Dual Renin-Angiotensin System Blockade in the ONTARGET Study: Clinically Relevant Risk for the Kidney?

Kunal Chaudhary, MD, Ravi Nistala, MD, MS, and Adam Whaley-Connell, DO, MSPH

Corresponding author
Kunal Chaudhary, MD
Department of Internal Medicine, Division of Nephrology and Hypertension, Harry S Truman Veterans Administration Medical Center, 800 Hospital Drive, Columbia, MO 65211, USA.
E-mail: chaudharyk@health.missouri.edu

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Inhibition of the renin-angiotensin system contributes to reductions in proteinuria and in progression of chronic kidney disease. Indeed, monotherapy with either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) has been shown to decrease proteinuria and slow the decline of chronic kidney disease, but incompletely. Therefore, there is increasing interest in whether combination strategies will provide more complete blockade of the renin-angiotensin system, which may translate into superior renoprotective and cardioprotective effects compared with either agent alone. There have been several reports on combination strategies. However, the recent report of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) has received much of the attention. The renal outcomes in ONTARGET suggest that combined ACE inhibitor and ARB therapy contributes to a higher rate of adverse renal outcomes than monotherapy. Therefore, this review explores data from ONTARGET in relation to other available evidence on the use of combination therapies.

Introduction

Proteinuria has long been used as a marker for the progression of chronic kidney disease (CKD) [1,2]. Numerous clinical studies demonstrate that proteinuria reduction is associated with a slower subsequent decline in glomerular filtration rate (GFR) [3–5], whereas a stable or increasing level of proteinuria is associated with a faster GFR decline [6,7]. Therefore, reductions in proteinuria have been used as a marker to correlate with renal survival. Current evidence supports the idea that inhibition of the renin-angiotensin system (RAS) with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) reduces both levels of proteinuria and the progression of CKD [8–10]. The antiproteinuric effect of RAS inhibition has been attributed to pharmacologic properties beyond those related to lowering of blood pressure alone [11,12]. Monotherapy with either an ACE inhibitor or an ARB has been shown to decrease proteinuria and slow the decline of renal function, but incompletely. In an effort to explore strategies for greater reductions in proteinuria, which may be translated into improved renal outcomes, investigators have sought to employ dual therapy with ACE inhibitors and ARBs.

The rationale for combination strategies with the addition of an ACE inhibitor to an ARB would be the ability to provide more complete blockade of the RAS, with renoprotective and cardioprotective effects superior to those provided by either agent alone [13,14]. There have been several recent reports of combination strategies, but the recent report of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) has received much of the attention. The results of ONTARGET suggest that combined ACE inhibitor and ARB therapy produced worse renal outcomes than those of patients who received monotherapy [15•]. Therefore, this review explores the ONTARGET data in relation to the available evidence regarding strategies using combination therapy.

Rationale for Combination Therapy

The RAS has been has implicated in the pathogenesis of cardiovascular disease (CVD) predominantly through elevations in angiotensin II (Ang II). Ang II is thought to be the major effector peptide of the RAS; the deleterious actions of oxidative stress, inflammation, and endothelial dysfunction as it relates to hypertension are mediated through the Ang II type 1 receptor (AT_1R). Inhibition of ACE, which controls conversion of Ang I

to Ang II, has been shown to decrease cardiovascular mortality [16–18]. Numerous large multicenter trials, such as the Heart Outcomes Prevention Evaluation (HOPE), the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), and the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA), have shown beneficial effects of ACE inhibitors on cardiovascular outcomes, independent of their blood pressure lowering effects [19–21]. ACE inhibitors have also been shown to reduce the risk of stroke by lowering blood pressure and to prevent complications of diabetes [8]. Importantly, similar data exist in regard to CVD risk reduction with the use of ARBs [22].

Therapy with an ACE inhibitor alone leads to the phenomenon of "Ang II escape," preventing a complete blockade because of alternative non-ACE pathways; ARBs, by directly blocking the receptor binding to Ang II, offset the escape effect seen with ACE inhibitors [23–25]. Several studies have demonstrated the beneficial effects of combining ACE inhibitors and ARBs. A meta-analysis involving 434 patients found that ACE inhibitor–ARB combination therapy yielded a greater drop in blood pressure (4/3 mm Hg) than monotherapy with these agents [26]. Many of the individual studies included in this meta-analysis were of short duration and had small sample sizes, and some of the earlier studies had used short-acting ACE inhibitors as a once-daily drug.

