

Aggressive RAAS Blockade and the Kidney after ONTARGET

BY PHILIP McFARLANE, MD, PHD, FRCP(C)

Drugs that block the renin-angiotensin-aldosterone system (RAAS) are the most commonly-used antihypertensives in Canada, with a combined prescription rate of about 1000/10 000 population.¹ Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) are prescribed to control blood pressure (BP). They are also prescribed to control end-organ damage independently of BP. For example, these medications improve survival in patients with systolic heart failure and in those at high cardiovascular (CV) risk. They also reduce the progression of kidney disease. This combination of both BP control and non-BP-mediated organ protection has led to a first-line indication for agents that block the RAAS across the cardiorenal spectrum. The Canadian Diabetes Association (CDA)² recommends the use of either an ACE inhibitor or an ARB for vascular protection in all patients with diabetes mellitus (DM) who are at high CV risk, regardless of their BP. This group of patients includes most adults with DM.

In some patients, blocking the RAAS with a full dose of an ACE inhibitor or an ARB does not fully suppress RAAS activity in all tissues. This fact has led many investigators to question whether more aggressive blockade of the RAAS could improve patient outcomes further. Many aggressive RAAS blockade strategies exist. For example, very high doses of either an ACE inhibitor or an ARB have been tested, as has combining these drugs with aldosterone antagonists such as spironolactone or eplerenone. In addition, newer agents such as the direct renin inhibitors (DRIs) have been tested in combination with traditional RAAS blockers. However, the most popular technique has been to combine an ACE inhibitor with an ARB. The recent CV mega-trial – the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET)³ – revealed that the ARB, telmisartan, could produce a similar degree of CV protection as the ACE inhibitor, ramipril. However, ONTARGET failed to reveal any advantage of an ACE inhibitor/ARB combination over either drug alone and it also demonstrated a higher adverse event rate in the combination arm. These findings have led the Canadian Hypertension Education Program (CHEP)⁴ to suggest that this combination not be used to control routine high BP. In addition, the Canadian Heart and Stroke Foundation⁵ has issued a warning about potential side effects with this combination.

This issue of *Endocrinology Rounds* examines the rationale behind RAAS blockade, both with conventional and aggressive strategies. It also discusses the results of ONTARGET and how they affect clinical practice. Since aggressive RAAS blockade is used primarily in patients with kidney disease, this discussion focuses primarily on this group of patients.

Why block the RAAS?

Stimulation of the RAAS raises BP due to the direct vasoconstrictive effects of angiotensin II and the ability of aldosterone to cause salt and water retention. However, RAAS activation has effects other than raising BP. Angiotensin II is a growth factor that



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St. Michael's Hospital
6121-61 Queen St. E.
Toronto, Ont. M5C 2T2
Fax: (416) 867-3696

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Table 1: Heart Outcomes Prevention Evaluation (HOPE) trial: Incidence of the primary outcome and of deaths from any cause¹¹

Outcome	Ramipril Group (n= 4645); n (%)	Placebo Group (n= 4652); n (%)	Relative Risk (95% CI)	Statistic	P ^a
MI, stroke, or death from CV causes ^b	651 (14.0)	826 (17.8)	0.78 (0.70–0.86)	–4.87	<0.001
Death from CV causes ^c	282 (6.1)	377 (8.1)	0.74 (0.64–0.87)	–3.78	<0.001
MI ^c	459 (9.9)	570 (12.3)	0.80 (0.70–0.90)	–3.63	<0.001
Stroke ^c	156 (3.4)	226 (4.9)	0.68 (0.56–0.84)	–3.69	<0.001
Death from non-CV causes	200 (4.3)	192 (4.1)	1.03 (0.85–1.26)	0.33	0.74
Death from any cause	482 (10.4)	569 (12.2)	0.84 (0.75–0.95)	–2.79	0.005

^a P values were calculated with use of the log-rank test; ^b In the substudy, 34 of 244 patients (13.9%) assigned to take a low dose of ramipril (2.5 mg/day) reached the composite endpoint, as compared with 31 of 244 assigned to take 10 mg of ramipril/day (12.7%) and 41 of 244 assigned to placebo (16.8%). The inclusion of the data from the low-dose group did not change the overall results (relative risk of the primary outcome, 0.78; 95% CI, 0.70–0.86); ^c All patients with this outcome are included.

