additive effect with the combination.

Discussion
The results of this meta-analysis suggest that the combination of an ACEI and ARB reduces BP by ∼4/3 mm Hg when compared with an ACEI or ARB administered as monotherapy. However, we were unable to determine whether this modest additive effect on BP was caused by a synergistic action of the ACEI–ARB combination, because of the way in which the majority of included studies had been designed. It is likely that any additive effect is attributable to an interaction between these two classes of drugs with different pharmacokinetic properties because studies measuring the peak/trough ratios of RAS blocking agents (ie, comparing the BP-lowering effect of an agent at peak and at the end-of-dosing interval) have shown higher ratios in ARBs compared with ACEI.19–21 In other words, an ARB administered once daily will generally lower BP significantly for 24 hours or more, whereas most ACEIs need to be administered at least twice daily to achieve the same effect.22–24 Ideally, studies comparing an ACEI–ARB combination against monotherapy should be designed to demonstrate a reduction in BP at peak, ie, showing a true additive effect, as well as at trough, which by itself may simply represent a pharmacological interaction of the two drug classes. In our opinion, appropriately designed studies would show that combined RAS blockade confers little advantage over monotherapy with an ACEI or ARB as far as additive effects on BP are concerned, and a number of strands of existing evidence lend support to this view. First, the COOPERATE study, which used the longest
acting ACEI trandolapril, showed no additional reduction in trough BP with combination therapy compared with monotherapy.\textsuperscript{12} Second, Morgan et al found that a combination of candesartan 16 mg plus lisinopril 20 mg (both once daily) had an additive effect on clinic BP only when compared with monotherapy with lisinopril 20 mg, but not when compared with lisinopril 40 mg or candesartan 16 mg or 32 mg.\textsuperscript{25} Finally, Forclaz et al have shown, in normotensive individuals, that a supramaximal dose of losartan achieves equivalent RAS inhibition to a combination of losartan plus lisinopril, particularly if the former is administered twice daily.\textsuperscript{26} In addition to concerns relating to dosage and dosage intervals, it should be emphasized that these studies were generally of short duration (4 to 8 weeks). With long-term ACE inhibition, loss of negative feedback of Ang II on the juxtaglomerular apparatus may result in reactive hypertension and increased angiotensin I generation.\textsuperscript{9} Furthermore, there is some evidence to suggest that angiotensin I may be converted to Ang II by ACE-independent enzymatic pathways such as chymase.\textsuperscript{27,28} Consequently, chronic ACE inhibition may not result in complete suppression of Ang II levels,\textsuperscript{7} and so it is possible that the combination of an ACEI and ARB might be more effective than monotherapy when administered for longer periods than generally used in these studies. However, it should be noted that the study of longest duration showed no difference between monotherapy and combination groups.\textsuperscript{12}

Combined RAS blockade reduced proteinuria by 30% and 39% compared with monotherapy with ACEIs and ARBs, respectively. One of the trials that could not be included in our meta-analysis of proteinuria reduction was designed to assess to effects of combined RAS blockade on progression of nondiabetic proteinuric chronic renal failure, in addition to reductions in proteinuria.\textsuperscript{12} After a mean follow-up period of 2.9 years, 11% of subjects receiving combination therapy reached the combined primary endpoint of doubling of serum creatinine or end-stage renal failure, compared with 23% on monotherapy with an ACEI or ARB (hazard ratio, 0.38 and 0.4 for combination versus ACEI and ARB, respectively), and proteinuria was reduced by 43%. Reductions in proteinuria were observed in diabetic nephropathy and nondiabetic chronic renal failure and were independent of BP reductions in 3 studies.\textsuperscript{12,29,30} This latter finding is consistent with meta-analyses examining renoprotective effects of ACEI monotherapy in patients with nondiabetic renal disease, which have concluded that there is benefit of ACE inhibition beyond that attributable to BP lowering.\textsuperscript{5,31} The antiproteinuric effect of an ACEI–ARB combination implies a synergistic action of these agents that is specific to the intrarenal RAS and occurs at plasma concentrations of ACEI or ARB below levels affecting systemic BP. There are data from animal studies supporting this hypothesis,\textsuperscript{32} but it is unclear from current evidence in humans whether higher doses of ACEI or ARB administered as monotherapy might have equivalent antiproteinuric effects to combination therapy. For example, lisinopril up to a dose of 40 mg daily reduces proteinuria in a stepwise fashion, but whether dosage increments beyond 40 mg would decrease proteinuria further is unknown.\textsuperscript{33} In contrast, trandolapril was found to have a maximal antiproteinuric effect at 3 mg daily during dose titration studies up to 6 mg daily, whereas combination therapy (trandolapril and losartan) effected a further significant reduction in proteinuria compared with ACEI alone administered at the maximal antiproteinuric dose.\textsuperscript{12} Further research is needed to determine the optimal antiproteinuric doses of ACEI or ARB when administered as monotherapy, and to explain why combination blockade appears to have a synergistic effect specifically on the intrarenal RAS. A major theoretical concern when co-administering ACEI and ARB would be the precipitation of acute renal failure or acute-on-chronic renal failure, and the occurrence of hyperkalemia. In fact, the incidence of these events in the studies reviewed in this article was extremely low, as indicated in Table 2. However, perhaps with the exception of the study by Nakao et al, none of these studies was of sufficient size and duration to properly assess the safety of combining ACEI and ARB.\textsuperscript{12} There is evidence from animal studies that maximal RAS blockade results in death in salt-depleted rats,\textsuperscript{14} and it is likely that humans co-prescribed an ACEI and ARB would be at risk for acute renal failure if they became salt- and volume-depleted. Therefore, until further studies are undertaken with adequate patient numbers and duration of follow-up to determine the safety of combination RAS blockade, patients on this treatment regime should have close monitoring of renal function and electrolytes, particularly if also receiving diuretics.

When stated, compliance with study medications appeared to be good and, with 1 exception,\textsuperscript{11} the remaining 5 studies that did not provide information on compliance were small (n=67, 17, 12, 10, and 23, respectively). Therefore, it is unlikely that inadequate compliance within the studies reviewed will have biased the overall result of our analysis. Conversely, our finding of a possible publication bias suggests that the true additive effect of an ACE–ARB combination may be <4/3 mm Hg we have found in this analysis.

Perspectives

This meta-analysis has found that an ACEI–ARB combination has a small additive effect on BP in hypertensive individuals compared with ACEI or ARB monotherapy. This additive effect is of questionable clinical significance and, furthermore, may simply be a consequence of the design of individual studies rather than representing a true additive effect of the combination. Further research, ideally comparing combination therapy with maximal or supramaximal licensed doses of ACEIs and/or ARBs, is therefore required to determine whether the addition of an ARB to an ACEI (or vice versa) is genuinely effective and safe in individuals with essential hypertension. We have shown that a combination of ACEI and ARB results in a clinically significant reduction in proteinuria in patients with chronic kidney disease and diabetic nephropathy already receiving an ACEI or ARB, and other studies have shown reductions in the progression of proteinuric CRF.\textsuperscript{12} A combination of an ACEI and ARB may therefore be useful in hypertensive patients with CRF and proteinuria, with the caveat that renal function and electrolyte balance is carefully monitored. Further studies are required to demonstrate that short-term reductions in proteinuria associ-
ated with an ACE–ARB combination in individuals with hypertension and diabetic nephropathy translate into reductions in clinical endpoints, before such a regime can be routinely recommended in this population.

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