Data on Combination Therapy

Cardiovascular outcomes

There are considerable data on heart failure outcomes with combination therapy. Val-HeFT compared the ARB valsartan with a placebo as an add-on to existing therapy, with over 90% of patients receiving an ACE inhibitor. There was no difference in the two groups in mortality. However, there was a decreased risk of hospitalization due to heart failure in the group receiving valsartan. Subgroup analysis of Val-HeFT showed that valsartan was beneficial in patients not receiving ACE inhibitors, but it had negative results when used in patients receiving β-blockers [27].

In the CHARM study, patients who were already receiving ACE inhibitors were randomized to receive either placebo or an ARB, candesartan (32 mg/d) [28]. Compared with placebo, there was a 15% risk reduction in the primary composite end point of cardiovascular mortality and hospitalization due to heart failure in the candesartan group. Both Val-HeFT and the CHARM study demonstrated that adding an ARB improved outcomes, particularly morbidity and mortality (but notably not mortality alone).

The Valsartan in Acute Myocardial Infarction Trial (VALIANT) looked at dual inhibition with captopril and valsartan in patients with recent myocardial infarction and heart failure. No differences were seen in the primary end point of death from any cause or in the secondary end points of mortality from cardiovascular causes, recurrent myocardial infarction, and hospitalization for heart failure [29]. A recent meta-analysis examining the above trials and some other heart failure trials suggests that the combination of ACE inhibitor and ARB results in more adverse effects such as hypotension, hyperkalemia, and declining renal function [30].

Renal outcomes

There have been several studies supporting the benefits of dual blockade with ACE inhibitors and ARBs in patients with proteinuria when compared with monotherapy with either an ACE inhibitor or an ARB (Table 1) [31–36]. In a meta-analysis of 49 studies, Kunz et al. [37•] found evidence that dual RAS blockade reduced proteinuria by 20% to 25% more than monotherapy with either agent. In yet another meta-analysis of 21 randomized trials involving patients with proteinuria, MacKinnon et al. [38] also demonstrated a greater reduction of proteinuria with combination therapy in both diabetics and nondiabetics. With the addition of an ARB to an ACE inhibitor, systolic blood pressure decreased by 4.5 mm Hg and diastolic BP decreased by 2.5 mm Hg. However, there was a small but significant increase in serum potassium of 0.11 mEq/L [38].

Investigators in the Candesartan And Lisinopril Microalbuminuria (CALM) study found that the combination arm experienced a greater drop in systolic blood pressure and proteinuria, which decreased 50% more in that group [31] (Table 1). The dose of lisinopril, the ACE inhibitor used in this study, was 20 mg/d. The CALM II study used a higher dose of lisinopril (40 mg/d) without significant differences in systolic blood pressure or albumin excretion rates in the combination arm [33]. Importantly, although the first CALM report [31] showed an increase in serum creatinine and potassium in the combination arm, this difference was not present in CALM II with the higher dose of ACE inhibitor [33].

Renal outcomes (time to doubling of creatinine or renal replacement therapy) were the primary end points in the COOPERATE study, conducted in patients with nondiabetic renal disease [34]. In this study, 11% of patients receiving combination therapy reached the primary end point, versus 23% of those receiving monotherapy. Indeed, there was a 60% risk reduction in the combination arm, independent of changes in blood pressure. However, once again the potassium levels were slightly higher in the combination arm. The methodology and statistical analysis in this trial have been criticized, however, so the results should be interpreted with caution [39].

