

Analysis of Recent Papers in Hypertension

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COMBINATION THERAPY WITH THE ANGIOTENSIN-CONVERTING ENZYME INHIBITOR RAMIPRIL AND THE ANGIOTENSIN RECEPTOR BLOCKER TELMISARTAN FAILS TO REDUCE RENAL EVENTS IN PATIENTS AT HIGH RISK FOR CORONARY HEART DISEASE: THE ONTARGET STUDY

Clinical practice guidelines recommend that initial treatment of hypertension in those with chronic kidney disease (CKD) includes either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB). Both classes of antihypertensive agents have demonstrated favorable reductions in proteinuria and improved other renal outcomes in patients with hypertension and CKD. In the absence of data from long-term outcome studies, the most suitable add-on antihypertensive medication for a patient with hypertension and CKD who is already receiving either an ACE inhibitor or an ARB but whose blood pressure (BP) remains above the recommended goal of 130/80 mm Hg remains unknown. Possibilities include a second drug that blocks the renin-angiotensin system (RAS) or a drug that works through a different mechanism. The Ongoing Telmisartan Alone and in Combination With Ramipril Global

Endpoints Trial (ONTARGET) provided an opportunity to investigate the renal effects of the ACE inhibitor ramipril, the ARB telmisartan, and their combination in patients at high risk for coronary heart disease (CHD) events.

To be eligible for participation in ONTARGET, individuals had to be at least 55 years of age and have a history of established atherosclerotic disease or diabetes with end-organ damage. Major exclusion criteria included known renal artery stenosis, uncorrected volume or sodium repletion, serum creatinine level >265 $\mu\text{mol/L}$, and uncontrolled hypertension (baseline systolic BP >160 mm Hg or baseline diastolic BP >100 mm Hg). After a 3-week single-blind run-in phase with eligible participants receiving increasing doses of both ramipril and telmisartan, participants were randomized in a double-blind fashion to therapy with either telmisartan 80 mg/d, ramipril 10 mg/d, or the combination of the two. The primary end point of ONTARGET was a composite of cardiovascular events (cardiovascular death, stroke, myocardial infarction, or hospitalization for heart failure). Prior to the unblinding of the study, the steering committee developed a statistical analysis plan to evaluate renal outcomes. The primary composite renal outcome was the first occurrence of any dialysis, renal transplant, doubling of serum creatinine value, or death. No cases of renal transplant were reported during the trial. The secondary renal outcomes included the composite of any dialysis and doubling of serum creatinine value; individual components of the primary renal end point; changes in estimated glomerular filtration rate (eGFR); progression of proteinuria (defined as newly developed microalbuminuria or macroalbuminuria); and any renal impairment leading to discontinuation of study medication (as defined by the treating investigator). The eGFR was defined using the Modification of Diet in Renal Disease (MDRD) formula. The primary analysis used a time-to-event approach

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and included all randomized participants in accordance with intention-to-treat analysis.

Overall, 25,620 participant (mean age, 66; baseline BP, 142/82 mm Hg; 64% previously on ACE inhibitor or ARB therapy) were randomized and included in the renal analysis. They were seen at 6 weeks and every 6 months thereafter until study completion. Serum creatinine was measured locally at the study sites without standardization before run-in, 6 weeks after randomization, after 2 years, and at study completion. Mean serum creatinine value at baseline was 93.7 $\mu\text{mol/L}$ and mean eGFR was 73.6 mL/min/1.73 m². Stage 3 or 4 CKD (eGFR <60 mL/min/1.73 m²) was noted in 6157 patients (24.0%), but only 263 (1.0%) participants had a baseline eGFR <30 mL/min/1.73 m². The urinary albumin:creatinine ratio was measured centrally before run-in, at 2 years, and at the final visit. Standard definitions were used to define microalbuminuria and macroalbuminuria. On entry, microalbuminuria was present in 13.1% of all participants, including 29.7% with diabetes and 9.2% without known diabetes. Macroalbuminuria was seen in 4% of all participants, including 12.2% with diabetes and 1.4% without known diabetes. Information about dialysis was requested at each visit, and a questionnaire was sent to each site at which dialysis occurred after the trial about the duration of dialysis and primary reasons for any acute dialysis. Acute dialysis was defined as a duration of renal replacement therapy of ≤ 2 months, with chronic dialysis being renal replacement therapy lasting > 2 months.

During a mean 56 months of follow-up, the frequency of the composite primary renal outcome (dialysis, doubling of serum creatinine level, or death) was similar with telmisartan (1147, 13.4%) and ramipril (1150, 13.5%) but increased with combination therapy (1233, 14.5%; hazard ratio [HR], 1.09; 95% confidence interval [CI], 1.01–1.18; $P=.037$). The secondary renal end point of doubling of serum creatinine level or dialysis was similar with telmisartan (189, 2.21%) and ramipril (174, 2.03%) but also increased with combination therapy (212, 2.49%; HR, 1.24; 95% CI, 1.01–1.51; $P=.038$). In the entire study, there were only 162 cases of dialysis (0.06%); the incidence of acute dialysis ($n=61$) was greater in the combination than in the monotherapy groups, but the incidence of chronic dialysis was similar in all 3 groups. The eGFR decreased more with telmisartan and with combination therapy than with ramipril alone, but the differences, although statistically significant, were small. Urinary albumin excretion

