

IN THE LITERATURE

Is Angiotensin-Converting Enzyme Inhibitor and Angiotensin Receptor Blocker Combination Therapy Better Than Monotherapy and Safe in Patients With CKD?

Commentary on Yusuf S, Teo KK, Pogue J, et al: Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 358:1547-1559, 2008 and Mann JF, Schmieder RE, McQueen M, et al: Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): A multicentre, randomised, double-blind, controlled trial. Lancet 372:547-553, 2008.

For many years, slowing the progression of chronic kidney disease (CKD) has been the “holy grail” of nephrologists. We know that for many patients with proteinuria, there is a progressive reduction in glomerular filtration rate (GFR) over time and a close relationship between extent of baseline proteinuria and the rate of disease progression. Numerous studies have shown that treating patients who have diabetic and nondiabetic CKD and proteinuria with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) reduces proteinuria and slows progression of CKD, and that the greater the reduction in proteinuria with these agents, the greater the benefit.¹⁻⁵ A synergistic effect of multipronged blockade of the renin-angiotensin-aldosterone system (RAAS) has also been proposed, utilizing dual or triple combinations of ACE inhibitors, ARBs, and aldosterone receptor antagonists.⁶⁻¹³ For the most part, these studies have shown that dual therapy is better in reducing proteinuria than single-drug therapy, while the role of triple therapy seems less clear. However, as will be discussed below, the primary end point of virtually all of these studies has been the effect on the potential surrogate outcome of proteinuria rather than a “hard outcome,” specifically progression of CKD and mortality; accordingly, the long-term safety and efficacy of this approach is not known. Recently, 2 reports from the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint

Trial (ONTARGET) provide some answers to this question.^{14,15}

WHAT DO THESE IMPORTANT STUDIES SHOW?

ONTARGET was a randomized, double-blind, noninferiority comparison of 3 treatment groups: the ARB telmisartan alone (80 mg daily), the ACE inhibitor ramipril alone (10 mg daily), and the combination of telmisartan and ramipril.¹⁴ The study enrolled individuals aged 55 years or older who had atherosclerotic cardiovascular disease or diabetes mellitus with associated end-organ dysfunction. More than 29,000 participants began a single-blind run-in phase during which they were given 2.5 mg ramipril alone for 3 days, followed by both 40 mg telmisartan and 2.5 mg ramipril for 7 days, and then both 40 mg telmisartan and 5 mg ramipril for 11 to 18 days. Participants were excluded for poor adherence, symptomatic hypotension (1.7%), hyperkalemia (0.8%), increase in serum creatinine (0.2%), personal preference, or death during this period. Ultimately, 25,620 participants were randomized to 1 of the 3 treatment groups, with approximately 8,500 individuals in each group. The primary outcome was a composite of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure. The main secondary outcome was a composite of death, myocardial infarction, or stroke; there were a variety of other secondary outcomes including “nephropathy.” The study was conducted at 733 centers in 40 countries. The median duration of follow up was 56 months.

The mean blood pressure was slightly lower throughout most of the study period in the combination therapy and telmisartan groups compared with the ramipril group, by a mean of 2.4/1.4 mm Hg and 0.9/0.6 mm Hg, respectively. The primary study outcome occurred in approximately 16%

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of each group, with no statistically significant differences among groups in the composite outcome, the components of the composite outcome, or any of the secondary outcomes with the exception of “renal impairment” (not predefined in the study protocol but as determined by each investigator), which was significantly more frequent in the combination therapy group (13.5%; RR, 1.33; 95% CI, 1.22 to 1.44; $P < 0.001$) than the ramipril (10.2%) or telmisartan (10.6%) groups. Initiation of dialysis was also more frequent with combination therapy, at 0.8% compared with 0.6% in each monotherapy group, although this did not reach statistical significance (RR, 1.37; 95% CI, 0.94 to 1.98; $P = 0.10$).

Study drug was discontinued in 23.7% of ramipril-treated participants and 21% of telmisartan-treated participants. Among those receiving both drugs, 22.7% stopped both drugs and 6.7% stopped one drug. The most common reasons for stopping were cough (ramipril or combination therapy) and hypotensive symptoms (all groups, but more so with combination therapy than telmisartan, and both groups more than ramipril). Doubling of serum creatinine occurred in 1.9% of ramipril-treated patients, 2% of telmisartan-treated patients, and 2.1% of combination therapy patients (nonsignificant). “Renal impairment” led to study drug termination in 1.1% of combination therapy patients, which was statistically greater than the 0.7% of ramipril-treated patients who stopped for this indication (0.8% of telmisartan-treated patients stopped because of renal impairment). Hyperkalemia (potassium > 5.5 mmol/L) occurred in 5.6% of combination therapy patients and 3.3% of patients in each monotherapy group ($P < 0.001$).