MI = myocardial infarction; CV = cardiovascular; CI = confidence interval. Copyright © 2000, Massachusetts Medical Society. All rights reserved.

increases extracellular matrix production, which promotes adverse remodelling and hypertrophy in the heart and contributes to the classical changes seen in diabetic nephropathy. It has also been implicated in contributing to endothelial dysfunction and vascular inflammation. All of these effects have led to studies of RAAS blockade in people with a variety of cardiorenal risk factors, as well as in those with established cardiac or renal disease.

ACE inhibitors have been shown to improve survival in patients following myocardial infarction (MI)⁶⁻⁹ and in those with heart failure.¹⁰ They are also associated with a reduction in the occurrence of MI and stroke and prolonged survival in patients with elevated CV risk.¹¹ ARBs appear to be equally effective in treating heart failure^{12,13} and post-MI cardiac damage.¹⁴

In type 1 DM, ACE inhibitors have been shown to prevent progression to renal failure and to improve survival in people with nephropathy.¹⁵ In type 2 DM, ACE inhibitors have been shown to reduce the likelihood of developing nephropathy,¹⁶ while ARBs have been shown to reduce the worsening of nephropathy^{17,18} and progression to renal failure.¹⁹ In non-diabetic kidney disease, ACE inhibitors have been shown to reduce the rate of loss of renal function.²⁰ ARBs and ACE inhibitors are likely to be equally protective in renal disease.^{21,22}

Taken as a whole, these trials demonstrate an impressive degree of organ protection across the cardiorenal spectrum. However, despite these interventions, cardiac and renal disease can continue to worsen. There are 2 possible reasons why progressive organ damage may occur despite RAAS blockade: either RAAS blockade is incomplete or further damage is being driven by factors unrelated to the RAAS.

Aggressive RAAS blockade – the rationale

One of the main reasons for predicting a potential role for aggressive RAAS blockade in some patients is that our understanding of the nature of the RAAS is

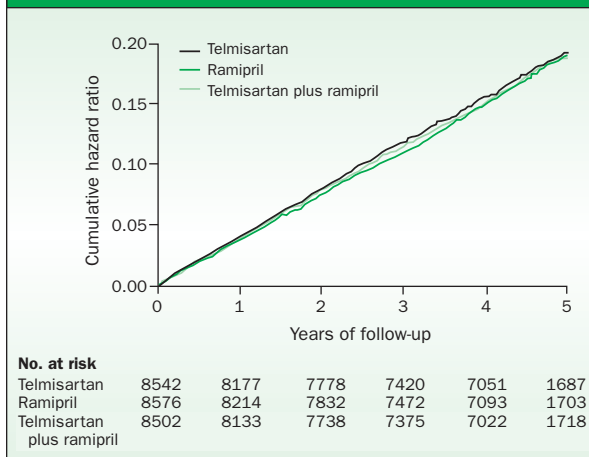
changing. Traditionally, the RAAS was viewed as a classical endocrine system with a variety of circulating components (eg, renin, angiotensinogen, angiotensin II) and a variety of tissues contributing these components (eg, renin from the kidney, ACE from the lung). Recently, however, we have become more aware of the importance of the RAAS as an autocrine/paracrine system.²³ Some tissues have all of the components needed to activate angiotensin II.²⁴ For example, the proximal convoluted tubule (PCT) in the kidney does not rely on other tissues to contribute components to locally activate the RAAS.^{25,26} This “tissue RAAS” activity can be stimulated in the heart and the kidney as the result of an injury. In the kidney, proteinuria induces local tissue RAAS activity that can be hundreds or even thousands of times higher than systemic RAAS activity. It is important to note that, although administration of an ACE inhibitor or an ARB almost completely inhibits systemic angiotensin II activity, it does not fully suppress intrarenal RAAS activity. Therefore, it is possible that patients with kidney damage may have ongoing local tissue RAAS activity despite conventional RAAS blockade, raising the possibility that more aggressive blockade could benefit these individuals.