In contrast to COOPERATE, the Irbesartan in the Management of Proteinuric Patients at High Risk

Table 1. Clinical trials leading up to ONTARGET

Study	Study design	Patient population	*N*	Treatment arms	Changes in combination arm vs monotherapy	Conclusions
CALM [31]	Prospective, randomized, parallel-group, double-blind. 24 wk follow-up	Hypertensive T2DM with micro-albuminuria; age 34–75 y	199	Lisinopril 20 mg vs candesartan 16 mg vs lisinopril 20 mg plus candesartan 16 mg	BP reduced 10/6 mm Hg; proteinuria reduced 34% for combination vs candesartan, NS for combination vs lisinopril; GFR, NS	Combination therapy more effective in reducing BP
Rossing et al. [32]	Randomized, double-blind crossover study, one center	Hypertensive T2DM with overt nephropathy; age 35–75 y	18	Lininopril/enalapril 20 mg or captopril 100 mg plus candesartan 8 mg vs ACE inhibitor plus placebo	SBP reduced by 10 mm Hg; proteinuria reduced 25%; GFR reduced 5 mL/min/1.73 m^2	Combination therapy reduces both BP and albuminuria
CALM II [33]	Prospective, randomized, parallel-group, double-blind, double-dummy study, one center. 12 mo follow-up	T1DM and T2DM	75	Lisinopril 40 mg vs lisinopril 20 mg plus candesartan 16 mg	SBP reduced by 4 mm Hg vs lisinopril (NS); proteinuria NS	Combination therapy not inferior to dose escalation of single agent
COOPERATE [34]	Prospective, randomized, double-blind, one center. 3 y follow-up	Nondiabetic renal disease	263	Losartan 100 mg vs trandolapril 3 mg vs losartan plus trandolapril	BP: NS	Primary end point of doubling of SeCr or ESRD was reached by 10/85 in combination arm vs 20/85 in trandolapril arm vs 20/86 in losartan arm
IMPROVE [35]	Multicenter, randomized, double-blind, placebo-controlled, parallel-group study	Hypertension with micro-albuminuria and high CV risk	405	Ramipril plus irbesartan vs ramipril plus placebo	BP reduced significantly in 17.3% vs 10.8% of patients; proteinuria, NS (but significant reduction in subgroup with overt nephropathy)	Subgroup of overt nephropathy patients had significant reductions in proteinuria
VALERIA [36]	Randomized, double-blind, parallel-group interventional study	Hypertension and micro-albuminuria	133	Valsartan 320 mg vs lisinopril 40 mg vs valsartan 320 mg plus lisinopril 20 mg	BP, NS; proteinuria significantly decreased	Combination therapy provided significant reduction in UACR independent of BP

ACE—angiotensin-converting enzyme; BP—blood pressure; CALM—Candesartan And Lisinopril Microalbuminuria; COOPERATE—Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease; CV—cardiovascular; ESRD—end-stage renal disease; GFR—glomerular filtration rate; IMPROVE—Irbesartan in the Management of Proteinuric Patients at High Risk for Vascular Events; NS—not significant; ONTARGET—Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; SBP—systolic blood pressure; SeCr—serum creatinine; T1DM—type 1 diabetes mellitus; T2DM—type 2 diabetes mellitus; UACR—urine albumin-to-creatinine ratio; VALERIA—Valsartan in Combination With Lisinopril in Hypertensive Patients With Microalbuminuria.

for Vascular Events (IMPROVE) study did not show greater proteinuria reduction in patients treated with combination therapy, despite greater blood pressure reduction in that arm of the trial [35]. On the other hand, and similar to COOPERATE, the VALERIA trial demonstrated that combination therapy led to greater reduction in proteinuria; the patients in this study receiving monotherapy were given the maximum doses of lisinopril or valsartan [36]. The blood pressure in the two groups did not differ.

Collectively, there have been conflicting results on renal outcomes with dual RAS inhibition; these contradictions have led investigators to attempt a more thorough investigation of combination therapy.

Results From ONTARGET

The ONTARGET investigators sought to compare the effects of an ACE inhibitor (ramipril), an ARB (telmisartan), or a combination of both in more than 25,000 patients with vascular disease (coronary, peripheral, or cerebrovascular) or diabetes with end-organ damage [40••]. Unlike many of the previous studies, ONTARGET enrolled patients with high risk for CVD but excluded patients with heart failure. In addition, maximal doses of ACE inhibitors and ARBs were tolerated in a majority of patients and follow-up was prolonged, as specified below. The objective was to compare the efficacy of telmisartan and ramipril and to determine whether the combination of telmisartan and ramipril was more effective than monotherapy in reducing the composite primary outcome of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure. Secondary outcomes were new-onset heart failure, diabetes mellitus, atrial fibrillation, dementia or cognitive decline, nephropathy, and revascularization procedures. There was no significant difference in primary outcome between the telmisartan and ramipril groups (RR with telmisartan, 0.98), and although the number of deaths in the ramipril group (1014) was lower than the number in the combination group (1065; RR, 1.07), the difference did not reach statistical significance.