A subsequent publication further detailed renal outcomes of the ONTARGET study.¹⁵ Serum creatinine was measured before the run-in phase, 6 weeks after randomization, at 2 years, and at the end of the study. Urine albumin and albumin-creatinine ratio were measured before the run-in phase, after 2 years, and at the penultimate visit. The primary outcome of this analysis was the composite of first occurrence of dialysis, kidney transplantation (of which there was none), doubling of serum creatinine, or death. Secondary outcomes included, among others, change in estimated GFR (eGFR) and progression of albuminuria.

Mean baseline eGFR in ONTARGET was 73.6 mL/min/1.73 m² and was greater than 60 mL/min/1.73 m² in more than two-thirds of participants. Geometric mean urine albumin-creatinine ratio was approximately 0.8 mg/mmol, equivalent to approximately 10 mg/g. Microalbuminuria was present in 13% (30% of those with diabetes and 9% of those without known diabetes) and macroalbuminuria was present in 4% (12% of those with diabetes and 1.4% of those without known diabetes).

The decline in eGFR from baseline to end of study was greatest in the combination therapy group (mean change of -6.11 ± 17.9 mL/min/1.73 m²) but also greater with telmisartan (-4.12 ± 17.4 mL/min/1.73 m²) than ramipril (-2.82 ± 17.2 mL/min/1.73 m²). The primary composite end point occurred with similar frequency in the ramipril and telmisartan groups (13.4%), but was more frequent (14.5%; RR, 1.09; 95% CI, 1.01 to 1.18; $P = 0.037$) with combination therapy. Doubling of serum creatinine occurred to a similar extent in each single-drug group but was more likely with combination therapy (HR, 1.24; 95% CI, 1.01 to 1.51; $P = 0.038$). Acute dialysis was more common in combination therapy patients (HR, 2.19; 95% CI, 1.13 to 4.12; $P = 0.020$) than with patients receiving either agent alone; long-term dialysis occurred with similar frequency in all groups. Combination therapy slowed the increase in albuminuria and prevented new onset of micro- and macroalbuminuria to a greater extent than monotherapy. Among subgroups, combination therapy provided no benefit in potentially high-risk participants such as those with diabetes mellitus and nephropathy, hypertension, and eGFR less than 60 mL/min/1.73 m², and tended to be harmful in lower-risk groups, such as those without diabetes, hypertension, microalbuminuria, and who had eGFR greater than 60 mL/min/1.73 m².

HOW DO THESE STUDIES COMPARE TO PRIOR STUDIES?

Several studies have examined the effects of ACE inhibitors, ARBs, and their combination on cardiovascular outcomes in patients with heart failure or other cardiovascular disease; as in the ONTARGET study, the ACE inhibitor is generally the comparator. These other studies were

discussed in an editorial accompanying the ONTARGET study¹⁶ and will not be specifically addressed here other than to note that the findings are mixed, with no mortality benefit in 1 study but a mortality benefit in a second study with an ACE inhibitor and ARB (although with increased mortality in patients who were also receiving a β -blocker).¹⁷⁻¹⁹ Both the ONTARGET and VALIANT¹⁷ (Valsartan in Acute Myocardial Infarction) studies showed that ARB and ACE inhibitor were equivalent vis-à-vis cardiovascular and overall mortality, but both found that adverse effects were more frequent and discontinuation or reduction in dose of study drug due to hypotension or broadly defined renal causes was greater with combination therapy than an ACE inhibitor alone.

The effects on proteinuria of combination treatment with an ARB and ACE inhibitor have been extensively studied and have been the subject of several systematic reviews and meta-analyses.¹⁰⁻¹³ Combination therapy reduces proteinuria in both diabetic and nondiabetic kidney diseases to a greater extent than either an ACE inhibitor or ARB alone (which are individually not different in this regard). This enhanced anti-proteinuric effect seems to be on the order of about a 25% greater reduction in proteinuria or a mean of about 0.5 g/d additional reduction in proteinuria.¹⁰ In many studies, it was not clear whether a maximal dose of the single agents was compared to dual therapy, and blood pressure-related effects were not entirely excluded. Most studies have been small ($N < 50$) and were less than 4 to 6 months in duration, with quite a few of 2 months or less in duration. In most studies, dual RAAS blockade was associated with at least a small decrease in GFR and increase in serum potassium; however, systematic assessment of adverse events has generally been lacking.¹²