increased at 2 years and at study end to a lesser extent with telmisartan than with ramipril or combination therapy, and once again the differences, though statistically significant, were small. The risk of new microalbuminuria, macroalbuminuria, or both was similar between telmisartan (949, 11.1%) and ramipril (1018, 11.7%) but was lower with combination therapy (888, 10.4%; HR, 0.88; 95% CI, 0.81–0.96; $P=.003$). In all of the subgroups analyzed, including those with and without diabetes, diabetic retinopathy, presence of microalbuminuria or macroalbuminuria, or decreased eGFR, there were no significant differences between telmisartan or ramipril in the incidence of the primary renal end point. Combination therapy demonstrated no clear benefit in reducing the primary renal end point in patients who were at the highest risk for renal disease—including those with hypertension, diabetes, diabetic nephropathy, or baseline decreased eGFR—but was associated with worse renal outcomes among patients at lower risk (those without hypertension, diabetes, microalbuminuria, or macroalbuminuria).

Among participants at high vascular risk, telmisartan's effects on major renal outcomes were no different than ramipril's. The combination of telmisartan and ramipril reduces eGFR and proteinuria to a greater extent than either monotherapy but led to a higher incidence of major renal outcomes.—Mann JF, Schmieder RE, McQueen M, et al; ONTARGET Investigators. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet*. 2008;372:547–553.

COMMENT

The main findings of this clinical study were that the primary renal outcome of dialysis, doubling of serum creatinine level, and death was similar with telmisartan and ramipril but was significantly more frequent with the combination of both drugs than with ramipril alone. In addition, the secondary outcome of dialysis and doubling of serum creatinine level was also more frequent with combination therapy. But before we place a moratorium on dual RAS blockade with combination ACE inhibitor/ARB therapy, we need to look more closely at this study and what it actually found.

Of the components of the primary outcome, death was the most frequent outcome, and its incidence was similar in all 3 treatment groups. There was also no difference between groups in the doubling of

serum creatinine level. In fact, the number of patients in whom serum creatinine doubled or who required dialysis was small, and both the composite primary and secondary outcomes were driven by the need for acute dialysis. The reasons for acute dialysis are difficult to interpret, and only 2 patients required dialysis for hyperkalemia. There was no increased need for chronic dialysis, which only occurred in 98 patients.

Strengths of this study include its large sample size, multiple clinically important renal end points, and length of follow-up. However, it is important to recognize that ONTARGET was neither a study of patients with hypertension nor a study of patients with baseline CKD. There was no minimum BP requirement for inclusion in ONTARGET, and the mean baseline BP was 142/82 mm Hg. Patients with baseline BP values >160/100 mm Hg were actually excluded from the study. Significant baseline renal dysfunction was also an exclusion criterion. Only 1% of included patients had a baseline eGFR <30 mL/min/1.73 m², and only 13.1% had evidence of microalbuminuria at baseline. This was not a study of patients usually seen in a busy nephrology practice. Patients were only seen every 6 months, and the majority of care was provided by primary care providers and not specialists in renal disease. In addition, values of creatinine and potassium were obtained only at baseline, at 6 weeks, at 2 years, and at study end: not the frequency that would be required in patients with advanced nephropathy. Furthermore, serum creatinine analysis was performed by each local laboratory, not by a central laboratory.

So, what can we conclude from the renal outcomes in ONTARGET? In patients without significant baseline CKD (the vast majority of patients in ONTARGET), the primary renal outcomes confirm the main findings of ONTARGET, which demonstrated that in patients without chronic heart failure or severe renal dysfunction, combination therapy with an ACE inhibitor and an ARB is no more beneficial than monotherapy with either drug and may lead to an increased risk of adverse events. The apparently contrasting effects of ACE inhibitor and ARB monotherapy on the surrogate renal end points of eGFR and albuminuria are interesting. In ONTARGET, ACE inhibitor monotherapy

appeared to have a more beneficial effect on eGFR, and ARB monotherapy appeared to have a more beneficial effect on the progression of albuminuria. However, since the differences were small and there was no significant difference in the incidence of the primary renal end point, the overall results seem to support use of either ARB or ACE inhibitor monotherapy in this patient population. The choice between these classes of antihypertensive agents in this population should continue to be made on the basis of cost and tolerability.

For patients with baseline CKD (few of whom were included in ONTARGET), the most appropriate choice of an RAS-blocking agent or agents remains unclear. A number of previous studies have demonstrated that in patients with baseline CKD, use of either an ACE inhibitor or an ARB as part of a treatment regimen can reduce the incidence of renal end points, including doubling of serum creatinine level or dialysis. As such, CKD is considered a compelling indication for using an ACE inhibitor or an ARB (in addition to other antihypertensive agents as needed to aggressively control BP to at least <130/80 mm Hg) by the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) and multiple other advisory committees. While many experts continue to suggest that dual blockade of the RAS in patients with CKD may be superior to monotherapy for renal outcome improvement, evidence to support this claim remains thin, and studies often cited as evidence for this position have significant methodological flaws. This analysis of ONTARGET neither confirms nor refutes this claim. Combination therapy led to a reduction in the progression of albuminuria. But since there was no difference in the primary end point among the subgroup of patients with baseline albuminuria, the hypothesis that combination therapy has important clinical benefits in this patient population remains unproven. Until more evidence is available, most physicians should refrain from using combination therapy with an ACE inhibitor and an ARB for renal protection, except perhaps in select cases as directed and followed by specialists in renal disease.