Aggressive RAAS blockade – renal outcomes

Extent of proteinuria is correlated with a higher chance of end-stage renal disease (ESRD),²⁷ while a fall in albuminuria after initiation of RAAS blockade portends a better renal outcome.²⁸ All of the aggressive RAAS blockade strategies described above have been associated with a reduction in proteinuria in patients with renal disease.²⁹⁻³³ However, few studies have examined how these strategies affect hard renal endpoints such as death or dialysis.

The Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-Converting-Enzyme Inhibitor in Non-Diabetic Renal Disease (COOPERATE) study³⁴ suggests that using a combination of an ACE inhibitor and an ARB in people with

Figure 1: ONTARGET: Kaplan-Meier curves for the primary outcome in the 3 study groups³



ONTARGET = Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial
 The composite primary outcome was death from CV causes, MI, stroke, or hospitalization for heart failure.
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nondiabetic kidney disease is associated with a lower rate of doubling of serum creatinine or ESRD than either agent used as monotherapy. Unfortunately, there have been concerns that this study is erroneous or fraudulent.³⁵

The single best study of aggressive RAAS blockade in renal disease is the Renoprotection of Optimal Antiproteinuric Doses (ROAD) trial.²² In this study, people with nondiabetic kidney disease were randomized to either standard doses of an ACE inhibitor, an ARB, or an uptitration strategy, in which the dose of the ACE inhibitor or ARB was progressively increased until either was 3 times higher than the usual maximum dose or there was no further antiproteinuric response. This up-titration strategy was associated with halving the risk of doubling of serum creatinine, ESRD, or death.

Aggressive RAAS blockade – the ONTARGET Study

The landmark Heart Outcomes Prevention Evaluation (HOPE) study was published in 2000.¹¹ It demonstrated that an ACE inhibitor could reduce CV morbidity and mortality in a broad group of high-risk patients, regardless of baseline renal or cardiac status (Table 1). This led to the recommendation of ACE inhibitors as first-line agents in many high-risk groups, both with and without hypertension. However, 2 questions persisted following the HOPE results:

- Would ARBs perform as well as ACE inhibitors for vascular protection?
- Would a combination of both an ACE inhibitor and an ARB be better than an ACE inhibitor alone?

Table 2: ONTARGET: Discontinuation of study medications and selected reasons for permanent discontinuation³

Variable	Ramipril (n=8576); n (%)	Combination (n=8502); n (%)	Combo vs Ram RR	P
Any discontinuation	2099 (24.5)	2495 (29.3)	1.20	<0.001
Hypotensive symptoms	149 (1.7)	406 (4.8)	2.75	<0.001
Syncope	15 (0.2)	29 (0.3)	1.95	0.03
Cough	360 (4.2)	392 (4.6)	1.10	0.19
Diarrhea	12 (0.1)	39 (0.5)	3.28	<0.001
Angioedema	25 (0.3)	18 (0.2)	0.73	0.30
Renal impairment	60 (0.7)	94 (1.1)	1.58	<0.001

RR = relative risk.
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ONTARGET was designed to answer these questions.³ In this trial, >25 000 people with known CV disease or DM with organ damage were randomized to either a full dose of an ACE inhibitor, a full dose of an ARB, or full doses of both in combination. The median follow-up was 56 months. The composite primary outcome in the 3 groups was death from CV causes, MI, stroke, or hospitalization for heart failure. The study demonstrated that the ARB was not inferior to the ACE inhibitor and there were very similar CV event and mortality rates in both groups (Figure 1). These results led the CDA to modify its guidelines to recommend ARBs as well as ACE inhibitors for vascular protection. However, the combination of an ACE inhibitor and an ARB was not superior to an ACE inhibitor alone and the side effect rate, including hypotensive symptoms, cough, syncope, and renal dysfunction (Table 2), was higher in the combination group. These robust conclusions led the CHEP to recommend that the combination of an ACE inhibitor and an ARB not be used for the treatment of hypertension without compelling indications.