Much of the enthusiasm for dual RAAS blockade in patients with CKD stems from the COOPERATE (Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor in Nondiabetic Renal Disease) study, the only large, long-term study that reported “hard” outcomes of GFR progression and/or development of advanced kidney failure rather than the surrogate outcome of proteinuria.²⁰ This Japanese study included 263 patients with nondiabetic kidney disease who

were treated with losartan (100 mg daily), tran-dolapril (3 mg daily), or both in a randomized, double-blind study. The primary end point was time to doubling of serum creatinine or end-stage renal disease (dialysis or calculated GFR ≤ 7 mL/min/1.73 m²). About half of the patients had IgA nephropathy; other primary glomerular diseases and hypertension accounted for most of the remaining patients. After 3 years of follow up, 11% of combination-therapy patients, but 23% of both single-agent groups, had reached the combined end point (HR, 0.38 to 0.40; $P = 0.016$ to 0.018). Combination therapy reduced proteinuria to a greater degree (75.6%) than monotherapy (42.1% to 44.3%). A benefit of combination therapy in terms of reaching the primary composite end point was seen regardless of the degree of proteinuria but was more marked with proteinuria of at least 1 g/d.

Unfortunately, some important and serious concerns about this study have been raised. Kunz and colleagues excluded the COOPERATE study from a recent meta-analysis¹² due to “serious implausibilities that contact with the publishing journal could not resolve . . . includ[ing] a highly unusual balance in the distribution of the 3 key baseline variables across 3 treatment groups, discrepancies between the reported statistical method and the results in the paper, and problems with patient stratification.” These and other problems with the study were reported in detail elsewhere.²¹ Others have also raised concerns about this study and the authors have acknowledged errors in data entry and management.²²

WHAT SHOULD CLINICIANS AND RESEARCHERS DO?

The ONTARGET study was not primarily a kidney disease study. Most participants had low levels of urinary protein and were not at high risk for kidney disease progression and hence would likely not have been treated with combination therapy specifically to slow kidney disease progression. Assessment of albuminuria and serum creatinine levels was infrequent, and kidney disease outcomes were not rigorously and consistently defined. High-quality randomized controlled trials examining long-term outcomes such as progression of CKD, development of ESRD, and mortality with ACE inhibitor, ARB, and

combination therapy in patients with higher levels of proteinuria and therefore high risk of kidney disease progression are needed. Notably, some studies are already underway, including VALID and VA NEPHRON-D (ClinicalTrials.gov registry numbers NCT00494715 and NCT0555217, respectively).

However, results of these trials remain years away, leaving us with the question of what to do until then? First, researchers should not conduct more short-term studies with proteinuria as the “important” outcome measure; the question of whether combination therapy reduces proteinuria more than monotherapy has probably been sufficiently asked and answered, at least in the short term. If the limited resources of time, funds, and patients willing to participate in clinical trials are to be committed to study of these drugs in patients with CKD, we ought to devote the resources to answering the questions that really need to be answered. I would argue similarly regarding use of aldosterone receptor antagonists⁸—they also reduce proteinuria, but the long-term impact on decline in GFR and mortality and the adverse event profile are not certain.

Second, somewhat contrary to other recent recommendations,²³ in light of the absence of evidence of a benefit on CKD progression and mortality and evidence of potential harm, I think clinicians could very reasonably look past the experimental rationale for combination RAAS blockade and studies using proteinuria as a surrogate outcome and avoid use of ACE inhibitor and ARB combinations until data of efficacy and safety are forthcoming. We must be mindful that there still remains some controversy as to whether RAAS blockade slows kidney disease progression substantially more than other agents producing equivalent blood pressure control.²⁴ Furthermore, the safety of dual (and even more so triple) RAAS blockade outside of clinical trials in which patients are carefully selected and monitored remains uncertain. There seems to be little justification for use of dual or triple therapy for the specific reason of slowing progression of CKD in patients without significant (at least 0.5 to 1.0 g/d) proteinuria, those who have good blood pressure control on full-dose monotherapy (with a diuretic), and those with well-preserved GFR who are at low risk of developing progression of CKD.²⁵ In patients with stage 3 to 4 CKD who

remain hypertensive with persistent proteinuria greater than 0.5 to 1.0 g/d, normal serum potassium concentration, and evidence of a decline in GFR on full-dose monotherapy (recognizing that the maximal antiproteinuric dose may be higher than the maximal antihypertensive dose) and appropriate diuretic treatment, dual therapy could be considered; whether the better combination is an ACE inhibitor or ARB with an aldosterone receptor antagonist rather than an ACE inhibitor–ARB combination remains unknown. Patients must be monitored very carefully for adverse effects on blood pressure, serum potassium, and GFR; as well as cough, angioedema, and other adverse events. Given the absence of reliable, reputable evidence that dual ACE inhibitor–ARB blockade slows CKD progression and improves mortality, and with evidence from ONTARGET and other studies that harm might ensue with this approach, one should quickly abandon dual therapy at the first sign of trouble.

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