The mean blood pressure prior to the run-in period was 141.8/82.1 mm Hg. At 6 weeks, the mean blood pressure was reduced by 6.4/4.3 mm Hg in the ramipril group, by 7.4/5.0 mm Hg in the telmisartan group, and by 9.8/4.3 mm Hg in the combination group. The patients in the combination group had the lowest blood pressure levels throughout the study period, with an average reduction of 2.4/1.4 mm Hg as compared with the ramipril group. A total of 784 patients (149 in the ramipril group, 229 in the telmisartan group, and 406 in the combination arm) permanently discontinued the randomized treatment because of hypotension. The number of patients having an increase in potassium levels of more than 5.5 mmol/L were similar in the ramipril and telmisartan groups (283 vs 287 patients), but the number was significantly higher in the combination therapy group (480; $P < 0.001$ vs ramipril).

As part of the prespecified analysis of ONTARGET, Mann and colleagues [15•] looked specifically at renal outcomes (dialysis, doubling of creatinine, and death) and changes in the surrogate markers of estimated GFR and proteinuria. After an initial 3-week run-in period, 25,620 participants in ONTARGET were randomly assigned to receive ramipril, 10 mg/d ($n = 8567$); telmisartan, 80 mg/d ($n = 8542$); or a combination of both drugs at the same doses. The median follow-up was 56 months. Intention-to-treat analysis was applied and it was found that the number of events for the composite primary outcome of dialysis, doubling of creatinine, and death were similar in the groups receiving monotherapy with telmisartan ($n = 1147$, 13.4%) and ramipril ($n = 1150$, 13.5%), but the number of primary events was significantly increased with combination therapy ($n = 1233$, 14.5%; $P = 0.037$). The relative risk of primary renal end points was similar in the ramipril and telmisartan groups (HR, 1.0; 95% CI, 0.92–1.09; $P = 0.968$), whereas it increased in the combination arm (HR, 1.09; 95% CI, 1.01–1.08; $P = 0.037$). The rate of loss of renal function was about 1 mL/min per year, which was significantly lower than the rates of 4 to 5 mL/min per year reported in other clinical trials with patients at high risk [12,41]. Secondary renal outcome events (initiation of dialysis and doubling of serum creatinine) were also more numerous in the combination group ($n = 212$, 2.49%; HR, 1.24; 95% CI, 1.01–1.51; $P = 0.038$) as compared with the ramipril group ($n = 174$, 2.03%; HR, 1.09; 95% CI, 0.89–1.34; $P = 0.42$) or the telmisartan group ($n = 189$, 2.21%). There were 162 cases of dialysis, of which 61 (31%) were acute dialysis. The incidence of chronic dialysis ($n = 98$) was similar between groups. The primary renal outcomes remained the same after removing the acute dialysis patients.

When considering these data, it is important to note that microalbuminuria was present in only 13.1% of all patients (29.7% of diabetics and 9.2% of nondiabetics). Macroalbuminuria was present in only 4.0% of all participants (12.2% of diabetics and 1.4% of nondiabetics). The mean urine albumin:creatinine ratio increased more in the ramipril arm (31%) and the telmisartan arm (24%) than in the combination therapy group (21%, $P = 0.0028$). The risk of developing new microalbuminuria or macroalbuminuria did not differ between the monotherapy groups but was lower with combination therapy than with ramipril (10.4% vs 11.7%, $P = 0.119$).

Although the ONTARGET study was not specifically powered for primary renal outcomes, the investigators had prospectively stated that the renal outcomes were the most important secondary end points with a specific statistical analysis plan. A total of 3500 primary renal events were recorded. Combi-

nation therapy showed greater decline in renal function and more cases of dialysis, doubling of serum creatinine, or both when compared with ramipril. No benefit of the combination therapy on primary renal outcome was seen in patients with either microalbuminuria or macroalbuminuria.