ONTARGET – renal outcomes

Although CV outcomes were not improved additionally by combination therapy in ONTARGET versus an ACE inhibitor or an ARB alone, there was hope that there may be some positive renal results, given the positive results of studies such as ROAD. Indeed, albuminuria increased less with combination therapy in ONTARGET and fewer patients in the combination arm progressed from microalbuminuria to overt nephropathy.³⁶ However, the rate of loss of renal function was highest in the combination group: -6.11 mL/min in the combination group; -4.12 mL/min

Table 3: ONTARGET: Secondary and other outcomes³

Outcome	Ramipril (n=8576); n (%)	Telmisartan (n=8542); n (%)	Combination therapy (n=8502); n (%)	Telmisartan vs ramipril RR (95% CI)	Combination therapy vs ramipril RR (95% CI)
Revascularization	1269 (14.8)	1290 (15.1)	1303 (15.3)	1.03 (0.95–1.11)	1.04 (0.97–1.13)
Hospitalization for angina	925 (10.8)	954 (11.2)	952 (11.2)	1.04 (0.95–1.14)	1.04 (0.95–1.14)
Worsening or new angina	567 (6.6)	536 (6.3)	538 (6.3)	0.95 (0.84–1.07)	0.96 (0.85–1.08)
New diagnosis of diabetes ^a	366 (6.7)	399 (7.5)	323 (6.1)	1.12 (0.97–1.29)	0.91 (0.78–1.06)
Any heart failure	514 (6.0)	537 (6.3)	478 (5.6)	1.05 (0.93–1.19)	0.94 (0.83–1.07)
New atrial fibrillation ^b	570 (6.9)	550 (6.7)	537 (6.5)	0.97 (0.86–1.09)	0.96 (0.85–1.07)
Renal impairment ^c	871 (10.2)	906 (10.6)	1,148 (13.5)	1.04 (0.96–1.14)	1.33 (1.22–1.44) ^d
Renal failure requiring dialysis	48 (0.6)	52 (0.6)	65 (0.8)	1.09 (0.74–1.61)	1.37 (0.94–1.98)

^a The number of patients included in this analysis were 5427 in the ramipril group, 5294 in the telmisartan group, and 5280 in the combination-therapy group. ^b This category includes only patients who did not have atrial fibrillation at baseline: 8296 in the ramipril group, 8259 in the telmisartan group, and 8218 in the combination-therapy group. ^c No specific definitions were used. A determination of renal impairment was based on the clinical investigator's report of an event that led to the discontinuation of a study drug. ^d $P < 0.001$. Copyright © 2008, Massachusetts Medical Society. All rights reserved.

with telmisartan; and -2.82 mL/min with ramipril, $P < 0.001$), although most of this difference was related to renal hemodynamic changes and was seen within the first 6 weeks. There was also more acute dialysis in the combination group (hazard ratio [HR] 2.19, 95% confidence interval [CI], 1.13–4.22, $P = 0.02$). There were no significant differences in the rate of doubling of serum creatinine or in the rate of progression of chronic kidney disease to the requirement for dialysis. ONTARGET failed to demonstrate an improvement in renal outcomes with combination therapy and, despite reducing albuminuria, demonstrated that there is an increased risk of acute renal failure with combination therapy (Table 3).³

Should we believe the ONTARGET renal results?

The ONTARGET trial was well designed and executed, with sufficient power to address its primary hypotheses. The conclusions from ONTARGET related to CV outcomes and mortality are extremely robust. However, ONTARGET did not study people with kidney disease and, therefore, its renal results should not be extrapolated to those with chronic kidney disease. The average urinary albumin to creatinine ratio (ACR) was well within the normal range and the differences in ACR at the end of the study were very small (1.06 with ramipril, 0.98 with combination therapy, $P = 0.0009$). Very few people progressed from microalbuminuria to overt nephropathy in ONTARGET (2.1% with ramipril, 1.6% with combination therapy; HR 0.76, 95% CI, 0.60–0.96, $P = 0.019$).

This stands in contrast to renal trials such as the Irbesartan MicroAlbuminuria type 2 diabetes in hypertensive patients (IRMA 2) study, where the progression rate was as high as 15%.¹⁷ At baseline, the mean glomerular filtration rate (GFR) in ONTARGET was reasonable and age-appropriate at about 74 mL/min. The rate of decline in GFR in ONTARGET ranged from between 0.26 and 0.55 mL/min per year. This represents a very slow loss of renal function in all groups, especially considering that the average decline in GFR in the general population is about 1 mL/min per year.³⁷ The rate of ESRD was also very low, with the dialysis rate in ONTARGET ranging between 0.56% and 0.74% over >5 years of follow-up. This stands in contrast to renal trials such as the Irbesartan in Diabetic Nephropathy Trial (IDNT), where the ESRD rate was almost 20%.¹⁸

In summary, the population studied in ONTARGET did not have a significant burden of kidney disease at baseline. As such, one would not expect a large number of renal events; indeed, the ONTARGET population lost less renal function than expected and only a very small number developed renal complications. It is impossible to demonstrate a renal benefit of aggressive RAAS blockade in a population without significant chronic kidney disease and a very low renal event rate. Therefore, the ONTARGET study does not contribute to our understanding of the effectiveness of aggressive RAAS blockade in people with kidney disease.

The sick day medication list

Although ONTARGET did not have sufficient renal events to make robust conclusions about the

efficacy of combination therapy in preventing renal events, the large population and long follow-up time does provide insights into the potential toxicity of combination therapy. Acute renal failure requiring dialysis was rare in ONTARGET, but it occurred twice as often in the combination therapy group. This insight provides an opportunity to recall that activation of the RAAS preserves BP and renal function during times when a person is dehydrated. Blockade of the RAAS can lead to acute renal failure if a person becomes intravascularly volume contracted (eg, during episodes of vomiting, diarrhea, or decreased oral intake). Patients should be given verbal instructions and a "sick day medication list" that lists the medications that should be put "on hold" if the patient is in danger of volume contraction. All RAAS blockers should be on this list, as should diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs). Some endocrinologists would likely consider putting metformin on the sick day medication list as well.

Conclusion

Blockade of the RAAS has become one of the primary interventions designed to slow the loss of renal function in both diabetic and nondiabetic kidney diseases. The nephrology community is now studying ways to block the RAAS more aggressively than seen with conventional doses of ACE inhibitors or ARBs. The initial renal studies are promising and larger endpoint trials are underway. Although the ONTARGET study demonstrated that there does not appear to be a role for ACE inhibitor plus ARB combination therapy for general vascular protection, it does not address the effectiveness of such a strategy in people with chronic kidney disease. The ONTARGET study does remind us that there are potential toxicities when blocking the RAAS and patients should be instructed to stop taking these medications during an acute illness. Aggressive RAAS blockade strategies for renal protection should only be considered in clinical settings where appropriate monitoring and follow-up can be provided to the patient.

Dr. McFarlane is Director of Home Hemodialysis and Live Kidney Donor Program, St. Michael's Hospital, and a Lecturer, University of Toronto.

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Abstract of Interest

Renoprotection of Optimal Antiproteinuric Doses (ROAD) Study: a randomized controlled study of benazepril and losartan in chronic renal insufficiency

HOU FF, XIE D, ZHANG X, ET AL.

The Renoprotection of Optimal Antiproteinuric Doses (ROAD) study was performed to determine whether titration of benazepril or losartan to optimal antiproteinuric doses would safely improve the renal outcome in chronic renal insufficiency. A total of 360 patients who did not have diabetes and had proteinuria and chronic renal insufficiency were randomly assigned to four groups. Patients received open-label treatment with a conventional dosage of benazepril (10 mg/d), individual uptitration of benazepril (median 20 mg/d; range 10 to 40), a conventional dosage of losartan (50 mg/d), or individual uptitration of losartan (median 100 mg/d; range 50 to 200). Uptitration was performed to optimal antiproteinuric and tolerated dosages, and then these dosages were maintained. Median follow-up was 3.7 yr. The primary end point was time to the composite of a doubling of the serum creatinine, ESRD, or death. Secondary end points included changes in the level of proteinuria and the rate of progression of renal disease. Compared with the

conventional dosages, optimal antiproteinuric dosages of benazepril and losartan that were achieved through uptitration were associated with a 51 and 53% reduction in the risk for the primary end point ($P = 0.028$ and 0.022 , respectively). Optimal antiproteinuric dosages of benazepril and losartan, at comparable BP control, achieved a greater reduction in both proteinuria and the rate of decline in renal function compared with their conventional dosages. There was no significant difference for the overall incidence of major adverse events between groups that were given conventional and optimal dosages in both arms. It is concluded that uptitration of benazepril or losartan against proteinuria conferred further benefit on renal outcome in patients who did not have diabetes and had proteinuria and renal insufficiency.

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