There has been considerable discussion regarding the renal outcomes. The data suggest that one cannot generalize the conclusions to individuals with diabetic nephropathy or significant proteinuria. It must also be pointed out that most subjects in this trial had normal renal function and were free of proteinuria. In fact, a subgroup analysis suggests that the poor outcomes observed with combination therapy occurred in patients with low renal risk—that is, those who were not diabetic, were not hypertensive, had neither microalbuminuria nor macroalbuminuria, and had no overt diabetic nephropathy [15•,42].

It should also be noted that although the mean blood pressure drop was slightly greater than 2 mm Hg in the combination arm, the dropout numbers due to episodes of hypotension were substantially higher in the combination arm than in either monotherapy arm. The ONTARGET participants were older, with a mean age of 66, and had known cardiovascular disease or diabetes with end-organ damage, with possibly compromised renal autoregulation. Close to one third of the patients were normotensive and thus at risk for hypotension. The incidence of hyperkalemia was significantly higher (nearly double) in the combination arm. In addition, a major adverse event in the combination arm was diarrhea, which may have exacerbated the renal injury by reducing renal perfusion.

Future Direction

A study primarily aimed at patients at risk for progressive CKD is still needed. The Long-Term Impact of RAS Inhibition on Cardiorenal Outcomes (LIRICO) study will compare the cardiorenoprotective effects of ACE inhibitors and ARBs in patients with albuminuria, and should clarify the role of dual blockade [43]. Another study in progress is the VA NEPHRON-D study, which is a randomized, double-blind, multicenter clinical trial to assess the effect of combination losartan and lisinopril, compared with losartan alone, on the progression of kidney disease in 1850 patients with diabetes and overt proteinuria [44].

There are alternative ways to inhibit RAS, which may complement the existing strategies while the search for an ideal approach continues. Aldosterone blockade as monotherapy or as a complement to other RAS inhibitors has been shown to be cardioprotective and renoprotective [45,46]. (However, the data on renal protection is scanty and comes from small-scale, short-term trials mainly looking at proteinuria as a marker for renal injury [47].) Additionally, direct renin inhibitors such as aliskiren have been used in combination therapy [48]. The AVOID study suggested that the reduction in the mean urine:creatinine ratio was 20% greater with dual blockade using aliskiren and losartan than with losartan alone, with a minimal further reduction in blood pressure [48]. Collectively, future work with direct renin inhibition or aldosterone blockade in combination strategies may have more potential to reduce cardiorenal risk.

Conclusions

ONTARGET confirms that in patients with high risk for CVD, monotherapy using either ACE inhibitors or ARBs confers similar cardiovascular and renal protection, with little additional benefit when used in combination. Compared with either type of monotherapy, combination therapy contributed to a worsening in renal end points, except possibly proteinuria. The conflicting results between major renal end points and proteinuria with dual RAS inhibition continues to raise the question of whether proteinuria is a suitable surrogate marker for those with CKD. Until further data emerge, combination strategies using RAS inhibition should be applied with close monitoring and not on a routine basis, except in patients with diabetic nephropathy or significant proteinuria.

Clinical Trial Acronyms

AVOID—Aliskiren in the Evaluation of Proteinuria in Diabetes; CALM—Candesartan And Lisinopril Microalbuminuria; CHARM—Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; COOPERATE—Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease; EUROPA—European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease; HOPE—Heart Outcomes Prevention Evaluation; IMPROVE—Irbesartan in the Management of Proteinuric Patients at High Risk for Vascular Events; LIRICO—Long-Term Impact of RAS Inhibition on Cardiorenal Outcomes; ONTARGET—Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; PROGRESS—Perindopril Protection Against Recurrent Stroke Study; VALERIA—Valsartan in Combination with Lisinopril in Hypertensive Patients with Microalbuminuria; Val-HeFT—Valsartan Heart Failure Trial; VALIANT—Valsartan in Acute Myocardial Infarction Trial; VA NEPHRON-D—Veterans Administration Nephropathy in Diabetes Study.

Disclosure

No potential conflicts of interest relevant to this article were reported.

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